Clinical Practice Guideline for Urinary Tract Infection in Children

NOTE:

More than 5 years have passed since the publication of this Clinical Practice Guideline, and **its validity has not been reviewed**.

Therefore, **it is unclear whether its recommendations remain valid**; they should therefore be treated with caution and applied in accordance with **clinical judgement and the individual circumstances of each patient.**

SNS CLINICAL PRACTICE GUIDELINES
MINISTRY OF HEALTH, SOCIAL AND EQUALITY POLICY

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Plan de Calidad para el Sistema Nacional de Salud
i+cs Instituto Aragonés de Ciencias de la Salud

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This CPG is an aid to decision making in health care. It is not mandatory nor does it replace the clinical judgment of medical personnel.

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Background

Initiatives to document the variability of clinical practice, analyse its causes and adopt strategies to eliminate it have led to significant improvements in professional practice and quality. One of the most important of these strategies was the preparation of the Clinical Practice Guidelines (CPG), a set of key recommendations based on a thorough systematic review of relevant scientific studies, for the purpose of responding to uncertainties in clinical practice.

The 2010 National Health Service (SNS) Quality Plan was compiled in response to the challenges facing the SNS: increasing the cohesion of the system, ensuring fairness in public health care, regardless of where this takes place, and ensuring that it is of the highest quality. Its objectives include the promotion of the development and use of CPGs linked to Health Strategies, thereby consolidating and extending the Health Guide Project.

The SNS Interterritorial Council approved the GuíaSalud Project in 2003 with the ultimate goal of improving quality in evidence-based clinical decision making, by setting up a system of training activities and a CPG register in the SNS which are freely accessible via the Internet. It is within this context that this **CPG for Urinary Tract Infection in Children** was prepared.

Urinary tract infection (UTI) is a common childhood condition whose management is affected by the presentation of non-specific signs and symptoms, especially in younger age children, and the uncertainty associated with its prognosis. UTI in children has a higher risk of complications than in adults, and a fear of these complications can in many cases result in inappropriate use of diagnostic tests and the use of unnecessary antibiotic treatments which are not without risk for the patient and the community at large.

The purpose of this CPG is to reduce the variability of clinical practice in the management of UTI in the paediatric population, by encouraging professionals to diagnose and therapeutically intervene in the most appropriate way possible.

It is aimed at all healthcare professionals involved in the diagnosis, treatment and care of children with UTI as well as their carers.

This guide is the result of the hard work of a multi-disciplinary group of professionals from different autonomous regions, and was reviewed by medical and nursing personnel belonging to various scientific societies in Spain.

The Quality Agency would like to thank everybody for their hard work and congratulate them on this CPG. We expect it to be of great help for both health professionals and carers, when attending to the care of children affected by this infectious condition; enabling safe, effective and patient-centred clinical decision-making.

CARMEN MOYA GARCÍA
Director General of the SNS Quality Agency

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Authorship and Collaborators

Guideline Development Group of the CPG for Urinary Tract Infection in Children

Ramón Carlos Areses Trapote. Specialist physician in Paediatrics
Paediatric Nephrology Unit, Donostia Hospital. San Sebastián.

José Antonio Castillo Laita. Specialist physician in Paediatrics
Fuentes de Ebro Healthcare Centre. Fuentes de Ebro. Zaragoza.

Joaquín Escribano Subías. Specialist physician in Paediatrics
Paediatric Nephrology Unit, Sant Joan de Reus University Hospital. Reus.

Gloria María Fraga Rodríguez. Specialist physician in Paediatrics
Paediatric Nephrology Unit, Sant Pau University Hospital. Barcelona.

Ángeles García Díaz. Nurse. Miguel Servet University Hospital,
Mother and Child Unit.
Zaragoza.

Susana García Rodríguez. Pharmacist. Aragon Institute of Health Sciences.
Zaragoza.

César Joaquín García Vera. Specialist physician in Paediatrics
Sagasta-Ruiseñores Healthcare Centre.
Zaragoza.

Andrés Gómez Fraile. Specialist physician in Paediatric Surgery
Doce de Octubre Hospital.
Madrid.

Juan David González Rodríguez. Specialist physician in Paediatrics
Paediatric Nephrology Unit, Santa Lucía General University Hospital.
Cartagena.

Jesús Grasia Romero. Specialist physician in Paediatric Surgery
Miguel Servet University Hospital Mother and Child Unit. Zaragoza.

César Loris Pablo. Specialist physician in Paediatrics
Paediatric Nephrology Unit, Miguel Servet University Hospital,
Mother and Child Unit.Zaragoza.

Juan Ignacio Martín Sánchez. Specialist physician in Preventive Medicine and Public
Health. Aragon Institute of Health Sciences Zaragoza.

Carlos Ochoa Sangrador. Specialist physician in Paediatrics
Virgen de la Concha Hospital. Zamora.

Lidia Rocha Gancedo. Nurse. Miguel Servet University Hospital,
Mother and Child Unit. Zaragoza.

Luis Miguel Rodríguez Fernández. Specialist physician in Paediatrics
Paediatric Nephrology Unit. University Health Complex of León (CAULE). León.

Teresa Serrano Frago. Nurse. Miguel Servet University Hospital,
Mother and Child Unit. Zaragoza.

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Blanca Valenciano Fuente. Specialist physician in Paediatrics
Paediatric Nephrology Unit, Mother and Child University Hospital Complex of Gran Canaria Las Palmas de Gran Canaria

Coordination

Clinical Area

César Loris Pablo. Specialist physician in Paediatrics
Paediatric Nephrology Unit, Miguel Servet University Hospital,Mother and Child Unit Zaragoza.

Methodological Area

Susana García Rodríguez. Pharmacist. Aragon Institute of Health Sciences. Zaragoza.

Juan Ignacio Martín Sánchez. Specialist physician in Preventive Medicine and Public Health. Aragon Institute of Health Sciences.Zaragoza.

Other Collaborations

José María Mengual Gil. Specialist physician in PaediatricsAna Isabel González Aragon Institute of Health Sciences.Zaragoza.

Carlos Pérez Méndez. Specialist physician in Paediatrics Cabueñes Hospital. Gijón.

Information Specialist

Irene Muñoz Guajardo. Information Support Technician. Aragon Institute of Health Sciences Zaragoza.

Information Design for Patients

Sofía Arguis Molina. Information Support Technician. Aragon Institute of Health Sciences. Zaragoza.

Logistical and Administrative Support

María Esther García Pomar. Aragon Institute of Health Sciences. Zaragoza.

Information Review for Patients

Isabelle Chaffurin. Information Review for Patients as a potential user. Zaragoza.
María Yamina Landos Falo. Information Review for Patients as a potential user. Zaragoza.
Jonathan Giraldez Sánchez. Information Review for Patients as a potential user. Zaragoza.

Expert Collaboration

Juana Abadia Mainer. Nurse. Miguel Servet University Hospital, Mother and Child Unit. Zaragoza.

Antonia Andréu Domingo. Specialist Physician in Microbiology and Parasitology Vall D´Hebron Hospital Barcelona.

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Mª del Mar Bruna Martín. Nurse.Miguel Servet University Hospital, Mother and Child Unit. Zaragoza.

Luisa Ceres Ruiz. Specialist physician in Paediatrics and Radiodiagnosis. Mother and Child Unit. Carlos Haya Health Complex. Málaga.

Laura Espinosa Román. Specialist physician in Paediatrics Paediatric Nephrology Unit. La Paz University Hospital. Madrid.

Juan José García García. Specialist physician in Paediatrics Sant Joan de Deu Hospital. Esplugues.

Víctor Manuel García Nieto. Specialist physician in Paediatrics and Nephrology. Nuestra Sra. de Candelaria Hospital. Santa Cruz de Tenerife.

Roberto Hernández Marco. Specialist physician in Paediatrics Paediatric Service. University Childen's Hospital of La Paz. Universidad Autónoma. Madrid.

Javier Pisón Chacón. Specialist physician in Paediatric Surgery. Hospital Complex of Navarra. Pamplona.

External review

Mar Espino Hernández. Specialist physician in Paediatrics Paediatric Nephrology Unit. Fundación Alcorcón University Hospital. Madrid.

Elena García Martínez. Specialist physician in Paediatrics Paediatric Nephrology Unit. Reina Sofía University Hospital. Córdoba.

Javier González De Dios. Specialist physician in Paediatrics General Universitary Hospital of Alicante. Alicante.

Serafín Málaga Guerrero. Specialist physician in Paediatrics Paediatric Nephrology Unit. University of Oviedo, Asturias Central University Hospital. Oviedo.

Juan Carlos Molina Cabañero. Specialist physician in Paediatrics Emergency Department. Universitary Children's Hospital Niño Jesús. Madrid.

Gloria Orejón Luna. Specialist physician in Paediatrics General Ricardos Healthcare Centre. Madrid.

Ángel Villanueva Mateo. Specialist physician in Paediatric Surgery. Donostia Hospital. San Sebastián.

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Collaborating Societies

Spanish Association of Paediatric Nephrology

Spanish Association of Paediatrics

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Spanish Association of Paediatrics for Primary Health Care

Spanish Association for Paediatric Surgery

Spanish Association for Infectious Diseases and Clinical Microbiology

Spanish Association for Paediatric Radiology

Spanish Association for Paediatric Emergency

Members of these societies have taken part as authors. Expert collaborators or external reviewers of the CPG

Declaration of interest: All members of the Development Group, as well as those who participated in the expert collaboration and external review, made the declaration of interest appearing in Annex 6

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Key questions

PROTECTION AND RISK FACTORS FOR UTI

1. Does a lack of hygiene when using a nappy affect the incidence of UTI?
2. Does a lack of hygiene related to the presence of oxiurasis affect the incidence of UTI?
3. Does breastfeeding give any protection against UTI?
4. Are uncircumcised boys more likely to have UTI?

CLINICAL DIAGNOSIS OF UTI

5. What is the validity of the clinical findings for diagnosis of UTI in children?

BIOLOGICAL DIAGNOSIS OF UTI

6. What is the method of choice for urine collection for diagnosis of UTI?
7. How should a urine sample be preserved and transported?
8. What is the most valid urine test for diagnosing UTI in children?
9. Is there any clinical finding or laboratory test to locate a suspected or confirmed UTI in children?

DIAGNOSTIC IMAGING FOR UTI

10. What is the most effective imaging test for the diagnosis of structural abnormalities of the urinary tract and/or kidney damage in children with UTI?

PREDICTING RISK OF CHRONIC KIDNEY DAMAGE

11. Are there clinical, radiological or laboratory criteria for predicting the risk of chronic kidney damage after a first febrile UTI?

HOSPITALISATION AND REFERRAL CRITERIA

12. What should be the hospitalisation criteria for children with suspected UTI?
13. When should a child with UTI be referred from primary care to special care?

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TREATMENT OF THE ACUTE PHASE OF UTI

14. When should antibiotic treatment for suspected febrile UTI start?

15. What is the most appropriate administration route for the antibiotic treatment of febrile UTI in infancy and childhood?

16. What is the most effective empirical antibiotic treatment for febrile UTI (APN) and afebrile UTI?

17. How safe and effective is a daily dose of aminoglycosides when these antibiotics are required in the treatment of UTI?

18. What is the most effective duration of antibiotic treatment in afebrile and febrile UTI?

19. What is the treatment of choice and its duration for lobar nephronia (acute focal nephritis) and renal abscess?

20. Does the use of symptomatic (anti-inflammatory) medication help improve symptoms or prevent kidney damage?

PROPHYLAXIS OF UTI

21. Does antibiotic prophylaxis help to prevent further UTI and/or kidney damage in infants and children without structural and/or functional abnormalities?

22. When antibiotic prophylaxis is deemed necessary, what antibiotics and doses should be recommended?

23. Is the use of prophylactic antibiotics effective in preventing further UTI or renal damage in children with structural and/or functional abnormalities of the urinary tract?

24. Are other measures effective in preventing UTI recurrence: e.g., uropathogenic strain vaccines, ascorbic acid, cranberry juice and probiotics?

PREVENTION OF UTI AND LIFESTYLE MODIFICATIONS

25. Does improving poor voiding habits help prevent UTI recurrence?

26. Does improving constipation help prevent UTI recurrence?

27. Does increasing fluid intake help prevent UTI recurrence?

PROGNOSIS

28. What is the risk of recurrent UTI in children with no known structural or functional abnormalities of the urinary tract with a first UTI, and what follow-up is required?

MONITORING UTI IN CHILDREN

29. Should a culture and/or systematic analysis of urine be performed in asymptomatic patients during or after antibiotic UTI treatment?

30. Should a culture and/or systematic analysis of urine be performed in asymptomatic patients with structural and/or functional abnormalities?

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31. What information should be provided to the families and carers of patients who have had a first UTI?

32. What monitoring is required for children with permanent renal damage after UTI?

ANTIBIOTIC PROPHYLAXIS IN CATHETERISED CHILDREN

33. Is the use of prophylactic antibiotics effective in preventing a new UTI and renal damage in asymptomatic children with an indwelling catheter?

34. Is prophylactic treatment recommended for children requiring clean intermittent catheterisation for voiding problems?

35. Is the use of antibiotic prophylaxis recommended in children undergoing catheterisation for single sampling (VCUG, CEUS, isotope VCUG, urine collection) or endoscopic procedures (cystoscopy, ureteroscopy, nephrostomy)?

CATHETER CARE

36. What is the best material or type of catheter to reduce UTI associated with short-term catheterisation?

37. Does the size of the indwelling catheter affect the risk of CAUTI?

38. Does cleaning the urethral meatus prior to inserting the catheter reduce the incidence of CAUTI?

39. Does routine care of the urethral meatus in patients under indwelling catheterisation reduce the incidence of CAUTI?

40. What type of catheter (coated or uncoated) is more appropriate for reducing UTI associated with intermittent catheterisation?

41. What is the most appropriate size catheter for reducing UTI associated with intermittent catheterisation?

42. What is the most appropriate insertion technique for intermittent catheterisation?

43. Does the catheter material used in single sampling catheterisation affect the risk of CAUTI?

44. Does the catheter size for single sampling catheterisation affect the risk of CAUTI?

45. Does cleaning the urethral meatus prior to single sampling catheterisation reduce the incidence of CAUTI?

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Levels of evidence and grades of recommendations

Table 1. Levels of evidence and grades of recommendation from SIGN for intervention studies[1]

Levels of evidence	
1++	High quality meta-analyses, systematic reviews of clinical trials or high-quality clinical trials with very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of clinical trials, or well-conducted clinical trials with little risk of bias.
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with high risk of bias.
2++	High quality systematic reviews of cohort or case-control studies. Cohort or case-control studies with very low risk of bias and with high probability of establishing a causal relationship.
2+	Well conducted cohort or case-control studies with low risk of bias and a moderate probability of establishing a causal relationship.
2-	Cohort or case-control studies with a high risk of bias and a significant risk that the relationship is not causal.
3	Non-analytical studies such as case reports and case series.
4	Expert opinion.
Grades of recommendation	
A	At least one meta-analysis, systematic review or clinical trial rated as 1++ directly applicable to the target population of the guide; or a body of evidence consisting of studies rated as 1+ and showing overall consistency of results.
B	A body of evidence consisting of studies rated as 2++, directly applicable to the target population of the guide and showing overall consistency of results; or evidence extrapolated from studies rated as 1++ or 1 +.
C	A body of evidence consisting of studies rated as 2+ directly applicable to the target population of the guide and showing overall consistency of results; or evidence extrapolated from studies rated as 2++.
D	Evidence level 3 or 4; or evidence extrapolated from studies rated as 2+.

Studies classified as 1- and 2- must not be used in the process of developing recommendations due to their high potential for bias

Good clinical practice *

√	Recommended practice based on clinical experience and the consensus of the editorial team.

* Sometimes the development group wishes to highlight an important practical aspect for which there is probably no supporting evidence. In general, these cases are related to an aspect of treatment generally accepted to be good clinical practice, and is evaluated as a point of good clinical practice. These messages are not an alternative to the recommendations based on evidence, but should be considered only when there is no other way of highlighting that aspect.

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Q	Evidence taken from relevant, good quality qualitative studies. This category is not included in SIGN.

Table 2. Levels of evidence and formulation of recommendations for questions about diagnosis[1]

Levels of evidence	Type of evidence
Ia	Systematic review with homogeneity of level 1 studies.
Ib	Level 1 studies.
II	Level 2 studies. Systematic review of level 2 studies.
III	Level 3 studies. Systematic review of level 3 studies.
IV	Consensus, expert opinion without explicit critical evaluation.
Level 1 studies	Comply with: • Masked comparison with a valid reference test (gold standard). • Adequate spectrum of patients.
Level 2 studies	Have only one of these biases: • Population not representative (the sample does not reflect the population where the test applies). • Inadequate comparison with the reference standard (gold standard)the test that will be evaluated is part of the gold standard, or the test result affects the implementation of the gold standard. • Comparison not masked • Case-control studies
Level 3 studies	Have two or more of the criteria described in level 2 studies.

Recommendation	Evidence
A	Ia or Ib
B	II
C	III
D	IV

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CPG Recommendations

Protection and risk factors for UTI

Lack of hygiene as a risk factor for UTI: using nappies and presence of oxiurasis

√	It is recommended to change nappies frequently.
D	It is recommended to rule out pinworm infection in girls with recurrent UTI.

Breastfeeding and its protective role against UTI

C	It is recommended to inform mothers of the benefits and the protective effect of breastfeeding when planning the feeding of their infants.
C	It is recommended to continue breastfeeding for at least 6 months.

Phimosis as a risk factor for UTI

B	It is recommended to explore and assess the foreskin in all boys with UTI, whether associated with structural abnormalities of the urinary tract or not.
√	Circumcision should not be routinely performed even though there is an association between circumcision and reduced risk of UTI.
C	It is recommended to try obtaining retraction of the foreskin by medical treatment in boys or infants with recurrent febrile urinary tract infection, with or without malformations or dysfunctions of the urinary tract associated with phimosis.
B	In those boys or infants with recurrent febrile urinary tract infection, with or without malformations or dysfunctions of the urinary tract associated with phimosis where phimosis persists after medical treatment, it is recommended to perform circumcision.

Clinical diagnosis of UTI

A	Clinical suspicion of UTI in children from the clinical manifestations requires laboratory confirmation, due to its low discriminative ability.
A	In children under 24 months of age with fever without focus it is recommended to take a urine test to rule out UTI.
A	In children over 24 months old, with symptoms of abdominal or back pain, fever, dysuria, frequency or both, or the onset of incontinence it is recommended to take a urine test to confirm UTI.

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Biological diagnosis of ITU

Urine collection method

B	For children who can control urination a midstream clean catch urine sample is recommended.
C	For children who cannot control urination that require immediate diagnosis and/or treatment, it is recommended to use a collection technique that minimises the risk of contamination (SPA or bladder catheterisation). The choice of technique should be subject to the level of training and resources of the health care centre.
C	For children who cannot control urination that do not require immediate diagnosis and/or treatment, use a well performed non-invasive urine collection technique (perineal bag or clean catch).
D	If the analysis of urine collected by a non-sterile technique (perineal bag) is contaminated, it is recommended to confirm it by taking a repeat sample using techniques that minimise the risk of contamination. The choice of technique will depend on the patient's clinical status, level of collection training and health care setting resources.
A	It is recommended to use ultrasound, if available, to improve the effectiveness of suprapubic aspiration, when this is chosen.
√	It is recommended that patient care points that offer suprapubic aspiration should have ultrasound.

Preserving and transporting urine samples

C	It is recommended to process urine samples within 4 hours so they are not affected by bacterial growth.
C	If it is not possible to start the urine culture analysis within 4 hours, it is recommended to refrigerate the urine to be used to detect bacteriuria immediately after collection.
C	When refrigeration is not possible and the urine is to be processed between 4 and 24 hours after collection, preservatives may be employed as major delays can lead to bacterial growth.
√	It is recommended not to consider the results of some urinary profile parameters (nitrite and glucose) from urine with chemical preservatives added, as they may not be valid.
√	When using chemical preservatives, ensure the minimum volume of urine sample recommended by the manufacturer is taken.

Diagnostic tests in urine

B	It is recommended to perform an urgent Gram-stain microscopic examination of urine and urine culture on infants under 3 months with suspected UTI.
B	It is recommended to perform a urine microscopic examination or, failing that, a dipstick test and urine culture on patients with suspected UTI who are younger than 2 years or who cannot control urination. If there is a strong clinical suspicion of UTI or the patient is at risk of severe disease, these tests must be performed urgently.

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B	For patients younger than 2 years or who cannot control urination, with suspected UTI, it is recommended to start antibiotic treatment after collecting the urine culture sample if they have bacteriuria or positive nitrites in a reliable urine sample (collected by SPA or catheter).
B	For infants at risk of severe disease (with fever of unknown origin) younger than 2 years or who cannot control urination, it is recommended to start antibiotic treatment after collecting the urine culture sample if they have bacteriuria or positive nitrites or leukocyturia in a reliable urine sample (collected by SPA or catheter).
B	In patients older than 2 years with suspected UTI who can control urination, it is recommended to perform a urine dipstick test. Perform a microscopic examination of urine, if available, only in dubious cases.
B	In patients older than 2 years with a high clinical suspicion of UTI (specific symptoms with the presence of nitrites or bacteriuria, with or without leukocytes), it is recommended to start empirical antibiotic treatment after collecting the urine culture.
B	In patients older than 2 years, with leukocytes only in urine, it is recommended to perform a urine culture, and consider starting antibiotic treatment depending on the likelihood of symptoms and the patient's clinical situation.
B	Do not treat or perform a urine culture on patients older than 2 years if no leukocytes or nitrites are found in the urine sample and clinical features are non-specific.
√	It is recommended to confirm UTI by urine culture when available. It is especially necessary in the following cases: • Children under 2 years or those who cannot control urination. • Where there is suspicion of upper tract UTI. • In any patient at risk of serious illness. • In any patient, when the dipstick results are inconclusive or do not agree with the clinical examination.

Localisation of UTI

√	Suspect acute renal affectation (APN) in the presence of high fever ≥38.5°C and/or systemic involvement.
C	Suspect acute renal affectation (APN) with high acute phase reactants CRP and/or PCT, especially the latter.
C	Suspect acute renal affectation (APN) with IL-6 in urine >15 pg/mL.
√	Suspect acute renal affectation (APN) with a defect in renal concentrating ability, i.e., reduced maximum urine osmolality checked by an appropriate diagnostic test.
B	If there are no symptoms and/or clinical signs (fever, abdominal pain or malaise) with normal or slight increase in acute phase reactants (CRP <20 mg/L, PCT <0.5 ng/mL, ESR <10 mm/h and/or IL-6 in serum <4 pg/mL) or normal spontaneous osmolality, do not suspect renal parenchymal involvement.

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√	Although analytical studies help in locating UTI, they are not routinely necessary for its management and treatment.

Diagnostic imaging for UTI

√	It is recommended to perform a urinary tract ultrasound after a first UTI if any of the following criteria apply to the patient: – Febrile UTI – No control over urination, and with no pre-natal or normal post-natal ultrasound. – Signs of urinary tract dysfunction. – Abdominal or bladder mass. – High creatinine levels. – UTI from a microorganism other than *E. coli*.
C	It is recommended to perform an ultrasound of the urinary tract in all children with recurrent UTI.
C	It is recommended to use techniques enhancing the ultrasound of the urinary tract, if available.
D	Do not perform routine DMSA in the acute phase for patients with UTI.
√	Consider selective use of DMSA in the acute phase, if available, if the result is important for the subsequent diagnosis of the patient (e.g., to decide treatment or complementary tests).
D	It is recommended to perform delayed DMSA scintigraphy (after 6 months) after a first febrile UTI if any of the following criteria apply to the patient: – Atypical evolution (persistence of fever >48 hours). – Signs of lower urinary tract dysfunction. – Abdominal or bladder mass. – High creatinine levels. – Septicaemia. – UTI from a microorganism other than *E. coli*. – Pathological findings in previous imaging studies (e.g., ultrasound, cystogram, DMSA).
√	Consider delayed DMSA scintigraphy (after 6 months) after a first febrile UTI if clinical, laboratory or radiological findings indicate a high likelihood of renal involvement.

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C	It is recommended to perform DMSA scintigraphy on paediatric patients with recurrent febrile UTI.
D	In general, it is not recommended to perform cystography (VCUG, radionuclide cystography or echo-enhanced cystography) on children after a first UTI, unless any of the following criteria apply to the patient: – Recurrent UTI. – Abnormalities in previous imaging studies (ultrasound or DMSA). – Signs of lower urinary tract dysfunction – Family history of VUR.
C	When performing a cystographic study in paediatric patients, it is recommended to use radionuclide cystography or echo-enhanced cystography, if available, instead of VCUG, unless lower urinary tract abnormalities are suspected.

Predicting the risk of chronic kidney damage

B	It is recommended to investigate renal injury in paediatric patients with VUR, as they present an increased risk of permanent injury.
B	It is recommended to investigate the presence of permanent renal damage in paediatric patients with recurrent febrile UTI.
B	An increase in acute phase reactants or renal ultrasound during febrile UTI, in isolation, should not be used as predictors of permanent kidney damage.
D	It is not recommended to investigate permanent renal damage by renal scintigraphy in paediatric patients with a first febrile UTI, based on the clinical presentation, delay in establishing treatment, patient's age or gender.

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Hospitalisation and referral criteria

Hospitalisation criteria for suspected UTI

√	A child with febrile urinary tract infection meeting any of the following criteria should be admitted to hospital: – Age less than 3 months old. – Affectation of the general condition, sickly appearance. – Vomiting or oral intolerance. – Dehydration, poor peripheral perfusion – Urinary system malformations: VUR, obstructive uropathy, renal dysplasia, single kidney. – Poor care or trouble monitoring. – Primary or secondary immunodeficiency. – Electrolyte or renal function abnormalities.
√	A child with febrile urinary tract infection meeting any of the following criteria may be admitted to hospital, but can also be treated under supervision on an outpatient basis: – High fever (≥38.5°C) in children of 3-6 months of age. – Persistence of fever after 48 hours of treatment. – Risk factors of an unusual bacteria type (recent antibiotic therapy, recent hospitalisation, catheterisation). – Family history of VUR or prenatal ultrasound with congenital hydronephrosis. – Recurrent febrile urinary tract infections. – Significant increase in acute phase reactants.
√	In all other cases, outpatient management of the patient is recommended.

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Referral to a specialist

√	Refer patients from primary care to specialist care if they meet any of the following criteria: – Febrile urinary tract infection and/or UTI in children under 2 years or in patients who cannot control urination and cannot be completely investigated in primary care. – Recurrent urinary tract infections. – Atypical UTI: fever >48 hours, unusual bacteria. – Structural abnormalities, single kidney and/or nephrourological functional abnormalities. – Permanent kidney damage confirmed by imaging studies or blood markers (urea, creatinine, cystatin C) or urine (proteinuria, maximum urinary osmolality). – Hypertension – Failure to thrive. – Family history of nephrourologic disease and/or CKD. – Anxious family and/or diagnostic confirmation.

Treatment of the acute phase of UTI

Start of empirical treatment

√	It is recommended to start early antibiotic treatment at the first suspicion of febrile UTI, as delaying the onset of antibiotic therapy in febrile UTI cannot be justified on safety grounds.

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Empirical therapy administration route

A	Oral administration is the recommended route of choice for antibiotic treatment of children with febrile UTI without known obstructive urological disease and no symptoms of a serious infection.
√	Intravenous antibiotic administration is recommended in children with suspected obstructive uropathy or high-grade VUR (IV-V), signs of septicaemia, uncontrollable vomiting or dehydration.
A	If antibiotic treatment is started intravenously, it is recommended to continue with oral administration when the patient's clinical condition allows it.
√	Clinically evaluate the patient after approximately 48 hours of antibiotic treatment by any route of administration.

Choice of empirical therapy

√	The choice of empirical antibiotic treatment for UTI must be based on knowledge of local resistance.
√	At present in Spain, for empirical antibiotic treatment of UTI without fever seems appropriate to use amoxicillin-clavulanate, 1st or 2nd generation cephalosporins, phosphomycin, nitrofurantoin or TMP-SMX if the sensitivity information provided by local laboratory permits.
√	At present in Spain, for PO empirical antibiotic treatment of UTI with fever seems appropiate to use 3rd generation cephalosporins, and as an alternative amoxicillin-clavulanate or 2nd generation cephalosporins (if sensitivity is greater than 80-90% for *E. coli*).
√	At present in Spain, for IV empirical treatment of UTI with fever seems appropriate to use 3rd generation cephalosporins IV (cefotaxime, ceftriaxone) or as an alternative an aminoglycoside (gentamicin, tobramycin), amoxicillin-clavulanate IV or 2nd generation cephalosporins IV. Other 3rd generation cephalosporins, such as ceftazidime, and other antibiotics such as amikacin, carbapenems and quinolones should be reserved for special circumstances.
√	At present in Spain, for patients younger than 3 months open to the possibility of infection with enterococci, associate ampicillin to the recommended treatment base.

Aminoglycosides and single daily dose administration

A	It is recommended to administer aminoglycosides in a single daily dose when required for the treatment of febrile UTI in children.

Duration of antibiotic treatment

A	The recommended antibiotic treatment duration for afebrile UTI/cystitis is 3-4 days.
√	The recommended antibiotic treatment duration for febrile UTI/APN is a standard duration of 7-10 days.

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Antibiotic treatment in lobar nephronia and renal abscess

√	As treatment of choice for ALN and renal abscess it is recommended to use 2 antibiotics, chosen according to local sensitivities, initially administered intravenously then PO after clinical improvement.
D	The recommended antibiotic treatment duration for ALN and renal abscess is 2-3 weeks.

Symptomatic medication in UTI treatment

	No studies of a suitable design were found to answer the question posed in this section.

Prophylaxis of UTI

Antibiotic prophylaxis in paediatric patients shown to have no structural or functional urinary tract abnormalities

A	Antibiotic prophylaxis should not be routinely given to children who have had a single UTI.
A	Antibiotic prophylaxis should not be given to children with ABU.
√	For children with recurrent UTI, it is recommended to evaluate the use of prophylactic antibiotics individually after appropriate study to rule out structural or functional abnormalities of the urinary tract, and taking into account the existence of resistant strains.

Choice of antibiotic and chemoprophylactic dose

√	It is recommended to take into account local resistance patterns when proposing prophylactic treatment, and try to select antibiotics with a narrower spectrum of action to prevent the upper airway bacteria from developing resistance to them.
√	Taking into account the above recommendation, it is recommended to use TMP or trimethoprim-sulfamethoxazole in patients older than 2 months of age, and nitrofurantoin in patients older than 2-3 years; as the use of prophylactic antibiotics or antiseptics cannot be prioritised due to the lack of available evidence.
√	In children under 2 months of age, or in any situation where nitrofurantoin or TMP or trimethoprim-sulfamethoxazole cannot be used, it is recommended to use as prophylactic antibiotic amoxicillin or 1st or 2nd generation cephalosporins.
√	Recommended prophylactic doses are as follows: – Nitrofurantoin: 1-2 mg/kg/day. – TMP-SMX: 2-3 mg/kg/day (of trimethoprim). – Trimethoprim: 2-3 mg/kg/day. – Any other antibiotic: a third or a quarter of the usual recommended dose.

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Antibiotic prophylaxis in paediatric patients with structural and/or functional abnormalities

B	It is recommended to use antibiotic prophylaxis in girls with VUR grades III-V for 1 year or until the degree of VUR is re-evaluated by cystographic examination.
√	It is recommended to use antibiotic prophylaxis in boys with VUR grades IV-V for 1 year or until the degree of VUR is re-evaluated by cystographic examination.
A	It is not recommended to use antibiotic prophylaxis neither in boys with VUR grades I-III nor in girls with VUR grades I-II.
C	It is recommended to use antibiotic prophylaxis in paediatric patients with dilated urinary tract and suspected obstruction until the diagnosis is confirmed and proper treatment for the obstruction is given.
√	It is not recommended to use antibiotic prophylaxis for non-obstructive dilatations of the urinary tract.

Other preventive measures: uropathogenic strains vaccines, ascorbic acid, cranberry juice and probiotics

√	There was insufficient scientific evidence to support a recommendation for the use of any of the following preventive measures: vaccines with uropathogenic strains, ascorbic acid, cranberry juice or probiotics.

Prevention of UTI and lifestyle modifications

C	Preventive measures aimed at reducing recurrences of UTI should be tailored according to the pattern of urinary tract dysfunction or urinary habits of the patient, and directed to achieve adequate fluid intake.
D	It is recommnended to investigate and address any constipation in children with UTI and/or signs of lower urinary tract dysfunction to prevent recurrence of UTI.

UTI prognosis

Risk of UTI recurrence in children

C	Following a first UTI, monitor patients with a normal urinary tract, especially boys under 12 months of age with a non-retractable foreskin, during the first year of evolution, as they have frequent recurrences.
D	Investigate voiding and bowel habits in children with UTI for their possible association with recurrent UTI.

Monitoring UTI in children

Urine culture and/or systematic urine analysis

D	It is not recommended to perform urine culture and/or systematic analysis during antibiotic treatment in children with UTI if the clinical course is favourable.

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D	It is not recommended to perform regular culture and/or systematic analyses of urine in asymptomatic children after UTI.
D	It is not recommended to perform regular culture and/or systematic analyses of urine in asymptomatic children with structural and/or functional abnormalities.

Information for families or carers to help in the diagnosis of UTI

Q	If UTI is suspected or diagnosed, it is recommended to inform the family, carers or patient (depending on age) about the need for early antibiotic treatment and the importance of completing it.
Q	It is recommended to warn of the possibility of recurrence and advise about appropriate preventive hygiene measures. Give guidance for recognising UTI symptoms (fever of unknown origin and urinary symptoms), and the need to seek medical advice if they appear.
D	It is recommended to give instructions on the collection of the urine sample and its preservation until the time of the test.
Q	It is recommended to inform about the prognosis, especially the risk of kidney damage and about the reasons for clinical monitoring and/or long-term treatment when required.
Q	It is recommended to inform about the scans to be performed, the reasons for them and what they consist of.

Monitoring children with permanent kidney damage after UTI

√	It is recommended to determine BP, PCr, glomerular filtration rate, proteinuria, microalbuminuria, alpha-1-microglobulin and maximum osmolality urine as markers of kidney damage and/or indicators of progression.
√	In children with permanent, bilateral and severe (Goldraich type 3-4) kidney damage, it is recommended to test with a dipstick and determine the BP every 6 months, or annually for children with unilateral or mild affectation (Goldraich type 1-2).
√	Follow the centre protocol for monitoring patients with impaired renal function. In case of impaired renal function it is recommended to follow the patient according to the centre protocol.
√	It is not recommended to routinely use ABPM in children with permanent kidney damage and no alteration in renal function, as its prognostic value is not clearly demonstrated.
√	Do not routinely use plasma renin levels as a prognostic marker for HT in children with permanent kidney damage.
√	Boys with permanent kidney damage require further monitoring of renal function and BP in adolescence.
√	Give pregnant adolescents with renal disease regular check-ups for the early detection of bacteriuria and foetal/maternal complications (e.g., BP abnormalities, impaired renal function, intra-uterine growth retardation, foetal loss or premature birth).

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Antibiotic prophylaxis in catheterised children

Antibiotic prophylaxis in children with indwelling catheters

√	It is recommended to use prophylactic antibiotics to prevent UTI in children with a temporary urinary catheter after hypospadias repair urethral surgery.
√	It is recommended to use prophylactic antibiotics to prevent UTI in children with a temporary urinary catheter after vesicourethral surgery.
√	It is not recommended to use antibiotic prophylaxis in children with a temporary urinary catheter for non-surgical reasons.

Antibiotic prophylaxis in children under intermittent catheterisation

√	It is not recommended to use antibiotic prophylaxis in paediatric patients under a clean intermittent catheterisation regimen.

Antibiotic prophylaxis in children catheterised for single sampling or endoscopic procedures

√	It is not recommended to give routine antibiotic prophylaxis to children prior to diagnostic procedures requiring a single catheterisation (cystoscopy, VCUG, CEUS, urodynamics, urine sampling).
√	Antibiotic prophylaxis may be considered when there is a risk from related illnesses (e.g., heart disease), recurrent UTI, atypical UTI, suspected VUR grade IV-V or abnormalities.

Catheter care

Short term catheterisation

√	It is recommended to use silicone catheters.
D	It is recommended to take into account the clinical experience of the team, individual patient assessment and anticipated catheterisation duration when choosing the catheter.
D	It is recommended to choose the catheter diameter size based on an individual patient assessment and taking into account features such as age, urethral size, as well as the propensity for blocking the catheter.
D	When in hospitals, it is recommended to insert the catheter with sterile equipment using the aseptic technique.
D	It is recommended to clean the meatus with sterile saline or sterile water before inserting the urethral catheter.
D	It is recommended to use a single-use sterile lubricant to reduce the pain, urethral trauma and risk of infection.
A	Daily personal hygiene with soap and water is all that is needed for the proper care and cleaning of the urethral meatus after inserting the catheter.
D	It is recommended that health professionals inserting the catheter have training and experience in the insertion and maintenance of urethral catheterisation.

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Intermittent catheterisation

√	It is recommended that patients requiring intermittent catheterisation try different types of catheter, become familiar with their use and choose one or the other according to their perceived comfort and handling.
√	It is recommended to use the most appropriate catheter diameter according to the patient age taking into account the patient urethra size.
√	Outpatients who have to perform intermittent catheterisation for bladder emptying should use a clean technique.
√	Patients requiring intermittent catheterisation should be instructed in how to do it themselves at the earliest possible age.
√	It is recommended to assess hospitalised or institutionalised patients individually before deciding on the intermittent catheterisation technique to use.

Single sampling catheterisation

√	For single sampling catheterisation, use the catheter material with which the health professional is most familiar; avoiding to expose the health professional and the patient to latex.
√	For single sampling catheterisation, choose the catheter size according to the age of the patient. It is recommended to insert the catheter until urine flows freely and avoid inserting an excessive length of catheter tube into the bladder.
√	It is recommended to use an aseptic technique with sterile media when performing single sampling catheterisation.

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1. Introduction

The approach to urinary tract infection (UTI) in children has changed over the last 30-50 years as a result of the introduction of antibiotics and improved diagnostic procedures. These changes have led to some uncertainty regarding the most suitable diagnostic and therapeutic procedures as well as how to monitor these patients. Usual management of these patients includes imaging study procedures, chemoprophylaxis and prolonged follow-up, which is a source of discomfort for patients and their families, leads to overuse of National Health Service (SNS) resources, and is all based on limited evidence. In Spain, there are many documents on the performance of UTI in children, including protocols from the Spanish Association of Paediatrics, the consensus document published in the *Anales de Pediatría* (Paediatrics Journal), the protocol of the Society of Paediatric Emergency and other protocols from various societies and hospitals, which have addressed the issue from different approaches. These are probably appropriate to the nature of the particular speciality, and in many cases based on the views and opinions of the authors. The study of Dr. Ochoa et al.[2-10] is probably the most in-depth, from the methodological point of view, being based on systematic reviews.

Moreover, the publication of the NICE Clinical Practice Guidelines (CPG)[11] represents a milestone in UTI management. It is based on systematic reviews and represents a major change from the concepts and interventions offered to date, which were mainly based on the document prepared in the 1990s by American Academy of Pediatrics.[12]

Therefore, it seems appropriate to prepare a CPG, which could answer questions that continue creating uncertainty and applicable in our environment as a tool to act on the diagnosis treatment and management of UTI. There are several reasons for compiling this CPG, elaborated upon below.

After respiratory tract infections, UTI is one of the most common bacterial infections in routine paediatric practice. It is estimated that 3-7 out of every 100 children will have UTI.[13-16] Moreover, there are wide variations in the interpretation of clinical signs which should guide us to a diagnosis of UTI, especially in younger children.[17,18]

Diagnosis can be particularly difficult in younger patients, and there is controversy and a wide variation in the methods used to diagnose UTI, mainly related to the collection of urine and diagnostic techniques.[10,19] A false positive diagnosis of UTI leads to unnecessary antibiotic treatment, sometimes hospitalisation and other potentially invasive tests being performed.[10]

There is also wide variability in the types of studies, mainly imaging, that have to be done after the diagnosis of a first UTI. It must be borne in mind that most of the existing protocols are based on the fact that UTI has long been the most important sign of suspected obstructive urinary tract malformations or vesicoureteral reflux (VUR), with the consequent kidney damage impairment. In this sense, it is now known that UTI itself may give rise to acute or chronic kidney disease without proof of the existence of VUR, or structural or functional abnormalities of the urinary tract. Many of these injuries will be unilateral with little impact on renal function.

The belief that the association of UTI with malformations or VUR, or just UTI itself, could develop into chronic kidney disease (CKD) has led to a series of proposals being developed for imaging studies, regardless of the intervention involved, especially since the prenatal diagnosis of urinary tract abnormalities was established. This has resulted in most malformations or high-grade VUR being diagnosed before the onset of UTI.[20-24]

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However, we now see that much of the UTI diagnosed is not associated with urinary tract abnormalities, but may depend on other factors which to date had not been given sufficient importance, e.g., the characteristics of the host or bacteria.[25]

To this must be added the uncertainty in the prognosis of UTI. There is a belief, not based on sufficient evidence, of the fatal evolution of UTI to CKD.[26,27]

Also, there are still questions regarding treatment: e.g., regarding the best antibiotic treatment, hospitalisation criteria, or whether or not to treat asymptomatic bacteriuria. Another important issue is chemoprophylactic treatment, whose indiscriminate use is not only not beneficial but also increases the number of antibiotic-resistant strains.[28]

To summarise, there is still significant variability and uncertainty in aspects of diagnosis, interpreting the clinical fact of an isolated UTI, indication of a diagnostic intervention and aspects of treatment and follow-up, which are sufficient to merit the preparation of this CPG.

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2. Scope and objectives

The objective of this clinical practice guideline (CPG) is for it to be used as a tool to improve clinical management of children with urinary tract infection (UTI). These patients are seen in various services - primary care, emergency departments and specialist care - with the involvement of many and diverse healthcare professionals: e.g., nursing, general paediatrics, paediatric nephrology, paediatric urology, radio-diagnosis and microbiology. The aim is therefore to provide relevant, standardised information to decrease the variability in care that exists today. It also seeks to provide relevant information to families and carers, to facilitate the diagnosis and monitoring of patients.

The target population of this guideline is children from one month to 18 years old with suspected UTI.

It also addresses the management of paediatric patients requiring catheterisation in the following situations: investigations and therapeutic-type catheterisation (both intermittent and indwelling catheterisation).

The text does not cover clinical issues concerning immuno-compromised paediatric patients; paediatric patients in intensive care units or other special care units, such as burns units, or those with virus, fungal or parasitic infections.

This guide is intended for health professionals in primary care and specialist care who offer assistance and care to paediatric patients with suspected UTI in both the public and private health service sectors. It is also aimed at patients and their carers.

The guide summarises the available evidence on the key issues of clinical management of UTI and aims to help healthcare professionals and patients share decision making. The recommendations presented here are not obligatory nor do they replace the clinical judgment of health care personnel.

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3. Methodology

The methodology used in developing this clinical practice guideline (CPG) comes from the '*Manual for CPG Development in the National Health Service (SNS)*'.[1]

The steps followed for the preparation of this guide started with the constitution of the guideline development group (GDG), composed of 15 clinical professionals from different health care settings, primary care and hospital care, as well as various specialities: nursing, paediatrics, paediatric surgery and paediatric nephrology. The GDG did not include patients or relatives, and it requested 3 potential users of information for patients (parents of young children) to review its contents.

Clinical questions were prepared and selected at successive meetings by brainstorming and subsequent prioritisation by the GDG, concluding with the questions contained in this guide related to epidemiology, diagnosis, treatment, prevention, monitoring UTI in children and catheter care in children. The clinical questions were prepared using the PICO format (Patient/Intervention/Comparison/Outcome).

After the questions were prepared, a literature search of databases and other specialist sources (Medline, Embase, Clinical Excellence, Trip Database, GuíaSalud, National Guideline Clearinghouse, GIN) was begun to find other national or international CPGs on a similar theme. This resulted in 12 guides being found, of which 5 were discarded, as the people, topics, interventions, date of issue or methodology did not meet the objectives and scope of this CPG. The 7 remaining guidelines[11,29-34] were evaluated using the AGREE instrument by 4 independent reviewers. The individual scores for these guides are available in Annex 1 (Table 13). It was agreed that only those guidelines that obtained scores above 85% for rigour of preparation would be considered suitable as a source of evidence in this guide. There were 5 eligible,[11,30,31,33,34], of which 3 focused exclusively on care of the catheterised patient and catheter care.[31,33,34]

These 5 guides became secondary sources of evidence for answering different clinical questions, and this is indicated in the different sections of the guide where findings or studies from them are referenced. *The methodology proposed by Osteba in his Asthma CPG Methodology Description Evaluation report*[1,35] was followed to modify and update the evidence from these guidelines.

For clinical questions addressed in this guide which were included in the NICE CPG,[11] the searches from 2006 were updated to June 2010 by modifying those used by NICE.[36] For the rest of the questions, new specific search strategies were developed: limiting them to the previous 10 years, except in exceptional cases where no appropriate studies were found, when they were not limited by date.

The search strategies combined terms in controlled language in each database (Mesh, Emtree, Decs) and free terms to improve and balance their sensitivity and specificity. The sources were Medline (Pubmed), Embase (Elsevier.com), CRD Databases, Cochrane Library, IBECs and LILACs. For the questions relating to catheters included in Chapter 18, the CINAHL database was also consulted. For questions regarding treatment, the clinical trials registry ClinicalTrials.gov was used.

Searches were tailored to the types of studies best suited to the question in Spanish, French, English and Portuguese.

An inverse search was made in those referenced articles, included and excluded, which were identified.. No systematic search was made of grey literature, although in some cases congress

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summaries were included in the volume of evidence due to its relevance, and given the absence of other studies.

The search results were initially screened by title and abstract. The selected studies were then subjected to a second screening by clinicians responsible for reading them. Those studies considered useful for answering the questions in this guide were evaluated and classified according to the levels of evidence proposed by SIGN for intervention studies, and according to the adaptation of levels of evidence from the Centre for Evidence-Based Medicine in Oxford, proposed by NICE for diagnostic test studies,[1] (Tables 1 and 2).

After critical appraisal of the evidence, recommendations were made according to formal assessment or reasoned judgment. In addition to the volume and quality of evidence, the GDG had to consider the applicability of the results, their consistency and their relevance in our National Health System or their clinical impact. For those clinical questions where the evidence was scarce, of low methodological quality (levels of evidence 1- and 2-) or inconsistent, recommendations were established based on group consensus.

After preparing a first draft, the text was submitted to a peer review process in 2 parts: the first focused solely on the recommendations and PICO questions, carried out by expert contributors; and the second by external reviewers. The expert contributors and peer reviewers were in most cases proposed as expert members by their respective scientific societies. The societies involved in preparing this guide, and also those represented by members of the development group, expert contributors and peer reviewers, were the Spanish Association of Paediatric Nephrology, the Spanish Association of Paediatrics, the Spanish Association of Paediatric Primary Care, the Spanish Society of Paediatric Surgery, the Spanish Society of Infectious Diseases and Clinical Microbiology, the Spanish Society of Paediatric Radiology and the Spanish Society of Paediatric Emergency.

It is planned to update the guide every 3 years, or less if new evidence that could alter some of the recommendations offered in this guide is available. Updates will be made on the electronic version of the guide, available at http://www.guiasalud.es.

The detailed information with the methodological process of the CPG (search strategies for each clinical question, critical reading sheets for the selected studies, tables summarising the evidence and formal evaluation) are available at the same address www.guiasalud.es.

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4. Definition and classification of urinary tract infection

The term urinary tract infection (UTI) covers a heterogeneous group of conditions with different etiologies, which have as their common factor the presence of bacteria in the urinary tract, as this is usually sterile, associated with variable clinical symptoms.

There are wide variations in the clinical presentation of UTI. In some individuals bacteriuria does not cause any symptoms, and when there are symptoms they may be very varied. In infants and young children, symptoms may be non-specific, such as irritability, vomiting, diarrhoea, refusing food and poor growth. Fever is present in most infants but may not be found in neonates. In older children, the symptoms are more specific, with the onset of fever, flank pain, positive renal fist percussion, as well as signs of bladder irritation, such as dysuria, frequency, urgency and incontinence. Laboratory tests usually show a leukocytosis with left shift, ESR, elevated CRP and PCT, either individually or in combination.

Classification of symptomatic UTI according to location is below:

- *Lower UTI or cystitis*

Only localised infections in the lower urinary tract (urethra, bladder). The most prominent symptoms are voiding, such as dysuria, frequency, urgency and urinary incontinence.[11]

- *Upper UTI or acute pyelonephritis (APN)*

Infections that reach and inflame the upper urinary tract (ureter, collecting system, renal parenchyma). The most important symptom is fever, especially in young children and infants. Macroscopically, the kidney shows inflamed tissue segments and, histologically, inflammation of the parenchyma and renal tubules with the presence of oedema.[11]

This classification is of great clinical relevance, because while APN can have significant consequences, such as renal scarring and in some cases progressive renal damage, cystitis is usually a benign condition without complications. Therefore, APN requires more aggressive treatment, further investigation and a longer follow-up than cystitis. However, in clinical practice, differentiating between these two types of UTI can be very difficult, especially in younger children.

In clinical practice, the term febrile urinary tract infection is often used to refer to APN, however, it should be clarified that this does not mean it is always accompanied by kidney damage. To establish the diagnosis of APN requires verification by scintigraphy, which is considered as the gold standard.

A UTI is considered to be *recurrent* if there are 2 or more episodes of APN; 1 APN episode and 1 or more of cystitis; or 3 or more episodes of cystitis.[11]

Table 3 shows the *risk factors* for UTI; Table 4 shows the defining features of an *atypical or complicated infection*; and Table 5, the risk factors *for underlying nephrourological disease.*[11]

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Table 3. Risk factors for UTI

- Appearance of serious illness
- Younger age
- High temperature and without focus
- White ethnic group
- Females
- Uncircumcised boys
- Other risk factors: e.g., presence of VUR or other structural abnormalities, siblings of children with VUR.

Adapted from the NICE GPC (2007)[11]

Table 4. UTI considered as atypical or complicated

- Those presenting with severe febrile syndrome and/or sepsis
- Low urine flow
- Abdominal mass or distended bladder
- High plasma creatinine
- No response to appropriate antibiotic treatment within the first 48 hours
- UTI from microorganisms other than Escherichia coli

Adapted from the NICE GPC (2007)[11]

Table 5. Risk factors for underlying nephrourological pathology

- History of previous UTIs
- Prenatal diagnosis of urinary tract abnormalities
- Family history of VUR or other renal disease
- Abdominal mass or distended bladder
- High blood pressure
- Presence of bladder and/or sphincter dysfunction
- Spinal cord injuries

Adapted from the NICE GPC (2007)[11]

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5. Epidemiology of UTI and its complications in children

Urinary tract infection (UTI) is one of the most frequent bacterial infections in infants and young children. Its incidence is influenced by age and sex, and it is difficult to estimate, as the existing epidemiological studies are very heterogeneous, with varying definitions of UTI, populations studied and methodologies used for collecting urine specimens.[11] In addition, children with UTI, especially smaller children, have non-specific symptoms, which means UTI sometimes goes unnoticed.[37]

Epidemiological studies published to date have evaluated the presence of UTI in different ways: annual incidence, cumulative incidence, prevalence and incidence in selected groups of patients according to age and/or sex, symptoms, etc.

It must be emphasised, however, that the incidence of acute disease tells us about the frequency of this disease over a period of time. It can also offer information on the risk of developing the disease for a particular group of individuals with certain features compared to other groups.

Prevalence is an appropriate estimate for chronic diseases but has limited applicability for short-term illnesses, such as UTI. In these types of short-term conditions, prevalence and incidence values are similar. This clinical practice guideline (CPG) addresses aspects of acute UTI and complications or situations that can be maintained over time. In these circumstances, one speaks therefore of prevalence.[11]

5.1 Incidence of UTI

5.1.1 Incidence of UTI at the population level

The Winberg et al. study, published in Sweden in the 1970s, found a UTI incidence at the population level in children under 11 years of 3% in girls and 1.1% in boys.[13]

A later study, by Hellstrom et al. in Sweden, calculated the cumulative incidence of UTI in children aged 7 at the population level from health surveys in schools, and found that the incidence in girls was 8.4% and 1.7% in boys. This same study also estimated the incidence of APN at the population level, and found the cumulative incidence was 2.7% in girls and 1.0% in boys (where APN was considered in cases with fever ≥38.5°C with elevated CRP (>20mg/L), or if the ability to concentrate was reduced).[38]

The Coulthard et al. study, carried out in the UK and published in the 1990s, estimated the incidence of UTI at the population level in children under 16 years of age, from hospital primary care referral data. The incidence was 11.3% in girls and 3.6% in boys. The study authors emphasised, however, that the data may have been overestimated, because 15% of cases had no bacteriological confirmation.[39]

A study conducted during the 1990s in Sweden found the incidence of UTI in children under 2 years of age to be at least 2.1% in girls and 2.2% in boys.[40]

The Conway et al. study, in a population of 74,974 children under 6 years registered at different primary care centres found an incidence of first UTI of 0.007 person-years, and an incidence

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of recurrent UTI of 0.12 person-years after a first UTI. In other words, 7 out of every 1,000 children under the age of 6 developed a UTI, and 12 out of every 100 children under the age of 6 who had had a first UTI developed recurrent UTI.[28]

Due to the differences between these studies regarding cut-off points, methods of classification and diagnosis, and increased awareness of the diagnosis of UTI in children,[39,40] it is difficult to establish the actual incidence of UTI at the population level.

5.1.2 Prevalence of UTI in selected patients

The following results were found from data quantifying the presence of UTI in paediatric patients with suspected urinary tract infections:

A retrospective cohort study in America found the prevalence of UTI in children (n=465) of 1 to 24 months of age presenting with fever (≥37.9°C) to the emergency department was 14% (95% CI, 11-17).[41]

A Shaikh et al. meta-analysis estimated the overall prevalence of UTI in infants (under 2 years of age) with fever (≥38°C), with data from 14 studies (n=20,566), and obtained an overall value of UTI of 7% (95% CI 5.5-8.4). This same study, using data from 4 studies (n=2,353), also estimated the overall prevalence of UTI in patients between 2 and 19 years of age with signs and symptoms referable to the urinary tract, with or without fever, and found a prevalence of UTI of 7.8% (95% CI 6.6-8.9).[42]

A Hellström et al. study of children under 7 years of age with UTI found a prevalence of APN of 59% for boys and 32% for girls, by considering APN those cases with fever ≥38.5°C and high levels of C-reactive protein (>20mg/L), or a reduced ability to concentrate.[38]

Other studies using renal scintigraphy (DMSA) found the prevalence of APN in children with febrile UTI was 50-80%, whereas in lower urinary tract UTIs, renal parenchymal inflammation occurred with little frequency.[43,44]

In children under 18 years' old after a first UTI, the Shaikh et al. SR and meta-analysis obtained a prevalence of acute damage in DMSA consistent with APN of 57% (95% CI 50-64) from the results of 29 cohort studies.[45]

5.1.3 Prevalence of UTI by age, sex and ethnic origin

Non-modifiable factors such as age, sex and ethnic origin of the patient influence the prevalence of UTI. There are several studies that show a higher prevalence of UTI in young boys, prevalence that reduces with increasing age.[46]

The Jodal et al. study performed in patients under 10 years of age with a first symptomatic UTI (n=1,177; 225 boys and 952 girls) found that 59% (133/225) of boys had their first UTI within 1 year of age, compared with 19% (181/952) of girls.[47]

The Hiraoka et al. study conducted in patients with febrile UTI (n=100; 64 boys and 36 girls) showed that 73% of cases had their first episode before age 7 months, with a breakdown by sex of 94% (60/64) of boys and 37% (13/36) of girls.[48]

The Ginsburg et al. study conducted in patients hospitalised for a first UTI episode (n=100; 62 boys and 38 girls), with a mean age of 2.1 months, showed that 75% of cases of UTI in the first 3 months of life occurred in boys and 25% in girls. Between 3 and 8 months old, 11% of UTIs occurred in boys and 89% in girls.[46]

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The Shaikh et al. meta-analysis also estimated the prevalence of UTI by age and sex for patients under 19 years of age, with signs or symptoms referable to the urinary tract, with or without fever, from data from 18 epidemiological studies (n=23,358). It found that infants with fever (<2 years of age) had a 7% overall prevalence of UTI, which decreased with age and varied with sex. Older children (>2 years of age) with signs or symptoms referable to the urinary tract and/or fever had a prevalence of 7.8% (Table 6).[42]

Table 6. Prevalence (95% CI) of ITU in infants of 0-24 months with fever, stratified by age, and children over 2 years with urinary symptoms and/or fever

	All	Girls	Boys	Circumcised	Not circumcised
Infants <3 months with fever	7.2% (5.8-8.6)	7.5% (5.1-10)	8.7% (5.4-11.9)	2.4% (1.4-3.5)	20.1% (16.8-23.4)
Infants 3-6 months with fever	6.6% (1.7-11.5)	5.7% (2.3-9.4)	3.3% (1.3-5.3)	—	—
Infants 6-12 months with fever	5.4% (3.4-7.4)	8.3% (3.9-12.7)	1.7% (0.5-2.9)	—	—
Infants 12-24 months with fever	4.5%	—	—	—	—
All infants (<2 years of age)	7.0% (5.5-8.4)	7.3% (5-9.6)	8.0% (5.5-10.4)	—	—
Patients > 2-19 years with symptoms of ITU and/or fever*	7.8% (6.6-8.9)	—		—	—

* Some of the children in this group of patients were under 2 years old. Data taken from the Shaikh et al. study (2008)[42]

Regarding ethnicity, available data suggest that in developed countries the prevalence of UTI is higher among white children. Shaikh et al. (2008) found the prevalence of suspected UTI of 8% (95% CI, 5.1-11.0) in white children to be higher than for black children, which was 4.7% (95% CI, 2 1-7.3).[42]

Chen et al. also studied the prevalence of UTI according to ethnic origin, and found a higher prevalence of UTI in Asians (22%), followed by white children (16%), Hispanics (16%) and finally African Americans (4%). The latter had a statistically significant (P=0.007) lower rate of urinary tract infection compared with the general population. The risk of UTI in white (OR 4.4; 95% CI, 1.5-12.6) and Hispanic children (OR 4.6; 95% CI 1.5-13.9) was 4 times higher than in black children. For Asians, this risk was 6 times higher (OR 6.5; 95% CI, 1.5-2.9).[41]

Children who have had a first UTI have recurrences more frequently, and most 3-6 months following the first episode. In the first 12 months of life, 18% of boys and 26% of girls had recurrences. After 1 year of age, it was uncommon for boys; however, for 40-60% of girls, recurrences can appear for many years.[49-51] Most recurrent infections are re-infections with different bacteria from the first manifestation.[13]

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5.2 Prevalence of asymptomatic bacteriuria

The term Asymptomatic bacteriuria (ABU) refers to the presence of bacteria in urine, after being detected repeatedly in urine samples during routine analytical control or health monitoring in a subject who has no symptoms. These infections occur mainly in girls of school age and lack any clinical significance.[11]

Bacteriuria was studied by Wettergren et al. (1985) via a mass screening programme of 3,581 children over 3 years. There were 3 samples taken at different times during the first year of life, using a bag, and confirmed by suprapubic aspiration. The authors described a prevalence of asymptomatic bacteriuria during the first year of 0.9% in girls and 2.5% in boys. They concluded that bacteriuria was statistically significantly higher ($P<0.01$) in boys under 2 months, while between 2-6 months and between 6-12 months there were no statistically significant differences. There was a higher prevalence of bacteriuria in girls than in boys ($P=0.06$).[52]

There are data in the literature indicating that ABU in children is benign and does not constitute a risk factor in the development of renal scarring. The Escherichia coli isolated in children with ABU is different from those that cause symptomatic infections, it is bacteria of low virulence, with greater sensitivity to the serum bactericidal effect and very poor adhesive capacity.

In most cases, the bacteriuria disappears spontaneously without treatment within a few months, and only exceptionally does it develop into symptomatic UTI. It has been shown that symptomatic UTI is not preceded by ABU. All these facts suggest that ABU is an independent entity rather than a precursor of symptomatic infection.[52]

A recent clinical trial reported that random treatment of ABU with antibiotics and no treatment both had no effect on long-term impairment in growth or maintenance of renal function.[53]

The use of antibiotics alters the low-virulence bacterial flora associated with ABU and increases colonisation by uropathogens at a preliminary stage to the development of symptomatic UTI. Therefore, sterilisation of urine is not indicated and is potentially dangerous. Furthermore, prophylactic treatment appears to induce an increase in the probability of occurrence of APN.[51]

5.3 Prevalence of acute complications in UTI

5.3.1 Renal abscess

Renal abscess (RA) is a potentially serious complication of UTI or bacteraemia. It is a very rare disease in children and its incidence or prevalence is unknown. The literature refers to isolated studies on a series of cases with a small number of patients only.[54,55]

The symptoms it produces are usually vague and non-specific, but include prolonged fever, back pain, abdominal pain, elevated ESR and leukocytosis. A positive blood or urine culture is much less constant. As a result, there may be a delay in diagnosis and confusion with other kidney infections, such as APN or acute lobar nephronia (ALN). Early detection, however, is essential to minimise any residual kidney damage.[54,55]

The diagnosis of RA is performed with ultrasound and CAT. Ultrasound is used as a screening technique and shows a well-circumscribed mass that includes hypoechoic areas corresponding to foci of liquefaction and mixed echoes caused by debris from the abscess cavity. The CAT is used to confirm the findings of the ultrasound or where such findings are equivocal. Ultrasound and CAT lead to accurate diagnosis in most cases.[54,55]

Material cited in this Clinical Practice Guideline, and its validity, has not been reviewed since the publication of this Clinical Practice Guideline.

RA may be the result of the haematogenous spread of an infection, but more often than not is a complication of ascending UTI. Therefore, structural abnormalities associated with the urinary tract are often found, favouring the rise of bacteria to the kidney. The most common isolates are *Staphylococcus aureus* in cases of haematogenous spread and *Escherichia coli* in ascending UTI. There have also been reported cases caused by anaerobic bacteria of intestinal origin or respiratory, oro-dental infections, etc.[54,55]

According to recent studies, if diagnosed early with an appropriate antibiotic treatment regimen (3-6 weeks), the progression of the abscess can be prevented and the need for surgical drainage significantly decreased.[54,55]

5.3.2 Lobar nephronia

Acute focal bacterial nephritis (AFBN), also known as acute lobar nephronia (ALN), like RA, is rare in children and its incidence/prevalence is unknown. A recent study found it occurs in 8.6% of all UTIs with fever, which is much higher than in other published series. This is probably due to an undervalued pathology.[56]

It is a localised renal interstitial bacterial infection and is considered to be the result of a complicated APN. In other words, it is found at the midpoint of the spectrum between uncomplicated APN and RA. It produces symptoms very similar to these 2 conditions and, as already mentioned, the differential diagnosis between them can be difficult, which may interfere with treatment and allow progress towards RA if not properly treated.[57]

Histologically, ALN is different from RA because it presents a hyperaemic zone with interstitial oedema and leukocyte infiltration, but without necrosis or liquefaction.[56,58] Ultrasound reveals a nephromegaly associated with a focused, hypoperfused lesion, with poorly defined and irregular boundaries, which may be hyper- or hypo-echoic, depending on the developmental stage of the process. In contrast, RA is presented as a lesion with clearly defined margins with thick walls and a central anechoic region. As with RA, CAT is the procedure giving a definitive diagnosis.[56,58]

5.4 Prevalence of VUR and other structural abnormalities in children with UTI

The prevalence of vesicoureteral reflux (VUR) in children diagnosed with UTI ranges in most studies between 18% and 38%. When investigating the prevalence of VUR in children after a UTI, the numbers vary between 17-34% for girls and between 18-45% for boys (Table 7).[11]

The estimated prevalence of VUR for all children at the population level is between 1-3%.[11] Estimates for the years 1950-70 are between 0.4-1.8%; however, some authors estimate that the actual prevalence in the healthy population during childhood is higher than these figures, mainly due to many cases of VUR evolving asymptomatically, without ever developing UTI and therefore going undetected.[30]

During childhood, 46-55% of patients diagnosed with VUR after UTI showed bilateral VUR.[11]

Also, complications of UTI, such as bacteraemia, are often more common in patients with severe VUR. The Honkinen et al. study found significant differences in the prevalence of VUR III-V in patients with bacteraemic UTI compared with patients with non-bacteraemic UTI (30% v 16%, P=0.02).[59]

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Table 7. Prevalence of VUR diagnosed by voiding cystourethrogram (VCUG) or other cystographic studies in children after UTI

Study	Sample features (n)	Age	Prevalence of VUR
Tseng 2007[60] (Taiwan)	CH of those admitted for first febrile UTI (142)	<2 years	29.6%
Giordano 2007[61] (Italy)*	CH of those admitted for recurrent UTI or APN (386)	1 month -12 years (mean 22 months)	36%
Parada 2005[62] (Spain)	CH after UTI (96)	0 months - 4 years (median 6 months)	18.7%
Bernard 2005[63] (Uruguay)	CH after UTI. Hospital and outpatients (116)	3 days - 14 years (median 10 months)	25%
Tsai 2004 (Taiwan)	CH of those admitted for first UTI (114)	1 month - 5 years (median 6 months)	29%
Chand 2003 (USA) †	CH for previous UTI (9.912)	0-21 years	31% in girls 18% in boys 39% <2 years 27% 2-6 years 20% 7-11 years 8% 12-21 years
Upadhyay 2003 (Canada)	Girls with dysfunctional voiding, and concomitant UTI (58)	4-11 years (mean 6.7 years)	33%
Zaki 2003 (Kuwait)	CH of those admitted for first UTI (174)	< 12 years	24% in girls 18% in boys 25% <1 year 18% 1-5 years 27% >5 years
Howard 2001 (Hong Kong)	CH with UTI (93)	< 5 years	25% in girls 45% in boys
Honkinen 2000 (Finland) †	CH with bacteraemic UTI (132)	1 week - 9.5 years (median 1.5 months)	30%
Honkinen 1999 (Finland)	CH with positive urine culture (184)	62% <2 years 37% ≥2 years	38%

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Study	Sample features (n)	Age	Prevalence of VUR
Sargent 1995 (USA)	CH for first UTI (309)	Girls: Median 48 months Boys: Median 12 months	29% in girls 30% in boys <1 year: 46% in girls 34% in boys <2 years: 44% in girls 30% in boys 2-4 years: 32% in children ≥5 years: 15% in girls 29% in boys
Messi 1988 (Italy)	CH with 1st symptomatic UTI (225)	0-14 years	18% 17% in girls 21% in boys 30% 0-12 months 14% 1-4 years 13% 5-14 years
Jodal 1987 (Sweden)	CH with 1st symptomatic UTI (1177)	<10 years	34% in girls 33% in boys
McKerrow 1984 (Scotland)	CH of paediatric surgery (572)	<13 years (7% >2 years	31%
CH: Clinical history; UTI: urinary tract infection; VUR: vesicoureteral reflux Diagnostic test: †VCUG or indirect radionuclide cystography; *Voiding echocystography			

Table adapted from the NICE GPC (2007).[11]

VUR is the most frequent alteration; however, the prevalence of major structural changes like hydronephrosis, obstruction and renal duplication cannot be established with accuracy, given the wide variation of the studies. However, from the McKerrow et al. (1984) and Smellie et al. (1981) studies, the NICE CPG estimated a prevalence of 6-7% for renal duplication and 2.5-7.5% for hydronephrosis in paediatric patients who had had a UTI.[11] The following table shows the studies from which the prevalence of structural abnormalities, excluding VUR, were taken, and those surgical intervention tributaries, excluding new interventions for VUR (Table 8).

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Table 8. Prevalence of structural abnormalities (excluding VUR and other renal parenchymal defects) diagnosed in children after a UTI

Study	Population (n)	Age	Total prevalence of abnormalities, excluding VUR	Prevalence of abnormalities SI tributaries, excluding interventions for VUR
Honkinen 2000	266	1 week-9.5 years: (median 1.5 months)	25/266 (9.4%)	14/266 (5.2%) †
Ring 1988	110	4 days-12 months: (median 3 months)	19/110 (17.3%)	17/110 (15.4%)
Burbige 1984	83	2 weeks-14 years	18/83 (21.7%)	18/83 (21.7%)
McKerrow 1984	572	0-13 years	15.4%	7.5%
Ginsburg 1982	86	5 days-8 months: (mean 2.1 months)	8/86 (9%)	3/86 (3.5%)
Smellie 1981	744 (498 without VUR and 246 with VUR)	0-12 years	67/498 (9%)	25/498 (5%)
Pylkkanen 1981	252	6-13 years	6/252 (2.4%)	3/252 (1.2%)
SI: Surgical intervention. *70% of total quantified abnormalities are renal scarring; †SI due to obstruction				

Table adapted from the NICE GPC (2007).[11]

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6. Etiology and pathogenesis of UTI

6.1 Bacterial profile and sensitivity pattern for UTI in our environment

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The treatment for urinary tract infection (UTI) will often have to be established empirically in the absence of information on the causative agent involved and its sensitivity to the different antibiotics commonly used. Although a urine culture is common in the management of UTI in children, unlike adults, sometimes the high degree of clinical suspicion or the patient's condition requires the establishment of empirical antibiotic therapy. The most likely etiology and its theoretical profile of antimicrobial sensitivity should be considered when choosing the antibiotic, before modifying the treatment in the light of disease development and microbiological study results. For the epidemiological information to be useful, it must come from studies in local health care settings, as there are significant local and regional differences in the sensitivity of the microorganisms involved.

A recent study published in Spain on the management of UTI in children reviewed the etiology of various series of paediatric patients with UTI, and the sensitivity that the uropathogens isolated in these series presented to the main antimicrobial agents (Tables 9-12). To establish the susceptibility profile of the least frequent uropathogens, UTI series from the general population (including adults and children) were also reviewed[2]. This review came to the following conclusions:

— *Escherichia coli* is the primary etiological agent of UTI in childhood (70-90% of cases). Therefore, its sensitivity pattern will usually determine the choice of empirical therapy.

— The predominance of *E. coli* is reduced in certain circumstances when other microorganisms increase their presence. Previous exposure to antibiotics, a history of hospitalisation and the presence of urinary abnormalities increase the likelihood that other microorganisms, such as *Proteus mirabilis, Klebsiella* spp. and *Pseudomonas aeruginosa*, are the agents responsible for UTI. *Enterococcus faecalis* must also be considered, especially in young children. More unusual organisms are the following: *Enterobacter cloacae, Streptococcus agalactiae*, *Staphylococcus* spp., *Serratia marcescens*, *Morganella morganii*, *Citrobacter* spp. and *Acinetobacter* spp. The clinical information available at the time of diagnosis does not predict the etiology with certainty, only staining tests and microscopic examination of the urine can help in selecting a particular treatment. This additional test, which is usually not available, should be considered in patients with high-risk UTI.

— In our environment, *E. coli* has a high percentage of resistance to ampicillin and to TMP-SMX, so these antibiotics are not suitable as empirical treatments, although TMP-SMX resistance has reduced somewhat in recent years. Among antibiotics that have a high activity against *E. coli* in Spain are 2nd and 3rd generation cephalosporins, phosphomycin, aminoglycosides and amoxicillin clavulanate. However, there is growing resistance to the amoxicillin-clavulanate combination in some areas. Similarly, resistance to 1st generation cephalosporins is variable and in some areas has risen to levels that may compromise their empirical use.

— Data on fluoroquinolones, from the series of isolates from the general population, suggest there has been a significant increase in resistance of *E. coli* to ciprofloxacin and other fluoroquinolones. The few paediatric series that analyse these antibiotics show minimum percentages of resistance. However, although the use of these antimicrobials in childhood is spreading, for the moment it is limited to the treatment of complicated UTI, as directed by culture and sensitivity.

— *Proteus mirabilis* has a sensitivity profile similar to *E. coli*, although some series of urine cultures in the general and paediatric population have shown a lower sensitivity to phosphomycin. *Klebsiella pneumoniae* has natural resistance to ampicillin, and maintains a high sensitivity to other antibiotics usually active against it. The emergence of *Klebsiella* strains producing extended-spectrum beta-lactamases may explain why some series, mainly those originating in a hospital, show a significant decrease in sensitivity to cephalosporins. *Pseudomonas aeruginosa* has a good sensitivity to carbapenems (imipenem and meropenem), piperacillin-tazobactam, ceftazidime, tobramycin and amikacin; this has reduced somewhat for ciprofloxacin and gentamicin.

— When choosing empirical therapy, it must be considered that although 2nd and 3rd generation cephalosporins have a profile significantly better than amoxicillin-clavulanate for enterobacteria, only amoxicillin-clavulanate can cover for a possible, although rare, *Enterococcus faecalis* infection. It must also be appreciated that a history of antibiotic therapy, hospitalisation or urinary abnormalities increases the risk that the agent is resistant to commonly-used antibiotics.

— Finally, given that no antibiotic can ensure 100% coverage for all possible microorganisms, high-risk UTI cases may need antibiotic combinations. To combat a possible enterococcus, ampicillin must be included in the combination. Also, if we want to cover for *Pseudomonas aeruginosa,* specific antibiotics should be associated, because classic combinations, including gentamicin, may be insufficient. Finally, in children it is rare to have to use carbapenems to cover for possible multidrug-resistant micro-organisms (*Klebsiella* strains with extended-spectrum beta-lactamases, *Acinetobacter and Pseudomonas*).

Additionally, the etiology and sensitivity data for this review have been completed with data from 9 subsequent national surveys.[64-72] Results for the series are tabulated, including exclusively paediatric samples (for etiology and resistance) and those that include the general population (for the resistance profile). Of the 9 studies reviewed, only two studies[65,67] showed detailed information on children. None of the series, whether from children or the general population, shows significant changes in the etiology profile or sensitivity pattern with respect to the results shown in the aforementioned review.

The results of the studies not included in the tables are summarised below:

Lerma et al. determined the susceptibility to betalactams from a selection opportunity of 203 isolates of *E. coli* from UTI in the general Spanish population, with various resistance phenotypes. All betalactams tested showed a high activity with a sensitivity approaching 100% against *E. coli* with susceptible and penicillinase-producing phenotypes. The strains with hyperproduction of penicillinase showed 100% resistance to cefuroxime and amoxicillin-clavulanate and 100% sensitivity to cefotaxime, piperacillin/tazobactam and meropenem. All antibiotics, except amoxicillin-clavulanate, showed high activity against strains resistant to TEM-type betalactamase inhibitors. Meropenem, cefminox and piperacillin/tazobactam showed the highest activity against strains with extended-spectrum betalactamase, followed by amoxicillin-clavulanate.[71]

Tamayo et al. found an overall prevalence of enterobacteriaceae producing extended-spectrum betalactamase of 3.6% (293/8139) in general population samples from several centres in Madrid.[72] For *E. coli*, the prevalence was 4.15% (279/6721). Tena et al. found a significant increase from 1.9% to 4.9% of the prevalence in strains of *E. coli* from UTI in the general population in Castile-La Mancha between 2003 and 2007.[70]

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Table 9. Characteristics of the revised series with data on the etiology of UTIs in children

Author Year	Period	Location	Sample	Most frequently isolated microorganisms (order of frequency and percentages)					Origin and sample features
				I	II	III	IV	V	
Gutiérrez-Solana 1987	1979-1985	Madrid	135	*E. coli* 90.3	*P.aeruginosa* 2.2	*S.epidermidis* 2.2	*P.mirabilis* 1.49	*K.pneumoniae* 0.7	Urine samples from 18 girls with recurrent UTI criteria
Vilanova 1989	1983-1988	Barcelona	30	*E. coli* 33.3	*Klebsiella* 26.6	*Enterobacter* 16.6	*Candida* 10	*Enterococo* 6.6	Positive urine cultures from 28 babies recently born in hospital
Gutiérrez 1989	1988	Granada	22	*E. coli* 50	*Enterococcus sp* 18.2	*C.albicans* 9.1	*P.vulgaris* 4.5	*P.mirabilis* 4.5	Hospitalised patients
Díaz-Cardama 1989	1989	Ourense	30	*E. coli* 70	*K. pneumoniae* 6.6	*P. mirabilis* 6.6			
Diaz-Diaz 1993	1992-1993	Gijón	224	*E. coli* 71.7	*Proteus sp* 13.4	*Enterococo* 7.2	*Enterobacter* 1.8	*Pseudomonas* 2.2	Overall from hospitalised children with UTI
			19	*E. coli* 73.7	*Proteus sp*	*Enterococo* 15.8	*Enterobacter* 5.3	*Pseudomonas*	Recently born babies
			94	*E. coli* 76.3	*Proteus sp* 11.8	*Enterococo* 4.3	*Enterobacter* 1.1	*Pseudomonas* 2.1	Infants
			111	*E. coli* 67.6	*Proteus sp* 17.1	*Enterococo* 8.1	*Enterobacter* 1.8	*Pseudomonas* 2.7	Children over 2 years
			126	*E. coli* 74.4	*Proteus sp* 14.4	*Enterococo* 4	*Enterobacter* 2.4	*Pseudomonas* 2.4	First UTI
			63	*E. coli* 65.1	*Proteus sp* 15.9	*Enterococo* 12.7	*Enterobacter* 1.6	*Pseudomonas*	Simple reinfection (less than 4 reinfections/year)
			35	*E. coli* 74.3	*Proteus sp* 5.7	*Enterococo* 8.6	*Enterobacter*	*Pseudomonas* 5.7	Frequent reinfection (4 or more infections per year)

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Canduela 1995	1993-1994	Laredo	12	*E. coli* 83	*Proteus sp* 8.3	*Klebsiella sp* 8.3			Patients who enter in emergency and remain hospitalised
Martínez 2001	1995-1999	Oviedo	484	*E. coli* 71	*P. mirabilis* 67	*K. pneumoniae* 73	*Other enterob.* 69	*P. aeruginosa* 58	Hospitalised patients and outpatients with UTI under 2 years
			211	*E. coli* 29	*P. mirabilis* 33	*K. pneumoniae* 27	*Other enterob.* 31	*P. aeruginosa* 42	Hospitalised patients and outpatients with UTI over 2 years
Hernández 2001	1995-2000	Community of Valencia	355	*E. coli* 78	*Proteus sp* 9	*K. pneumoniae* 4	*P. aeruginosa* 3	*Enterobacter* 3	Hospitalised patients and outpatients
Ochoa 2004	1995-2001	Zamora	756	*E. coli* 68	*P. mirabilis* 6.2	*P. aeruginosa* 4.2	*E. cloacae* 3	*S. agalactiae* 2.8	Positive urine cultures from hospitalised patients and outpatients
Capdevila 2001	1999	Barcelona	131	*E. coli* 90.1	*P. mirabilis* 3.1	*K. peumoniae* 3.1	*E. cloacae* 2.3		Previously healthy infants in hospital with first UTI
Fernández Díaz 200865	1996-2006	Gijón	106	*E. coli* 81.1	*Enterococcus faecalis* 6.6	*Enterobacter cloacae 4.7*	*Klebsiella pneumoniae* 2.8	*Klebsiella oxytoca* 1.9	Recently born admitted to hospital
Pardo 2008[67]	2006	Gijón	292	*E. coli* 71.9	*Proteus sp* 13.6	*Enterococcus faecalis 5.4*	*Klebsiella pneumoniae 2.1*	*Pseudomonas aueruginosa 1.7*	Samples from hospital and primary care (45%)

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Table 10. Sensitivity (percentages) of E. coli to the antibiotics most commonly used in paediatric and national general population series

Author Year	Period	Percentage sensitivity to antibiotics											Sample	
		AMP	AMC	C1G	C2G	C3G	NIT	GM	TMP SMX	NAL	FF	CIP	Type	Origin
Díaz-Díaz 1993	1992-1993	39.4	90.6	57.5	99.4	100	—	100	61.9	—	—		c	Gijón
Martínez 2001	1995-1999	49	—	92	97	100	95	96	82	—	—		c	Oviedo
Hernández 2001	1995-2000	20	85	80	95	99	90	95	65	—	99		c	Comunidad Valencia
Ochoa 2004	1995-2001	36.7	93.3	95	99.3	100	94.4	96.6	77.3	—	100		c	Zamora
Andreu 2005	2002	41.3	90.8	—	—	95.8	94.3	—	66.1	—	98	77	b *	Spain
Andreu 2008[64]	2008													Total (Spain)
		39.3	91.9		91.1	93.1	96.2		68	65.5	98.3	76.1	b *	Andalucía
		34.9	91.5		80.1	79.7	96.1		62.7	61.5	99.2	74.5	b *	Aragón
		32.7	93.2		93.2	95.2	93.1		63.3	59.2	98.6	74.8	b *	Asturias
		27.9	81.7		78.6	90.8	87		72.5	73.2	99.2	71	b *	Castilla y León
		41.9	94.9		93.7	100	96.2		68.6	65.5	95.6	79.4	b *	
		36.5	89.3		97.6	98.9	98.4		70.3	71.8	98.2	84.7	b *	Cataluña
		41.8	94.3		88	91.1	95.9		65.7	60.9	97.4	68.4	b *	Madrid
		36.3	89.7		89.7	89	95.9		63.7	59.7	98.5	62.7	b *	Community of Valencia
		63.2	95.6		98.5	98.5	98.5		75	80.1	99.3	87.5	b *	Galicia
		50.6	97		95.9	98.2	100		77	72.3	99.4	87.1	b *	Basque Country
Caro Narros 2007[69]	2007	42.9	88.7	82.4	91.4	96.7	90.6	90.5	69.3	63.8	94.1	76.6	b *	Segovia
		37.2	87.6	81	89.7	93.1	88.9	89.3	68.4	61.6	93	74	*	Total
		42.4	89.3	83.3	92.4	95.7	91.6	91.2	69.8	65.1	94.7	78.2	*	*Hospital
														*Outpatient
Fernández Díaz 2008[65]	1996-2006	43.9	98.8	78.8	96.3	97.6		97.6	80.5					
	1996-2001	44.7	84.2	58.3	83.3	91.7		91.7	80				c	Gijón
	2001-2006	38.8	92.5	75.4	85.5	91		94	74.2					
Lorente Garín 2005[66]	1997-2001	38.2	89.5	94.4			92.9		68.8		99.1	70.9	a *	Barcelona
Pardo 2008[67]	2006	39.8	95.3	97.2		98.1	99.1	99	79.6		98.6	96.7	b	Gijón
Rodríguez López 2005[68]	1992-2003	35,6	94.3	91.7	94	98.6	91.9	91.2	64.1	65.7	98.6	78	b *	Córdoba
	2003		92		91	95	96	93	64	59	98	72	b *	
Tena 2010[70]	2003-2007	37.7	86.7		87.3	96.2	96.2	92.4	67.3	60.5	97.6	75.4	b *	Castile La Mancha
	2007	35.7	85.7		86.1	94.7	96	91.4	66	59.8	95.5	72.3		

AMC: amoxicillin-clavulanate; AMP: ampicillin; C1G, C2G, C3G: cephalosporin 1st, 2nd and 3rd generation; CIP: ciprofloxacin; GM: gentamicin, FF: phosphomycin, NAL: nalidixic acid; NIT: nitrofurantoin, TMP-SMX: trimethoprim-sulfamethoxazole.
a: UTI in outpatients; b: UTI inpatients and outpatients; c: UTI in hospitalised patients; *General population.

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Table 11. Sensitivity of Proteus spp to the main antibiotics in different series

Author Year	Period	Percentage sensitivity to antibiotics											Sample	
		AMP	AMC	C1G	C2G	C3G	NIT	GM	TMP SMX	NAL	FF	CIP	Type	Origin
Díaz-Díaz 1993	1992-1993	50	96.7	86.7	93.3	96.7	—	100	56.7	—	—		c	Gijón
Martínez 2001	1995-1999	75	—	100	100	100	100	100	86	—	86		c	Oviedo
Hernández 2001	1995-2000	40	40	80	90	95	25	85	60	—	—		c	Community of Valencia
Ochoa 2004	1995-2001	60.5	100	93	100	100	0	100	74.4	—	83		c	Zamora
Andreu 2005	2002	61.6	93.9	—	—	96.4	0	—	62.1	—	76	83	b *	Spain
Lorente Garín 2005[66]	1997-2001	56.6	92.9	98.4	—	—	1.2	—	61.9	—	84.4	78	a *	Barcelona
Pardo 2008[67]	2006	60.5	100	90.7	—	100	9.3	90.2	69.8	—	92.2	97.6	b	Gijón
Rodríguez López 2005[68]	1992-2003	54.4	95.3	89.6	98.5	100	14.3	90.2	53.2	84.2	89.7	91.5	b *	Córdoba
	2003	—	97	—	97	100	—	91	49	81	88	94	b *	

AMC: amoxicillin-clavulanate; AMP: ampicillin; C1G, C2G, C3G: cephalosporin 1st, 2nd and 3rd generation; CIP: ciprofloxacin; GM: gentamicin, FF: phosphomycin, NAL: nalidixic acid; NIT: nitrofurantoin, TMP-SMX: trimethoprim-sulfamethoxazole.
a: UTI in outpatients; b: UTI inpatients and outpatients; c: UTI in hospitalised patients; *General population.

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Table 12. Sensitivity of Klebsiella spp. to the major antibiotics in different series

Author Year	Period	Percentage sensitivity to antibiotics											Sample	
		AMP	AMC	C1G	C2G	C3G	NIT	GM	TMP SMX	NAL	FF	CIP	Type	Origin
Martínez 2001	1995-1999	—	—	—	77	50	50	50	47	—	37	—	c	Oviedo
Hernández 2001	1995-2000	0	0	75	85	100	60	90	75	—	—	—	c	Community of Valencia
Ochoa 2004	1995-2001	—	90.9	72.7	86.4	95.5	90	95.5	100	—	88		c	Zamora
Andreu 2005	2002	0	94.5	—	—	97.7	67.1	—	93.2	—	78	93	b *	Spain
Lorente Garín 2005[66]	1997-2001	0	90.8	97.4	—	—	59.3	—	93.8	—	91.1	89.1	a *	Barcelona
Pardo 2008[67]	2006	60.5	100	90.7	—	100	9.3	90.2	69.8	—	92.2	97.6	b	Gijón
Rodríguez López 2005[68]	1992-2003	—	95.5	93.5	94	100	76	98	94.2	90	81.8	94	b *	Córdoba
	2003	—	89	—	86	100	84	95	89	91	72	94	b *	

AMC: amoxicillin-clavulanate; AMP: ampicillin; C1G, C2G, C3G: cephalosporin 1st, 2nd and 3rd generation; CIP: ciprofloxacin; GM: gentamicin, FF: phosphomycin, NAL: nalidixic acid; NIT: nitrofurantoin, TMP-SMX: trimethoprim-sulfamethoxazole.
a: UTI in outpatients; b: UTI inpatients and outpatients; c: UTI in hospitalised patients; *General population.

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6.2. Mechanism of action of bacteria on the urinary tract

6.2.1 Bacteriological data

Except in the neonatal period, during which UTI may occur haematogenously,[46] in most cases it occurs by gram-negative bacteria ascending from the intestines (enterobacteriaceae) which contaminate the perineal area.[2,64,73]

Of these, *Escherichia coli* is by far the organism isolated most often, causing about 80-90% of all UTIs in children. The remaining infections are caused by other enterobacteriaceae, such as *Proteus mirabilis, Klebsiella pneumoniae, Citrobacter and Enterobacter.* Infection with *Proteus mirabilis* occurs more frequently in males, probably because of the presence of this germ in the balanopreputial sac.[2,64,73]

A small number of infections are caused by gram-positive cocci. Among them, the most frequent is *Enterococcus* and, to a lesser extent, the group B *Streptococcus* and other gram-positive cocci. These germs are most common in newborn children, although UTI caused by gram-negative bacteria is also found in newborns. *Staphylococcus aureus, Staphylococcus epidermidis and Staphylococcus saprophyticus* can also cause UTI, but very rarely.[2,64,73]

Hospitalised patients with a history of their urinary tract being inspected by instrumentation, can also catch urinary tract infections caused by bacteria typically found in hospitals, such as *Pseudomonas aeruginosa, Serratia* and *Staphylococcus. Candida albicans* usually occurs preferentially in patients who are immuno-compromised or who have been subjected to urinary catheters for long periods of time after a prolonged use of broad-spectrum antibiotics.[2,64,73]

Viruses have a limited role in causing infections, although the adenovirus and BK virus frequently cause haemorrhagic cystitis, especially in immuno-compromised patients.[74,75] Anaerobic faecal flora rarely causes UTI, despite being far more abundant than *E. coli* in the faeces.

6.2.2 Pathogenesis

The pathogenesis of UTI is complex and many factors (bacterial, immunological, anatomical, urodynamic, and genetic, for example.) may influence its location, course and prognosis. The existence of an individual and genetic predisposition to developing UTI is now accepted. Predisposed children have a lower defence against gram-negative bacteria, especially *Escherichia coli*, which is the germ that causes most UTIs and is the most studied. The severity of the UTI: APN, cystitis or asymptomatic bacteriuria, will depend on the host's defensive capability and the virulence of the bacteria.[76]

There is clinical and experimental evidence that bacteria (enteric) ascend through the urethra from the intestine in UTI.[77,78] After colonising the periurethral area, the bacteria reach the bladder and from there reach the kidneys through the ureters.

6.2.3 Bacterial factors

The ability of microorganisms to adhere to uroepithelial cells is the primary cause of the initial colonisation of the bladder mucosa and the subsequent rise of bacteria to the upper urinary tract. This can occur even in the absence of structural abnormalities like VUR.

Adherence to uroepithelial cells is achieved through specialised filamentous structures called pili or fimbriae located on the bacterial capsule.[79]

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There are several types of fimbriae: Type 1 fimbriae are often found in bacterial strains causing cystitis and asymptomatic bacteriuria (34%), and hardly ever in APN (5%).[80,81] It was recently reported that this type of fimbriae did not contribute to the inflammatory response in the mucosal uroepithelium in UTI.[82]

E. coli strains with type 2 or type P fimbriae are present more in patients with APN symptoms (76-94%) than cystitis (19-23%), asymptomatic bacteriuria (14-18%) and in faeces of healthy individuals (7-16%).[83,84]

It was recently shown that P fimbriae are encoded by a group of 11 genes (pap gene cluster) and are carriers of a specific adhesin, Gal(alpha 1-4) Gal-binding PapG adhesin.[85] This adhesin is essential in the pathogenesis of renal infection and binds to specific receptors, the glycosphingolipids, of epithelial cells lining the urinary tract.[86] Mutations have been described in some of these genes that prevent the expression of some P fimbriae, preventing some strains of bacteria from adhering to the uroepithelium.[87]

6.2.4 Host factors

When uropathogenic bacteria invade the urinary tract there is an immune response from the uroepithelial cells that plays a vital role in a patient's susceptibility to UTI.

Recently discovered were a family of receptors called toll-like receptors (TLR) which are expressed in uroepithelial cells acting as sentinels, and have the ability to recognise certain molecules associated with uropathogenic bacteria.[88]

To date, 11 TLRs have been identified, of which TLR 2, 4 and 11 have the greatest importance in the pathogenesis of UTI. TLR2 identifies lipoproteins in gram-positive bacteria, and TLR4 the lipopolysaccharide endotoxins of uropathogenic bacteria such as *E. coli*. TLR11 also recognises uropathogenic bacteria and protects the kidney from ascending infection. However, so far the role of this receptor in human UTI has not been established.[88-91]

Under normal conditions, *E. coli* fimbriae bind to the specific receptors mentioned above, recruiting TLR4 and releasing a transmembrane signal that triggers the production of various inflammatory mediators, such as cytokines, chemokines, defensins, complement system proteins and other adhesive peptides. This leads to an inflammatory response from the renal tissue and the arrival of immune cells such as neutrophils from the capillaries. Although this removes the bacteria, the effects of the inflammatory process can be destructive for the host itself, with the formation of scar tissue at the site of inflammation. In other words, the scar formation is more a consequence of the inflammatory process than a direct result of the bacterium itself.[88]

In ABU, the uropathogenic bacteria lose the expression of many virulence factors and have little ability to induce any immune defence from the mucosal uroepithelium. Thus, experimental studies and clinical trials in children with ABU have observed a reduced expression of TLR4, relative to control subjects. As a result, these patients may be asymptomatic for long periods of time without provoking a destructive response from the host; i.e., the lack of response of the mucosal uroepithelium may be a protective mechanism against renal damage.[92]

Local production of chemokines, including the main example IL-8, is central to the migration of neutrophils from the capillary wall to the tubular lumen, where they interact with pathogens, destroying them. It is precisely the uropathogenic bacteria with P fimbria that stimulate their release in the renal epithelial cells.[88,93,94]

Experiments with mice have shown that those not expressing the IL-8 receptor do not produce the proper migration of neutrophils. Also, KO mice for the cytokine receptor IL-8 (CXCR1) are more prone to developing APN and renal scarring, due to a dysfunction in the response of

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these neutrophils. Clinical studies describe children prone to APN having a reduced expression of the cytokine receptor IL-8, with respect to controls.[95]

The Tamm-Horsfall protein is the most abundant protein in urine and is expressed exclusively in the ascending limb of the loop of Henle. There is recent evidence that this protein plays an important role in the immune response of the urinary tract antibacterial defence. It acts as an endogenous modulator for the activation of granulocytes, monocytes, etc; prevents the colonisation of uropathogenic bacteria; and, by binding to type 1 fimbriae, interferes with the bacteria attacking the urinary tract. It may also have a pro-inflammatory role, due to inducing the maturation of dendritic cells through a complex mechanism involving the activation of TLR4 and the transcription factor NF-kB.[88]

The bacteria are capable of activating the complement system, leading to their opsonisation. However, as well as bacterial clearance, activating the complement may lead to tissue damage in the host. Experimental studies have shown that inhibition of the complement system decreases the inflammatory response and potentially reduces the degree of tissue damage.[88]

The body's immune response during UTI includes the local release of β-defensins by the renal epithelium and α-defensins by neutrophil infiltrates, which, among other effects, leads to the death of pathogens.[88,96] There are also molecules that adhere to the vascular endothelial cells, which are critical for the inflammatory cells to leave circulation and infiltrate the surrounding tissue towards the local inflammatory process.[88]

To summarise, the local molecular events referred to as a result of interaction between the urinary tract cells and pathogenic bacteria seem to be a determining factor in the clinical consequences of UTI. The inter-individual variability of cell response, probably related to some polymorphisms of candidate genes, may be responsible for the increased susceptibility of some individuals to contract recurrent UTI and develop progressive renal damage. When the molecular basis of the pathogenic mechanisms in UTI is better understood, susceptible individuals will be better identified. This in turn will lead to more specific treatment strategies which are more effective at preventing complications.[88]

6.2.5 Other defence mechanisms

Urine is an excellent medium for bacterial growth, and when bacteria reach the bladder they multiply easily.

One of the defence mechanisms against bacterial growth in the urinary tract is based on urination itself, which leads to a continuous shedding of surface epithelial cells that are attached to the bacteria. The bacteria are washed from the bladder through repeated urination and the sterility of urine depends largely on there being no interruption in urine flow.[97,98]

Urinary tract obstruction with urine stasis, either due to a mechanical process in relation to a congenital abnormality (e.g. hydronephrosis, ureterohydronephrosis, duplication, ureteroceles or valves), or a functional problem in connection with a dysfunction bladder, for example, is one of the most important predisposing factors for UTI and renal damage. Increased residual volume and bladder distension as a result of an obstruction promote bacterial growth.[99,100]

As already mentioned, bladder dysfunctions (e.g., urinary urgency syndrome, dysfunctional voiding with detrusor sphincter dissynergia and lazy bladder syndrome), are predisposing factors for recurrent UTI, especially in women. This is because they result in conditions like increased residual urine volume or a dilated bladder with intravesical pressure elevation.[101,102]

Similarly, there is a correlation between constipation and recurrent UTI. While this may be the result of mechanical factors related to compression of the bladder and the bladder neck by the

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faeces, it is more likely to depend on the coexistence with dysfunctional voiding and incomplete emptying of the bladder (dysfunctional elimination syndrome). Improved bowel habits usually decrease the incidence of recurrent UTI, especially if associated with a regular voiding pattern.

Sexual activity is one risk factor for acute cystitis, especially in sexually active adolescents; however, this is much less frequent in men.[103,104]

6.2.6 Vesicoureteral reflux

VUR leads to infected urine in the bladder ascending towards the upper urinary tracts without the bacteria having to be especially virulent. In a study of children with recurrent APN, only 36% of infections due to *E. coli* with P fimbriae were affected by VUR.[105]

Of children with VUR, 25-50% had their first sign of a UTI,[106] compared with 0.4-1.8% who did not.[107,108]

In the presence of VUR, approximately 80-90% of patients with febrile UTI have an abnormal DMSA,[44,109,110] and this is particularly true when the reflux is moderate to severe (grade IV-V). The probability of these patients having APN is 2 times higher (67%) than those with mild reflux (32%) and those with no reflux (34%).[106,111]

However, most patients with an altered DMSA did not have VUR (60-68%) at the time of the study.[106,111-113] This underlines the importance of host defence factors and bacterial virulence in the pathogenesis of APN in children. It also supports the theory that reflux is not essential for APN to occur, although reflux is a factor favouring its occurrence, especially if severe.

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7. Protection and risk factors for UTI

7.1 Lack of hygiene as a risk factor for UTI: Using a nappy and Oxiurasis

Key questions:

- Does a lack of hygiene when using a nappy affect the incidence of UTI?
- Does a lack of hygiene related to the presence of oxiurasis affect the incidence of UTI?

The periurethral area is colonised by anaerobic and aerobic bacteria from the gastrointestinal tract, which are part of the defensive barrier against pathogens. Some circumstances, such as the use of certain nappies in children who are not yet toilet-trained[114] or infestation by pinworm (*Enterobius vermicularis*), especially in schoolgirls,[115] can upset the balance of this barrier and be risk factors for urinary tract infection (UTI), by promoting the periurethral colonisation of pathogenic bacteria from faeces.

A study in 2 paediatric hospitals in Finland, included in the NICE CPG, investigated the role of different types of nappies (superabsorbent, normal and washable cotton) and care habits as a risk factor for UTI in 196 cases admitted for a first episode of UTI (104 girls, 92 boys, mean age 0.60 years, range 0.03-2.89 years) and 196 controls hospitalised for other causes (104 girls, 92 boys, mean 0.62 years, range 0.02-2.76 years). Both cases and controls wore nappies day and night. The study found no significant differences in the type of nappy used: superabsorbent (OR 0.95, 95% CI 0.62-1.46), normal (OR 1.04, 95% CI 0.69-1.57), washable cotton (OR 1.00, 95% CI 0.46-2.16); nor in the care habits (number of nappies used daily, number of stools per day, frequency of washing the buttocks, time without a nappy per day and frequency of nappy rash).[11]

Case-control study 2+

A Japanese study investigated the association between the nappy changing frequency and the presence of UTI in 128 children not yet toilet-trained (age 2 months to 2.5 years) treated at an outpatient paediatric clinic due to fever ≥38°C with no symptoms consistent with upper respiratory tract infection. There were 32 children with UTI (14 boys and 18 girls, age 1.2±0.6 years) with UTI who had a significantly lower frequency of nappy changes (P<0.0001); also, the number of stools per day was 0.5-5.0 (mean 1.4±1.0) and the number of nappy changes was 3-8 (mean 4.7±1.4). Whereas in the controls, 96 children were without UTI (52 boys and 44 girls, age 1.1±0.6 years), the number of stools per day was 0.5-5.0 (mean 1.6±1.1) and the number of nappy changes was 5-11 (mean 7.5±1.4).[116]

Case-control study 2-

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A hospital study in Iran studied the type of nappy (superabsorbent, normal, and washable cotton) as a risk factor for UTI in hospitalised girls (age 1-24 months): 59 (age 9.57±6.06 months) for a first UTI and 59 (age 9.60±5.80 years) there for other reasons (usually surgery). Those with UTI had a greater use of the superabsorbent nappy (62.71% vs 35.59%, OR 3.29, P=0.005) and more use of the normal nappy in girls without UTI (64.41 % vs 37.29%, P=0.005). There were no differences between the groups regarding the number of nappies used per day (P=0.15) nor time between nappy changes (*P*=0.14).[114]	Case-control study 2-
A study in Turkey evaluated the presence of *Enterobius vermicularis* eggs in 55 girls (age 6.7±3.1 years) diagnosed with UTI and 55 girls (age 7.0±3.9 years) with no history of UTI. The study showed that 36.4% of girls with UTI had pinworm eggs in the perianal and/or perineal region, compared to 16.4% of girls in the control group (*P*<0.05). There were no statistically significant differences by age in the 1-6 year age group (16% of girls with UTI had pinworm eggs vs 12% in the control group), while in the 7-14 year age group, 53% of girls with UTI had pinworm eggs compared to 19% in the control group (*P*=0.012).[117]	Case-control study 2+
A study included in the NICE CPG conducted in the United States assessed the presence of pinworm in 41 girls (mean age 5.5 years) with a history of recurrent UTI and 58 girls (mean age 6.4 years) without. The study showed that 22% (9/41) and 5.2% (3/58) of girls, respectively, gave a positive Graham test.[11]	Case-control study 2-
A study in Turkey evaluated the presence of urinary symptoms and bacteriuria in 380 schoolgirls: 150 (39.5%) with a positive Graham test and 230 (60.5%) with a negative. There were no statistically significant differences (*P*>0.05) in the frequency of dysuria in those positive (18.7%) and negative (14.8%) for pinworms. In contrast, girls testing positive for pinworms had a statistically significant (*P*<0.05) increased frequency of nocturia (45.3% vs 6.1%, *P*<0.05), nocturnal enuresis (26% vs 10.9%) and bacteriuria (12% vs 3%).[118]	Case-control study 2-
A study in Chile assessed the frequency and type of genital inflammation and urinary tract infection in 35 girls (aged 1.5-14 years) infected with *Enterobius vermicularis*. The study showed that 14 cases (40%) had dysuria, 10 cases (29%) foul-smelling urine, 2 cases (6%) cloudy urine, 1 case (3%) of haematuria, 4 cases (11%) of primary enuresis, and only 1 case (3%) of UTI.[115]	Case Series 3

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Evidence summary

2+	There were no significant differences in the type of nappy (superabsorbent, normal and washable cotton) or care habits (number of nappies used daily, number of stools per day, frequency of washing the buttocks, time without a nappy per day and the frequency of nappy rash) in children with UTI and those without.[11]
2-	There is a significant association between less frequent nappy changes and the presence of UTI in children younger than 2.5 years (P<0.0001).[116]
2-	There is a significant association between the use of superabsorbent nappies and an increased risk of UTI in girls under 2 years (P=0.005).[114]
2+	Girls with UTI have a higher prevalence of pinworm eggs in the perianal and/or perineal region compared to girls with no history of UTI (36.4% vs 16.4%).[117]
2-	There is a higher prevalence (P<0.05) of bacteriuria and urinary symptoms (nocturia, nocturnal enuresis) in school-age girls with a positive pinworm test.[118]
3	Among girls infected with *Enterobius vermicularis*, an increase in UTI cases was not found.[115]

Recommendations

√	It is recommended to change nappies frequently.
D	It is recommended to rule out pinworm infection in girls with recurrent UTI.

7.2 Breastfeeding and its protective role against UTI

Key question:

- Does breastfeeding give any protection against UTI?

Breastfeeding has a protective effect on a number of childhood infections, such as acute gastroenteritis, respiratory infections and acute otitis media. Breast milk contains immunoglobulins (especially the secretory immunoglobulin IgA), oligosaccharides, glycoproteins with anti-adhesive properties and cytokines; they are all anti-infection factors.[119] There is less evidence on the protective effect of breastfeeding against UTI.

A study conducted in Sweden and included in the NICE CPG investigated the association between breastfeeding and the risk of a first febrile UTI in 200 children (89 boys and 111 girls, age 0.98±1.15 years, range 0-6 years) attending the hospital with a first symptomatic UTI, and 336 children (147 boys and 189 girls, age 0.97±1.15 years) without any history of UTI. The risk of UTI was observed to be higher in non-breastfed children than those exclusively breastfed (HR 2.30, 95% CI 1.56-3.39, P<0.001). This protective effect depended on the length and sex of the child. A longer duration of breastfeeding was associated with a reduced risk of UTI: the risk of UTI increased more rapidly if breastfeeding was stopped at 2 months of life than at 7 months. The protective effect was stronger in girls than in men, with the risk of UTI in non-breastfed girls having a HR of 3.78, and the risk in non-breastfed boys with a HR of 1.63, (P=0.0491).[11]

Case-control study 2+

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A study conducted in Iran with 50 hospitalised children under 1 year old with UTI (21 boys and 29 girls, age 8.7±3.3 months) and 50 healthy children (25 boys and 25 girls, age 9.1±2, 9 months), after routine home visits, showed that a statistically significant number of exclusively breastfed children had a lower risk of UTI than those who received breast milk substitute (OR 0.1, 95% CI 0.027-0.329) and those on a mixed breastfeeding/breast milk substitute diet (OR 0.33, 95% CI 0.124-0.866). Similarly, children receiving the mixed feeding had a lower risk than those who received breast milk substitute only (OR 0.3, 95% CI 0.091-0.920). This study also showed that breastfeeding for over 6 months was associated with a reduced risk of UTI compared with a duration less than or equal to 6 months (OR 0.29, 95% CI 0.121-0.714). [120]

Case-control study 2+

An Italian study of 128 children under 6 months old (81 boys and 47 girls) hospitalised with UTI and 128 controls (81 boys and 47 girls) admitted with an acute illness (excluding those diagnosed with acute diarrhoea or a breathing infection, since breastfeeding confers protection against these diseases) showed that 50% of cases were breastfed (either exclusively or mixed) compared to 73% of controls. Those breastfed had a statistically significantly reduced risk of UTI (OR 0.38, 95% CI 0.22-0.65). [121]

Case-control study 2+

A retrospective study in the United States assessed the risk factors for recurrent UTI in 84 children with UTI (52 girls and 32 boys, mean age 4.8 years, range 2.3-7.2 years), under 6 months old at the time of diagnosis without abnormalities by radiography, during a mean follow-up period of 4.4 years. The study showed that 31% of children with recurrent UTI had received less than 4 months of breastfeeding, compared to 46% of children without recurrent UTI; however, this difference was not statistically significant (P=0.297). [122]

Cohort study 2-

A study in the United States evaluated the effect of breastfeeding as a protective factor on a sample of 315 children younger than 3 months admitted for an emergency or to the paediatric clinic via a urine culture analysis. The study concluded there were no significant differences in the risk of UTI in breastfed infants and those fed on breast milk substitute.[119] However, the findings of this study cannot be assumed as valid, given the significant methodological limitations of the study and inadequate statistical analysis of the data that the authors performed.[123]

Cohort study 2-

Evidence summary

2+	The risk of first febrile UTI increases in non-breastfed children, compared with those exclusively breastfed (HR 2.30, 95% CI 1.56-3.39, P<0.001).[11]
2+	Children exclusively breastfed had less risk of UTI than those receiving breast milk substitute or a mixed feeding (OR 0.1, 95% CI 0.027-0.329) and (OR 0.33, 95 % 0.124-0.866), respectively. In turn, children receiving the mixed feeding has less risk of UTI than those on breast milk substitute (OR 0.3, 95% CI 0.091-0.920).[120]

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2+	Breastfed children (exclusive or mixed) had less risk of UTI (OR 0.38, 95% CI 0.22-0.65).[121]
2+	Breastfeeding for more than 6 months is associated with a reduced risk of UTI (OR 0.29, 95% CI 0.121-0.714).[120]
2+	The longer the duration of breastfeeding, the lower the risk of UTI after stopping.[11]
2-	Children breastfed for less than 4 months had no statistically significant difference in the recurrence rate of UTI (P=0.297).[122]

Recommendations

C	It is recommended to inform mothers of the benefits and the protective effect of breastfeeding when planning the feeding of their infants.
C	It is recommended to continue breastfeeding for at least 6 months.

7.3 Phimosis as a risk factor for UTI

Key question:

- Are uncircumcised boys more likely to have UTI?

The aim of this review was to assess whether the presence of phimosis, which involves insufficient urinary flow and retention of secretions in the coronal sulcus, is related to the existence of UTI and, if so, if it would need to be corrected by appropriate measures.

A SR of 12 studies (10 in North America) included in the NICE CPG evaluated the effects of circumcision on the risk of developing UTI. The subgroup meta-analysis, conducted according to the study design, showed that in children of 1-3 years of age (data from 4 cohort studies), in children aged 1 month to 5 years of age (data from 7 case control studies) and in children aged 3 months to 10 years of age (data from 1 RCT), circumcision reduces the risk of UTI (OR 0.13, 95% CI 0.07-0.24), (OR 0.13, 95% CI 0.07-0.23) and (OR 0.13, 95% CI 0.06-2.63), respectively. The overall result of the meta-analysis showed a beneficial effect for circumcision in reducing the risk of UTI (OR 0.13, 95% CI 0.08-0.20).[11]

SR of different study types 2++

A study included in the NICE CPG conducted in the United States on a population of 28,812 newborns during 1996 (including 14,893 boys, of whom 64.9% were circumcised in the neonatal period), found that the average age of diagnosis of UTI was 2.5 months in uncircumcised boys, 4.5 months in circumcised boys and 6.5 months in girls.

Additionally, data from a second cohort study of 20,587 newborns in 1997 followed for the first 12 months of life calculated the following for the incidence of UTI in the first year of life: 1/47 (2.15%) in uncircumcised males, 1/455 (0.22%) in circumcised males, and 1/49 (2.05%) in girls. The probability of a first UTI in uncircumcised boys during the first year of life was 9 times higher than in circumcised boys (OR 9.1, 95% CI 5.2-15.7, P<0.001).[11]

Cohort study 2++

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A study included in the NICE CPG conducted in the US on the population of all newborns in military hospitals (n=427,698), found that circumcised boys were less likely to suffer a UTI in the first year of life than uncircumcised ones (0.09% vs 1.0%, *P*<0.001).[11]	Cohort study 2+
An Australian study included in the NICE CPG of 144 boys with UTI (median age 5.8 months) and 742 boys without UTI (median age 21 months) found that 1.4% of children with UTI were uncircumcised compared to 6.3% of children without UTI (P=0.02).[11]	Case control study 2+
A study in South Korea on a sample of 190 children (158 uncircumcised boys and 32 girls) diagnosed with first UTI (mean age at diagnosis 4.1±2.5 months) investigated the incidence of recurrent UTI and related risk factors (including phimosis) for 1 year. Children who had physiological phimosis with a non-retractable foreskin (125 boys, 79.1%) were administered hydrocortisone ointment 2 times daily for 2-4 weeks; physiotherapy was carried out, and the parents invited to wash the urethral meatus of the child once daily. At the end of treatment, the foreskin was retractable in 75 boys (60%). The study showed that the recurrent UTI rate was lower in children with a retractable foreskin (either originally or after treatment) than those with a non-retractable foreskin: 17.6% (19/108) vs 34.0% (17/50), *P*=0.022. After using multivariate logistic regression, the same study showed that for boys the presence of a non-retractable foreskin (OR 8.8; 95% CI 3.2 to 24.5), the presence of APN (OR 4.6, 95% CI 1.6-13.0) and the age of 6 months or less (OR 72.7, 95% CI 10.3-489) increased the likelihood of developing recurrent UTI.[124]	Cohort study 2+
A US study of the population of boys born in the state of Washington during 1987-1996 (354,297 boys) studied those circumcised at birth while in the hospital (n=130,475 males, 37%). It estimated the rate of complications associated with circumcision and calculated the number of patients needed to harm (NNH). The study showed that 287 (0.2%) of the total circumcised males had complications related to circumcision occurring during the neonatal period and during hospital stay, while 33 (0.01%) of the uncircumcised males (n=223,822) had complications. The number of patients needed to harm (NNH) was 476, meaning that a complication can be statistically expected after every 476 circumcisions performed.[125]	Cohort study 2+
A meta-analysis of 4 prevalence studies estimated the prevalence of UTI in boys circumcised at 3 months at 2.4% (95% CI, 1.4-3.5) vs 20.1% (95% CI, 16.8-23.4) for uncircumcised boys.[42]	SR of prevalence studies 3

The GEG took into account the consistency between the various studies that show an association between circumcision and the reduced risk of UTI when making their recommendations. The evidence comes from studies in healthcare settings where circumcision is a common surgical practice for hygienic reasons or religious beliefs, especially in North America and in Muslim

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and Jewish people. This is why US and UK medical literature usually propose circumcision as a necessary practice to prevent urinary tract infections.

However, the GEG believes that phimosis must not treated by surgical techniques alone, as there are other less aggressive procedures, especially for children whose foreskin can be retracted, who tend to be those older than 7-8 months of age. Furthermore, the practice of circumcision is not without potential complications, including bleeding, infection and/or meatal stenosis, if not done properly.[30] Therefore, the GEG considers that medical treatment to retract the foreskin must first be considered in recurrent febrile UTI associated with phimosis.

Evidence summary

2++	Circumcision is associated with a decreased risk of UTI (OR 0.13, 95% CI 0.08-0.20).[11]
2++	During the first year of life, uncircumcised boys have a 9 times higher probability of presenting a first UTI than circumcised boys (OR 9.1, 95% CI 5.2-15.7).[11]
2+	Circumcised boys are less likely to suffer a UTI in the first year of life than uncircumcised boys (0.09% vs 1.0%, $P<0.001$).[11]
2+	1.4% of boys with a history of UTI are circumcised, compared to 6.3% of boys with no history of UTI ($P=0.02$).[11]
2+	A non-retractable foreskin increases the likelihood of suffering a recurrent UTI (OR 8.8, 95% CI 3.2-24.5).[124]
2+	Medical treatment (hydrocortisone ointment 2 times a day and physiotherapy) for 2-4 weeks helps to retract the foreskin in 60% of boys with physiological phimosis.[124]
2+	When circumcision is indicated to prevent UTI, the benefits outweigh the possible complications, as only 1 complication is expected for every 476 circumcisions performed during hospital stay at birth (NNT 476, $P<0.001$).[125]
3	The prevalence of UTI in circumcised boys under 3 months is 2.4% (95% CI 1.4-3.5), compared with 20.1% (95% CI 16.8-23.4) for uncircumcised.[42]

Recommendations

B	It is recommended to explore and assess the foreskin in all boys with UTI, whether associated with structural abnormalities of the urinary tract or not.
√	Circumcision should not be routinely performed even though there is an association between circumcision and reduced risk of UTI.
C	It is recommended to try obtaining retraction of the foreskin by medical treatment in boys or infants with recurrent febrile urinary tract infection, with or without malformations or dysfunctions of the urinary tract associated with phimosis.
B	In those boys or infants with recurrent febrile urinary tract infection, with or without malformations or dysfunctions of the urinary tract associated with phimosis where phimosis persists after medical treatment, it is recommended to perform circumcision.

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8. Clinical diagnosis of UTI

Key question:

- What is the validity of the clinical findings for diagnosis of UTI in children?

Clinical suspicion of UTI in children is based on a series of signs and symptoms of variable specificity.

For children in the preverbal stage, the symptoms are very non-specific; with fever of unknown origin remaining the most widely used in normal clinical routine, although the probability of it being due to a urinary tract infection is only 5-7%.[12,42]

For children in the verbal phase, urinary symptoms such as incontinence, dysuria or urinary frequency point to a process of inflammation of the lower urinary tract. These cystourethral symptoms are not always due to a urinary tract infection; and following these, there may be vulvovaginitis, oxiurasis, crystalluria or functional voiding disorders.[126,127.]

The presence of fever or back pain suggests a renal parenchymal involvement.

Therefore, this question is aimed at defining the discriminative power of the various signs and symptoms suggestive of a urinary tract infection in children.

The NICE CPG included 11 descriptive studies to answer the above question. The studies found were divided according to 2 different scenarios: children attending emergency departments and children in primary care. The first group consisted of 8 studies with a total of 1,797 cases aged between 2 weeks and 14 years; the second group consisted of 3 studies with a total of 101 cases.[11]

Case series 3

A series of recommendations were established from the prevalence data of various signs and symptoms, with a table showing the importance of different clinical manifestations of UTI in pre-verbal and verbal children (Table 14, Annex 1).

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A SR of 12 prospective studies (11 of them different to those in the NICE CPG) included a total of 8,837 children under 18 years, divided into those older and younger than 24 months. The SR calculated the likelihood ratios of the different signs and symptoms in the 2 age groups: in isolation and in combination

SR of Diagnostic test studies Ia

The most important clinical symptom in determining UTI in children under 2 years of age (of whom there were more than 7,000 cases over the 8 studies) was the magnitude and duration of the fever; a combination of both gave the most discriminating results:

Fever >40°C (2 studies): LR+ 3.3 (95% CI 1.3-8.3) and LR- 0.66 (95% CI 0.35-1.25); LR+ 3.2 (95% CI 0.7-15.6) and LR- 0.93 (95% CI 0.80-1.08).

Fever of more than 24 hours duration (1 study): LR+ 2.0 (95% CI 1.4-2.9) and LR- 0.90 (95% CI 0.83-0.97).

Combination of fever >39°C for over 48h, with fever of unknown origin (1 study): LR+ 4.0 (95% CI 1.2-13.0).

Children in the pre-verbal stage had other possible non-specific signs and symptoms of UTI (gastrointestinal symptoms, jaundice, irritability, foul-smelling urine, failure to thrive, refusing food, suprapubic pain, haematuria, malaise and crying), but they had a low predictive value in most cases, with a LR+ less than 2.[18]

These non-specific signs and symptoms were extremely diverse in the various studies included in the NICE CPG, reaching up to 60% of the cases.[11]

Case series 3

In those over 24 months of age (of whom there were more than 1,000 examined over 4 studies), the presence of abdominal pain (LR+ 6.3, 95% CI 2.5-16.0), appearance of new incontinence (LR+ 4.6, 95% CI 2.8-7.6), back pain (LR+ 3.6, 95% CI 2.1-6.1), dysuria, frequency or both (LR+ range 2.2-2.8) were the most useful symptoms in detecting UTI.[18] There were doubts about whether these coefficients could be applied in practice. The data for each symptom came from different studies.

SR of Diagnostic test studies Ia

In the verbal stage there are other symptoms (cloudy or foul-smelling urine, haematuria, vomiting) which may also point to the presence of UTI in children, but are of little predictive power with a LR+ around 1.[18]

In the various studies included in the NICE CPG, these other verbal phase symptoms (cloudy or smelly urine, haematuria, vomiting) were of very low prevalence: less than 20%.[11]

Case series 3

Other considerations that the GDG took into account were related to the need to weigh the effectiveness of the clinical presentations for definitive diagnosis of UTI and its major clinical impact, as demonstrated in the SR, by calculating likelihood ratios for the different signs and symptoms alone or in combination, in the 2 age groups, such that the post-test odds of having a UTI from the initial clinical signs did not exceed 30% (even after the combination of various signs and symptoms).[18] The GDG concluded therefore that a suspected diagnosis would require confirmation by urine analysis.

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Evidence summary

Ia	In children aged 0-24 months, the presence of fever >39°C for more than 48 hours without apparent source of fever is the most useful clinical manifestation for identifying a UTI (LR+ 4.0, 95% CI 1.2-13.0).[18]
Ia	In children over 24 months of age, the presence of abdominal pain (LR+ 6.3, 95% CI 2.5-16.0), back pain (LR+ 3.6, 95% CI 2.1-6. 1), dysuria, polakiuria or both (LR+ range 2.2-2.8) and the emergence of new incontinence (LR+ 4.6, 95% CI 2.8-7.6) are the most useful symptoms for detecting UTI.[18]
Ia	All signs and symptoms present in children under 24 months of age had small changes in the probability of confirming UTI (LR+<5, LR->0.2).[18]
Ia	Most symptoms present in children over 24 months of age had small changes in the probability of confirming UTI (LR+<5, LR->0.2).[18]
3	Children in the pre-verbal phase had non-specific signs and symptoms (gastrointestinal symptoms, jaundice, irritability, foul-smelling urine, failure to thrive, food refusal, suprapubic pain, haematuria) that may indicate UTI.[11]
3	Children in the verbal phase had some symptoms (cloudy or foul-smelling urine, haematuria, vomiting) that may indicate UTI.[11]

Recommendations

A	Clinical suspicion of UTI in children from the clinical manifestations requires laboratory confirmation, due to its low discriminative ability.
A	In children under 24 months of age with fever without focus it is recommended to take a urine test to rule out UTI.
A	In children over 24 months old, with symptoms of abdominal or back pain, fever, dysuria, frequency or both, or the onset of incontinence it is recommended to take a urine test to confirm UTI.

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9. Biological diagnosis of UTI

9.1 Urine collection method

Key question:

- What is the method of choice for urine collection for the diagnosis of UTI?

Unlike for other age groups, in childhood it is usually considered necessary to confirm diagnosis of a urinary tract infection microbiologically.[9] A valid diagnosis of urinary tract infection (UTI) is essential to prevent too many or too few inappropriate diagnostic or therapeutic procedures. Therefore, collecting urine samples suitable for cultivation is very important.

The ideal urine collection method should be simple, valid, cost-effective and acceptable for children, families and carers. There are 2 methods used for urine collection in our environment: 'clean catch' for children who can control urination and an adhesive perineal bag for those who cannot.[128,129] However, these techniques involve some risk of contamination, especially the perineal bag, leading to false positive or uninterpretable urine cultures. This risk depends on the thoroughness of cleaning the perigenital area and, in the case of perineal bags, the frequency of device replacement and monitoring to remove the emitted urine as soon as possible. Some collection techniques used in other countries (e.g., sterile pads) are barely used in our environment.

When assessing the adequacy of a urine collection technique, both its diagnostic validity and the cost of any diagnostic errors incurred must be considered. Undiagnosed UTI will result in a therapeutic delay and a possible increased risk of kidney damage; whereas, UTI misdiagnosed due to urine contamination can initiate a series of inappropriate diagnostic and therapeutic procedures.

Suprapubic aspiration (SPA) is considered the reference urine collection technique,[12] but it is invasive, uncomfortable for the child, and depends largely on the ability of health workers and the bladder urine volume available. Bladder catheterisation is also invasive, is easier to perform than SPA and allows for the collection of small amounts of urine, but does not completely rule out the risk of contamination.[130] Both SPA and bladder catheterisation are routinely recommended as confirmatory tests for compromised patients who need immediate treatment.[9]

The criteria used for the interpretation of urine cultures have a major impact on the evaluation studies of diagnostic tests for urinary tract infection. Firstly, there is no absolute consensus for the microorganism count considered significant for each urine collection technique;[131] and secondly, the interpretation of mixed growths like contaminated urine is also heterogeneous. A urine culture result reported as contaminated leads to clinical uncertainty and a delay in diagnosis. While, in the evaluation of diagnostic tests, it distorts the evaluation of validity, as a large number of samples cannot be classified. To solve this problem, many studies choose to exclude or misclassify these samples, without providing sufficient information for us to adjust for their results.[132] In response to the question of which urine collection method is the most appropriate, the patient's clinical situation (the importance of quick diagnosis or treatment) and their ability to control urination should be taken into account. The validity, feasibility and acceptability of the various techniques available will be assessed for each circumstance.

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9.1.1 Diagnostic validity of a urine sample collected via clean catch

A SR included in the NICE CPG analysing data from 5 studies comparing clean catch with SPA showed acceptable diagnostic validity indicators: a sensitivity range of 75-100% and specificities of 57-100%. The weighted positive and negative likelihood ratios were 7.7 (95% CI 2.5-23.5) and 0.23 (95% CI 0.18-0.30), respectively.[11]

SR of diagnostic test studies II

Two studies with very few patients - one with 60 circumcised male infants and the other with 49 infants (22 boys and 27 girls) - found acceptable diagnostic accuracy indicators for clean catch over SPA (sns: 100% and 88.9%, spc: 97.3% and 95%).[133,134]

Diagnostic test studies II

One study comparing the diagnostic validity of samples collected by clean catch with catheterisation found a similar rate of false positives for the diagnosis of UTI in urine samples from uncircumcised boys in both methods, but with higher micro-organism counts in the clean catch method. However, this study did not use a reference technique[135]

Diagnostic test study III

9.1.2 Diagnostic validity of urine collected in a sample bag

A SR included in the NICE CPG analysed data from 3 studies evaluating the diagnostic validity of a urine samples from a collection bag. The first compared a urine collection bag with catheter urine collection in children under 5 years old (LR+ 5.5, LR- 0.24) and children up to age 11 (LR+ 3, 9, LR- 0.3). The other 2 studies included in the SR compared urine from a collection bag with urine collected via SPA, obtaining very different LR- results with: LR+ 7.7, LR- 0.04 and LR+ 5.4 LR- 0.55. The SR concluded that there were insufficient data to draw conclusions about the use of urine collection bags.[11]

SR of diagnostic test studies II

A study included in the NICE CPG compared the contamination risk for urine samples collected by bag with samples from catheters. The study concluded that the urine collection bag is associated with an increased risk of contamination (OR 13.3, 95% CI 11.1-16.7).[11]

Cohort study 2+

A study included in the NICE CPG compared the contamination rate for urine samples collected by bag versus those collected by clean catch in children under 2 years old. The study observed a higher rate of contamination in the urine from collection bag samples (11/23 contaminated samples versus 0/23).[11]

Case series study 3

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A study included in the NICE CPG compared the validity of a urine sample for dipstick analysis collected by a bag and by catheter. The results were LR+ 2.24, LR- 0.24 for the bag and LR+ 23.67, LR- 0.30 when collected by catheter.[11]

Diagnostic test study III

A study included in the NICE CPG compared dipstick test results for urine samples collected by bag with those from bladder catheterisation. The leukocyte esterase results were LR+ 4.75 and LR- 0.29 by bag and LR+ 14.33 and LR- 0.15 by catheter. For nitrite, the results were LR+ 12.5 and LR- 0.76 by bag and LR+ 0.77 and LR- 0.58 by catheter.[11]

Diagnostic test study III

A study in Spain compared the utility of urine culture analysis sampling by perineal bag with that collected by bladder catheterisation or SPA, as a method of diagnosing urinary tract infection in children without bladder control. The study found a high prevalence of false positives 36/42 (86%), with a PPV of 14% for urine collection by perineal bag.[129]

Diagnostic test study III

One study estimated the prevalence of false positives in urine samples collected by bag with SPA in children under 24 months admitted with suspected UTI. The study found a high prevalence of false positives (73.7%) for the diagnosis of UTI in the urine samples collected by bag than with SPA.[136]

Diagnostic test study III

One study estimated the validity of urine samples for culture analysis collected by bag compared to those by catheterisation in children under 3 years of age with fever of unknown origin. The study found a high percentage of false negatives (29%) for the diagnosis of UTI from the urine bag samples. This finding, at variance with that observed in other studies, would call into question the conclusion that negative urine culture results from samples collected by bag rule out UTI.[137]

Diagnostic test study III

One study assessed the validity of the urine dipstick analysis for samples collected by bag and catheterisation for the diagnosis of UTI in children under 2 years old. The study found that leukocyturia results were not valid in urine collected by bag.[138]

Diagnostic test study III

9.1.3 Diagnostic validity of a urine sample collected by sterile pads

A SR included in the NICE CPG analysed data from 4 studies of the diagnostic accuracy of urine samples collected using sterile pads. Three of the studies compared samples collected by pad and by bag. The fourth study compared samples collected by pad and by SPA. The SR concluded that there were insufficient data to draw conclusions on using urine collection pads.[11]

SR of diagnostic test studies II

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A study included in the NICE CPG conducted in Britain found that contamination rates were reduced for pads kept on for less than 30 minutes.[11]	RCT 1+
A study investigated the views of families on 3 methods of urine collection in infants: clean catch, bag and pad. The families preferred the pad, followed by the bag (more distressing) and finally by clean catch (more difficult).[11]	Observational study 3

9.1.4 Other comparisons

A SR included in the NICE CPG included a study comparing the results of urine culture samples from early stream bladder catheterisation with the results from late stream samples, which showed strong agreement.[11]	SR of diagnostic test studies II
A cohort study compared the success rate of various brands of collection bags in the UK in terms of applicability and operation.[11]	Cohort study 2+
A study in Israel compared the levels of pain using a visual analogue scale for catheterised children and those undergoing SPA. The study concluded that the pain associated with SPA was greater than that associated with bladder catheterisation.[11]	RCT 1+
Three studies evaluated the performance of conventional SPA with ultrasound-guided SPA, and concluded that ultrasound checking for the presence of urine increased the success rate.[11]	RCTs 1+
Two clinical trials with methodological limitations had mixed results when comparing the success of SPA and bladder catheterisation for collecting urine and the volume obtained. One of the tests[139] concluded that catheterisation supplied more volume of urine and on more occasions, while the other test[140] found no difference in the effectiveness of the two techniques.	RCTs 1-

When making recommendations, the GDG took into account the limitations in our country regarding the possible application and widespread use of some of the methods included in the volume of evidence for collecting urine. For example, sterile pads are not used here, although it would be useful to evaluate their efficacy with specific studies. SPA cannot be performed routinely in primary care and ultrasound guidance is also not usually available. Also, catheterisation cannot always be performed in primary care at all times, even though the technique does not require special hospital environment resources In the daily practice in primary care it is not in widespread use. Similarly, urine collection by an invasive method should be assessed when there are circumstances that might prevent the sample to be processed within the recommended time and will therefore run a high risk of contamination.

Further aspects that the GDG also took into account are related to the impact of the urine collection technique on the patient and its validity. False positives in diagnosis have a major impact on healthcare resources (on hospitalisation, drugs, imaging studies, etc), whereas febrile UTI left untreated due to false negatives or a delay in diagnosis may be responsible for permanent kidney damage. In short, contaminated urine cultures cause uncertainty and delay in diagnosis.

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The urine collection method has shown a direct relationship with the percentage of false positives, false negatives and contaminated urine as well as having an impact on the validity of urine profile parameters. The use of non-sterile techniques involves a greater risk of false positives and contaminated urine, and the use of safer diagnostic methods in children who cannot control urination involves the use of more aggressive methods. There are few studies evaluating the pain and immediate side effects of these techniques, and there are no studies evaluating the long-term consequences of diagnostic methods that may need to be used several times before the patient has control over urination.

Evidence summary

II	Clean catch urine samples give acceptable diagnostic validity indicators when compared with samples from suprapubic puncture (SPA).[11,133,134]
2+/3	Urine bag samples are at high risk of contamination compared with those obtained by bladder catheterisation or clean catch.[11]
III	Urine collection bag samples have a high prevalence of false positives (86% and 73.7%).[129,136]
III	Dipstick parameter validity depends on the urine collection technique. Urine samples collected by perineal bag have a lower validity than those of bladder catheterisation.[11,138]
1+	Ultrasound-guided SPA is more successful than conventional.[11]
1+	The pain associated with SPA is greater than that associated with bladder catheterisation[11]
II	There are insufficient data on the diagnostic accuracy of urine collection using sterile pads.[11]

Recommendations

B	For children who can control urination a midstream clean catch urine sample is recommended.
C	For children who cannot control urination that require immediate diagnosis and/or treatment, it is recommended to use a collection technique that minimises the risk of contamination (SPA or bladder catheterisation). The choice of technique should be subject to the level of training and resources of the health care centre.
C	For children who cannot control urination that do not require immediate diagnosis and/or treatment, use a well performed non-invasive urine collection technique (perineal bag or clean catch).
D	If the analysis of urine collected by a non-sterile technique (perineal bag) is contaminated, it is recommended to confirm it by taking a repeat sample using techniques that minimise the risk of contamination. The choice of technique will depend on the patient's clinical status, level of collection training and health care setting resources.
A	It is recommended to use ultrasound, if available, to improve the effectiveness of suprapubic aspiration, when this is chosen.
√	It is recommended that patient care points that offer suprapubic aspiration should have ultrasound.

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9.2 Preserving and transporting urine samples

Key question:

• How should a urine sample be preserved and transported?

Urine is a good medium for bacterial growth, so urine samples are easily contaminated. It is well known that a delay in processing culture samples allows the multiplication of contaminating flora, which affect the validity of the results.[141,142] Therefore, urine should be processed as soon as possible to prevent this problem. However, for outpatients it is difficult to prevent a delay between collecting and analysing the urine. To prevent contamination, the sample can be treated physically (via refrigeration) or chemically (by adding preservatives).[143,144] However, there are doubts about whether the use of these means influences the quality of the samples. Therefore, when interpreting a urinalysis the conditions under which the sample was collected, stored and transported should be taken into account, as they may affect the validity of both the cultivation and profile parameters (with urinary dipstick or microscopic examination).

It is therefore important to establish the recommended storage and transportation conditions for urine specimens collected for culture, with consideration of the delay time allowed, the usefulness of various physical and chemical techniques of preservation, as well as the consequences that these factors have on the interpretation of results, for both urine cultures and urinary profile parameters.

Findings taken from the NICE CPG[11] from observational studies are summarised below. These are mostly using adult urine samples collected by clean catch, or increasing dilutions of different bacteriological strains, under different preservation conditions.

Two studies showed that both refrigeration and different commercial chemical preservative preparations keep bacterial growth stable during the first 24 hours; however, for some microorganisms, decreased growth was observed with chemical preservatives when urine was stored for more than 24 hours.[11]	Observational studies 2+/3
One study observed no differences in the isolates and culture results from urine samples collected and maintained by chemical preservatives with those collected and transported by a conventional system (with or without cooling) for a period less than 24 hours.[11]	Diagnostic test study III
Three studies showed that urine samples kept under refrigeration or chemical preservatives for 24 hours produced a small percentage of false positives or false negatives.[11]	Observational studies 3/3/III
Two studies showed that chemical preservatives do not seem to interfere with the results of the various urinary profile parameters. The first study showed concordant results for glucose, ketones, bilirubin and blood in urine maintained with and without preservatives. The second study evaluated whether the preservatives in the urine sample interfere with dipstick results: in all cases, the test strip detected the presence or absence of leukocytes and nitrites.[11]	Observational studies III/2+

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Two studies evaluating the effect of the passage of time on bacterial multiplication in urine samples stored at room temperature without chemical preservatives, showed that urine samples had significantly increased bacterial growth after more than 4 hours delay in performing the culture analysis.[11]	Observational studies 3
Two studies assessed the evolution of the growth of various microorganisms in sterile urine samples stored at different temperatures. For one study, a progressive increase in the growth of bacteria was seen in samples incubated at room temperature (25°C), but there were hardly any changes in samples stored at 4°C. The second study showed no change in bacterial growth in urine preserved for more than 24 hours at 0.5°C, 5°C and 10°C, but at temperatures higher than 15°C progressive growth was observed.[11]	Observational studies 3
One study evaluated the influence of urine volume stored in tubes containing chemical preservatives, and observed that the preservative had a toxic effect on various microorganisms for low volumes of urine.[11]	Observational study 3

As well as this evidence from the NICE CPG,[11] the following 2 studies with methodological limitations were found.

A study assessing the effect of different tubes and preservatives on the dipstick urinary profile parameters and flow cytometry found that urine samples could be transported at 20°C the same day of collection if preservatives were used, with minimal changes in urinary parameters, except for nitrite and glucose. Flow cytometry with UF-100 seemed sensitive to undissolved remains of the preservative (interpreted as red blood cells). The limitations of the study meant any difference between the tubes and preservatives used could not be established.[145]	Diagnostic test study III
The second study evaluated the stability of the urine samples held at room temperature without preservatives at various time intervals (0, 2, 4 and 6 hours). It found that urine samples could be stored at room temperature for 2 hours without preservatives with no significant changes in automated microscopy results (flow cytometry or particle analysis). After 2 hours of storage, a deterioration in the quality of the samples was noted, with lysis of erythrocytes, leukocytes, casts and excess bacterial growth, although this was not statistically significant until after 6 hours of sample collection (P<0.05).[146]	Diagnostic test study III

There were other considerations regarding the application and generalization of the evidence to Spain that the GDG took into account when making the recommendations. The GDG considered that the evidence reviewed was generally applicable in Spain, for both the samples used (although many of them were from adults) and the physical and chemical techniques studied and the results evaluated. However, it must be noted that the common practice in Spain is to refrigerate urine samples to preserve them for analysis. The use of preservatives would be justified only in exceptional circumstances, e.g. sampling of outpatients, when refrigeration, delivery and processing cannot be done within 24 hours.

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Evidence summary

2+/ 3	Both refrigeration (at 2- 8°C) and the addition of various commercial chemical preservative preparations inhibit bacterial growth during the first 24 hours.[11]
3/ III	In urine samples preserved by refrigeration (2-8°C) or chemical preservatives, there were no differences found in the isolates and antimicrobial sensitivity for the first 24 hours.[11]
III[11,145]/2+11	There was some inconsistency in the urinary profile parameter results for urine samples with preservatives. One study showed that chemical preservatives hardly changed the urinary profile parameters results of glucose, ketones, bilirubin and blood, while another study found similarly for the parameters leukocytes and nitrites.[11] However, a third study showed changes in the parameters glucose and nitrites in urine samples kept with preservatives.[145]
3	Urine samples collected and stored at room temperature showed significant bacterial growth after 4 hours.[11]
3	The use of standard amounts of preservatives in small quantities of urine samples may inhibit bacterial growth.[11]

Recommendations

C	It is recommended to process urine samples within 4 hours so they are not affected by bacterial growth.
C	If it is not possible to start the urine culture analysis within 4 hours, it is recommended to refrigerate the urine to be used to detect bacteriuria immediately after collection.
C	When refrigeration is not possible and the urine is to be processed between 4 and 24 hours after collection, preservatives may be employed as major delays can lead to bacterial growth.
√	It is recommended not to consider the results of some urinary profile parameters (nitrite and glucose) from urine with chemical preservatives added, as they may not be valid.
√	When using chemical preservatives, ensure the minimum volume of urine sample recommended by the manufacturer is taken.

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9.3 Diagnostic tests in urine

Key question:

- What is the most valid urine test for diagnosing UTI in children?

Rapid diagnosis of UTI in children is critical for early treatment to improve patient prognosis.[147] However, often clinical symptoms of UTI in infancy are not sufficiently clear for an initial diagnosis,[46,148] so other diagnostic tests need to be done while awaiting urine culture results.

The degree of validity of diagnostic tests will condition our attitude: if a valid diagnostic test is positive, it may justify starting empirical therapy in compromised patients or those with clinical symptoms highly suggestive of UTI. By contrast, it would seem advisable to await the outcome of the culture test for patients without clinical symptoms or those with non-specific or general symptoms, or where the diagnostic test is not valid enough,. Between the two scenarios, there are a number of combinations of clinical and/or analytical probability, leading to diagnostic uncertainty unlikely to help in decision-making.

Diagnostic tests for UTI are based mainly on examining a urine sample with reagents or microscopically.[130] The most used method is insertion of a dipstick into urine. The dipstick has a series of dry reagents arranged along it which react by changing colour if certain components are present in the urine: leukocytes (leukocyte esterase), nitrites, blood and proteins. Microscopic examination consists of identifying leukocytes or bacteria in the urine; however, it is less used, as it more time-consuming and requires equipment availability and adequate training. There are other less commonly used tests, such as the semi-quantitative culture technique, which allows direct seeding of the urine in clinics with no laboratory infrastructure, but results take several hours at least.

In the diagnosis of UTI, the results of the different parameters can be interpreted individually or together (in series or in parallel). Depending on the results, the probability that a given patient has UTI is estimated; however, for children at least, the diagnosis is based on urine culture.[9]

9.3.1 Diagnostic accuracy of the dipstick reactive strip

Findings taken from the NICE CPG[11] from a SR which includes data from 38 studies evaluating the results of dipstick test strips for diagnosing UTI are summarised below.

A SR with data from 23 studies using culture cultivation and 14 studies using a combination of culture cultivation and microscopy showed nitrites with a pooled LR+ 15.9 (95% CI 10.7-23.7) and pooled LR- 0.51 (95% CI 0.43-0.60), while leukocyte esterase had a pooled LR+ 5.5 (95% CI 4.1-7.3) and LR- 0.26 (95% CI 0.18-0.36). For both parameters there was significant heterogeneity between studies with methodological flaws in some of them.[11]

SR of diagnostic test studies II

The same SR identified 9 studies analysing the simultaneous presence of nitrite and leukocyte esterase. The presence of both in urine showed a pooled LR+ 28.2 (95% CI 15.5-43.4) and pooled LR- 0.37 (95% CI 0.26-0.52), while the presence of one or the other, analysed from data from 15 studies, showed a pooled LR+ 6.1 (95%CI 4.3-8.6) and pooled LR- 0.20 (95% CI 0.16-0.26).[11]

SR of diagnostic test studies II

Most of these views have ceased since the publication of the Clinical Practice Guideline, and is rarely has not been reviewed

This SR also analysed the diagnostic value of the detection of proteins, glucose and blood, from 2, 4 and 1 studies, respectively. None of these indicators were useful for the diagnosis of UTI.[11]

SR of diagnostic test studies II

A meta-analysis based on data from 2 studies, totalling a small number of urine samples with UTI (n=62), showed that the simultaneous presence or absence of nitrite and leukocytes in urine had better LR+ and LR- in children older than 1-2 years old, although only the LR+ difference was statistically significant. The presence of nitrite and leukocytes in urine in patients aged over 1-2 years had LR+ 28.79 (95% CI 13.92-59.52) and in children under 1-2 years LR+ 7.74 (95% 1.88-31.93). The absence of nitrite and leukocytes in urine showed in patients older than 1-2 years LR- 0.19 (95% CI 0.09-0.40), and in children under 1-2 years, LR- 0.32 (95% CI 0.16-0.63).[11]

SR of diagnostic test studies II

In addition to studies taken from the NICE guide,[11] we incorporate data from a SR[149] evaluating the diagnostic accuracy of different rapid tests in urine, microscopy (bacteriuria with and without Gram-stain and pyuria) and dipstick (nitrite and leukocyte esterase), using data from 95 studies with urine culture as the reference standard (95,703 under 18 years of age and 94,664 urine samples). The objectives of this study were to establish whether the rapid test in urine was sensitive enough to avoid having to perform a urine culture when the results were negative and to compare the accuracy of test strips with the microscopic analysis of urine.

The SR was based on data from 15 studies (13 of them included in the previous SR) of 6,492 patients and 13 studies (8 of them included in the previous SR) of 5,751 patients. It estimated similar values to those described previously for sns and spc for the various dipstick parameters. The presence of leukocyte esterase or nitrite had an estimated value for sns of 0.88 (95% CI 0.82-0.91) and spc of 0.79 (95% CI 0.69-0.87), (LR+ 4.2 and LR- 0.15). The presence of both parameters on the dipstick showed an estimated value of sns of 0.45 (95% CI 0.30-0.61) and spc of 0.98 (95% CI 0.96-0.99), (LR+ 22.5 and LR- 0.56).[149]

SR of diagnostic test studies II

9.3.2 Diagnostic accuracy of microscopy

Data from a SR of 27 studies comparing microscopy with culture, or culture and automatic microscopy, was included in the NICE CPG[11] and is shown below.

The SR data analysed from 27 studies for the presence and absence of pyuria gave pooled estimates of LR+ 5.9 (95% CI 4.1-8.5) and LR- 0.27 (95% CI 0.20-0.37). For bacteriuria, from data analysed over 22 studies, the results were LR+ 14.7 (95% CI 8.7-24.9) and LR- 0.19 (95% CI 0.14-0.24). For both parameters, there was significant heterogeneity between studies with methodological flaws in many of them.[11]

SR of diagnostic test studies II

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The simultaneous presence of pyuria and bacteriuria analysed from data from 8 studies in the SR gave pooled values of LR+ 37.0 (95% CI 10.9-125.9) and LR- 0.21 (95% CI 0.13-0.36); while the presence of pyuria or bacteriuria gave pooled values of LR+ 4.2 (95% CI 2.3-7.6) and LR- 0.11 (95% CI 0.05-0.23).[11]

SR of diagnostic test studies II

In addition to studies taken from the NICE guide,[11] we incorporate data from a SR[149] evaluating the diagnostic accuracy of different rapid tests in urine, microscopy (bacteriuria with and without Gram-stain and pyuria) and dipstick (nitrite and leukocyte esterase), using data from 95 studies with urine culture as the reference standard (95,703 under 18 years of age and 94,664 urine samples). The objectives of this study were to establish whether the rapid test in urine was sensitive enough to avoid having to perform a urine culture when the results were negative and to compare the accuracy of test strips with the microscopic analysis of urine.

The SR showed that the most accurate rapid urine test is detection of bacteriuria by Gram-stain microscopy: sns 0.91 (95% CI 0.80-0.96), spc 0.96 (95% CI 0.92-0.98), (LR+ 22.3 and LR- 0.09). The detection of leukocytes by microscopy [sns 0.74 (95% CI 0.67-0.80), spc 0.86 (95% CI 0.82-0.90), (LR+ 5.3 and LR- 0.3)] is as accurate as the leukocyte esterase detection by dipstick [sns 0.79 (95% CI 0.73-0.84), spc 0.87 (95% CI 0.80-0.92), (LR+ 6.0 and LR- 0.24)].

SR of diagnostic test studies II

The SR therefore concluded that no rapid test is sensitive enough to identify all children with UTI without collecting a urine culture, since the detection of bacteriuria by microscopy, despite being the most accurate test, had an estimated false negative rate of 9%. Nevertheless, the authors of the SR believed that screening for bacteriuria by Gram-stain microscopy is the best single test and, if available locally and the results are reported quickly, is the only test that would be needed to provide guidance about empirical antibiotic therapy.[149]

9.3.3 Comparison of dipstick and microscopy by age

The NICE CPG[11] re-analysis of the studies assessing dipstick and microscopy by age group (younger and older than 2 years) is shown below, with the aim of establishing the diagnostic validity by patient age.

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Microscopy (pyuria >10 WBC per field with moderate bacteriuria) had better LR+ results in children under 2 years than over 2 years old: LR+ 15.6 (95% CI 4.16-58.44) and LR+ 10.84 (95% CI 5.95-19.75), respectively.

The dipstick (positive leukocytes and nitrite), however, had better results for LR+ in children over 2 years: LR+ 27.1 (95% CI 11.44-64.21) and LR+ 6.24 (95% CI 1.14-34.22), respectively.

Both methods (microscopy with pyuria >10 WBC per field, along with moderate bacteriuria; and positive leukocyte and nitrite with dipstick) had better LR- results in children over 2 years than under 2 years: LR- 0.51 (95% CI 0.35-0.73), LR- 0.17 (95% CI 0.07-0.41) and LR- 0.66 (95% CI 0.44-0.97) and LR- 0.31 (95% CI 0.13-0.71), respectively.

For children under 2 years there is little difference in the LR- results between microscopy (pyuria >5 WBC per field with little bacteriuria) and dipstick (positive leukocytes and nitrite): LR- 0.27 (95% CI 0.07-0.99) and LR- 0.31 (95% CI 0.13-0.71), respectively.

However, all estimates have very wide and overlapping ranges, suggesting that they rely on small samples; therefore, the comparison is significant only for LR+ with the dipstick in children younger and older than 2 years (LR+ 6.24, 95% CI 1.14-34.22) and (LR+ 27.1, 95% CI 11.44-64.21), respectively.[11]

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9.3.4 Diagnostic accuracy of flow cytometry

There were 10 studies found evaluating the validity of different flow cytometry devices (Sysmex UF-100 and UF-1000, IRIS IQ ELITE and BACSyS-40i) on urine samples from the general population, including some samples from paediatric patients. No study describes the results for children separately, and some have significant methodological limitations. Overall, the validity of the various flow cytometry parameters is no better than for microscopic examination or the dipstick. Although several studies have suggested that the absence of bacteriuria and leukocytes in cytometry would be a sufficiently sensitive result to exclude the diagnosis of UTI, the observed results do not allow a reliable estimate of the sensitivity applicable to children. Therefore, it is too risky to decide whether or not to perform urine culture based on these results, although it might be useful to delay the start of antibiotic treatment.[150-159]

Diagnostic test studies III

9.3.5 Other comparisons

A SR of 5 different studies included in the NICE CPG assessed the validity of the combination of different dipstick parameters against urine culture as a reference standard. Four studies evaluated a different combination of parameters: nitrites, blood or positive protein; nitrites, blood or positive LE; nitrites, blood and positive LE; nitrites, LE or positive protein; and 2 studies evaluating a combination of nitrites, LE and positive protein. The SR concluded that the information was insufficient to draw conclusions, but that further studies were needed in the evaluation of the combination of nitrites, LE and positive protein. This combination gave results of sns 96%, spc 99%, LR+ 69.2 and LR- 0.04 in one study, and sns 89%, spc 72%, LR+ 3.1 and LR- 0.17 in the second.[11]

SR of diagnostic test studies II

A SR of 8 studies included in the NICE CPG compared the validity of a culture plate for the diagnosis of UTI with a conventional culture. Most of the studies included in the SR have a number of methodological limitations (population not representative, no information on whether it was blind, no detailed information on the reference standard or on the test index). The culture plate gives a pooled value for LR+ of 14.6 (95% CI 6.7-31.8) and pooled LR- of 0.23 (95% CI 0.14-0.39). The results of individual studies showed significant heterogeneity for both LR+ and LR- (P<0.001).[11]

SR of diagnostic test studies II

A study included in the NICE CPG assessed culture plate performance over 5 primary care centres, in daily clinical practice conditions and depending on the incubation time (24 hours vs 48 hours). The study gave results of sns 73% (95% CI 66-80) and spc 94% (95% CI 88-98) after 24 hours of incubation. The accuracy of the culture plate was worse when performed in daily practice conditions than under experimental conditions.[11]

Diagnostic test studies II

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Additional considerations taken into account by the GDG when making their recommendations concerned the applicability of the volume of evidence and its relevance and impact. Although the diagnostic tests evaluated, and the patients from which the samples were taken were comparable and representative of those found in Spain, there may be differences between the type of samples analysed in the studies evaluated and those used in clinical practice here (most were collected using non-sterile techniques). This may lead to changes in the validity of the parameters and therefore in pre-and post-test probabilities; therefore, the resulting probability estimates must be adapted to clinical scenarios here.

Regarding the relevance of the findings on the lesser accuracy of the dipstick in children under 1-2 years, the group took into account the fact that it was based on the results of 2 small studies whose findings could be more related to the quality of the urine samples than to age. The same may have happened in the re-analysis by the NICE CPG[11] when comparing dipstick and microscopy.

For the culture plate, the GDG decided not to include the reviewed evidence in the recommendations because this test is not used in our clinical practice and because it did not replace the rapid tests nor the reference urine culture.

The GDG therefore considered that the usefulness of available diagnostic tests was contingent on the consideration of the pre-test probability or prevalence of UTI in each clinical setting. Any decision on the diagnosis of UTI, on whether or not urine culture is performed and whether empirical antibiotic treatment is started should be tailored to the patient's clinical situation.

Likewise, the tests results may be negative, despite the patient's clinical symptoms. In that case the clinical data would need to be reassessed, in case any diagnostic test needed repeating or a therapeutic decision made based on the patient's clinical situation.

Evidence summary

II	For a urine sample, the presence of nitrites by dipstick increases the likelihood of a positive culture being found (LR+ >10).[11]
II	The absence of leukocytes by dipstick reduces the likelihood of a positive culture in the urine sample (LR- close to 0.20).[11]
II	Both parameters (nitrite and leukocytes) detected by urine dipstick further increases the likelihood of a positive culture in the urine sample (LR+ >20), but does not provide absolute diagnostic certainty.[11,149]
II	Neither parameter (nitrites or leukocytes) being detected by dipstick further decreases the likelihood of a positive culture in the urine sample, but does not provide diagnostic certainty (LR- ≤0.20).[11,149]
II	The presence or absence of bacteriuria on microscopic examination increases or decreases, respectively, the likelihood of a positive culture in the urine sample (LR+ >10 and LR- <0.20).[11]
II	The absence of leukocytes on microscopic examination reduces the likelihood of a positive culture in the urine sample (LR- <0.30).[11]
II	Both parameters (bacteriuria and leukocytes) detected by microscopic examination of a urine sample increase the likelihood of there being a positive culture (LR+ >20).[11]

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II	Neither parameter (bacteriuria or leukocytes) detected by microscopic examination of a urine sample decreases the likelihood of there being a positive culture (CPN about 0.10).[11]
II	The dipstick (leukocyturia plus nitrites) has a better LR+ in children over 2 years of age than for children under 2 years: LR+ 27.1 (95% CI 11.44-64.21) compared with LR+ 6.24 (95% CI 1.14-34.22).[11]
II	There were no differences in the determination of pyuria by dipstick or microscopy. The determination of bacteriuria by Gram-stain microscopy is the best isolated test, and can also guide the selection of antibiotic therapy.[149]
III	There is insufficient information to establish the validity and usefulness of flow cytometry for diagnosing UTI in childhood. However, it is hoped that the different parameters have the same validity indicators to those of equivalent dipstick or microscopic examination parameters. The absence of bacteriuria and pyuria in a flow cytometry examination implies a low risk of UTI, although this cannot be completely ruled out.[150-159]

Recommendations

B	It is recommended to perform an urgent Gram-stain microscopic examination of urine and urine culture on infants under 3 months with suspected UTI.
B	It is recommended to perform a urine microscopic examination or, failing that, a dipstick test and urine culture on patients with suspected UTI who are younger than 2 years or who cannot control urination. If there is a strong clinical suspicion of UTI or the patient is at risk of severe disease, these tests must be performed urgently.
B	For patients younger than 2 years or who cannot control urination, with suspected UTI, it is recommended to start antibiotic treatment after collecting the urine culture sample if they have bacteriuria or positive nitrites in a reliable urine sample (collected by SPA or catheter).
B	For infants at risk of severe disease (with fever of unknown origin) younger than 2 years or who cannot control urination, it is recommended to start antibiotic treatment after collecting the urine culture sample if they have bacteriuria or positive nitrites or leukocyturia in a reliable urine sample (collected by SPA or catheter).
B	In patients older than 2 years with suspected UTI who can control urination, it is recommended to perform a urine dipstick test. Perform a microscopic examination of urine, if available, only in dubious cases.
B	In patients older than 2 years with a high clinical suspicion of UTI (specific symptoms with the presence of nitrites or bacteriuria, with or without leukocytes), it is recommended to start empirical antibiotic treatment after collecting the urine culture.
B	In patients older than 2 years, with leukocytes only in urine, it is recommended to perform a urine culture, and consider starting antibiotic treatment depending on the likelihood of symptoms and the patient's clinical situation.
B	Do not treat or perform a urine culture on patients older than 2 years if no leukocytes or nitrites are found in the urine sample and clinical features are non-specific.

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√	It is recommended to confirm UTI by urine culture when available. It is especially necessary in the following cases: • Children under 2 years or those who cannot control urination. • Where there is suspicion of upper tract UTI. • In any patient at risk of serious illness. • In any patient, when the dipstick results are inconclusive or do not agree with the clinical examination.

9.4 Localisation of UTI

Key question:

- Is there any clinical finding or laboratory test to locate a suspected or confirmed UTI in children?

Locating urinary tract infection (UTI) in children has therapeutic and prognostic implications. Scintigraphy is considered the "gold standard" or reference standard in the diagnosis of APN.

Given these considerations, the diagnostic validity of certain clinical signs and symptoms (fever and its duration, vomiting, diarrhoea, abdominal pain, food refusal, irritability) as well as blood and urine biochemical data (CRP, PCT, ESR, leukocytosis, PMN, Osm_u, MA_u, NAG_u, low molecular weight proteinuria, interleukins) are evaluated for the diagnosis of APN, with reference to the results of renal scintigraphy (DMSA).

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9.4.1 Diagnostic accuracy of clinical signs and symptoms

The NICE CPG includes data from a SR analysing the diagnostic accuracy of different clinical variables vs DMSA from 5 studies in children. SR of diagnostic test studies II

Two of them compared the presence of fever with DMSA for the diagnosis of APN, with unsatisfactory results: fever ≥39.1°C (sns 64% and spc 40%, LR+ 1.1 and LR- 0.89) and fever ≥38ºC (sns 87% spc 64%, LR+ 2.4 and LR- 0.23).

Another 2 studies evaluated clinical symptoms of APN (back pain, chills, nausea, vomiting, fever or lumbar contracture), with results that are not ideal but that show high specificity (sns 57% spc 100%, LR+ 4.5 and LR- 0.49), (sns 71%, spc 100%, and LR+ 26.6 LR- 0.319), respectively.

Finally, one study analysed physical examination signs and altered laboratory variables together (leukocytosis, band neutrophils, urinalysis), whichi gave very high sensitivity (sns 98% spc 33%, LR+ 1.5 and LR- 0.09).[11]

In addition to the results included in the NICE CPG, 11 studies were found of diagnostic tests that evaluated the validity of the presence of various clinical signs and symptoms for the diagnosis of APN. The results of the different studies are not satisfactory but are summarised below.

One study showed that the duration of fever until the start of treatment was significantly associated with acute damage in DMSA, such that fever in patients with acute injury lasted 5.11 + 3.17 days vs 2.67 + 1.93 days in patients without acute injury (OR 1.35, *P*=0.001).[160] Diagnostic test study III

One study showed an increased risk of abnormalities in DMSA with a duration of fever until the start of treatment ≥48 hours (OR 4.93, 95% CI 1.00-24.23), treatment response time (≥24h) (OR 6.17, 95% CI 1.01-37.85) and fever (≥39°C) (OR 8.09, 95% CI 1.85-35.39).[161] Diagnostic test study III

One study showed a statistically non significant increased risk of abnormalities in DMSA with a duration of fever to onset of treatment ≥48h (OR 2.53, 95% CI 0.82-7.75).[162] Diagnostic test study III

One study found significant differences in the duration of fever before hospitalisation (2.57±1.98 days vs 1.80±1.60 days, P<0.001) and time to resolution of fever (2.46±1.84 vs 1.40±1.51, *P*=0.001) between patients with and without APN in DMSA, but found no differences between groups regarding the presence of fever (>38.5°C; *P*=0.979).[163] Diagnostic test study III

Another study found significant differences in the duration of fever prior to treatment in patients with acute damage in DMSA compared with those with a normal DMSA (67±39.6 hours vs 44±40.7 hours, P=0.035) but found no differences in the maximum temperature between the groups.[164] Diagnostic test study III

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One study found differences only in the presence of diarrhoea (P=0.038) between patients with a positive and those with a negative DMSA. The study showed no significant differences for any of the other clinical variables (vomiting, irritability, neurological symptoms), including the presence of fever (≥38°C; *P*=0.114).[17]

Diagnostic test study II

Three studies found no differences for the different clinical variables studied (T ≥38.5°C and duration of fever[165]; T ≥38°C, vomiting and/or diarrhoea, decreased appetite[166]; and T ≥38.5°C, abdominal pain, vomiting[167]) for patients with APN and patients without abnormalities in the DMSA.

Diagnostic test studies II[165],[166]/ III[167]

Two studies[168,169] showed high sensitivity for the presence of fever.

For T >38.5°C, one study had sns values of 86% (95% CI 72-93) and spc values of 75% (95% CI 59-86); (LR+ 3.4, 95% CI 1.9-6.0) and (LR- 0.19, 95% CI 0.09-0.41).[168]

For T ≥ 38°C, the second study had sns values of 100% (95% CI 82-100) and spc values of 53% (95% CI 0.3-0.73), (LR+ 2.12, 95% CI 1.23-3.52) and (LR- 0).[169]

Diagnostic test studies II[168]/III[169]

9.4.2 Diagnostic accuracy of blood analysis parameters (CRP and PCT)

The NICE CPG compared the diagnostic validity of CRP (with different cut-off points) with DMSA, based on data from 7 studies included in a SR.

In 3 studies, CRP concentrations of 20 mg/L showed sns values of >85%, but with spc values of 19-60%; LR+ 1.2-2.2 and LR- 0.18-0.23. In the other 3 studies, CRP concentrations of 200-880 mg/L gave sns values of 64-70% and spc values of 55-68%; LR+ 1.5-2.0 and LR- 0.53-0.58. Finally, in one study, concentrations of CRP of 20μg/L showed sns values of 14% and spc of 100%, LR- 0.86.[11]

SR of diagnostic test studies II

In addition to the SR studies, the NICE CPG identified another 4 studies that evaluated the diagnostic accuracy of different analytical parameters in blood vs DMSA. Their findings are summarised below.

A study in paediatric patients with moderate to severe injury by DMSA showed that high CRP levels correlated with the severity of renal damage in DMSA in the acute phase.

CRP concentrations of 20 mg/L and 50 mg/L had sns values of 94% and 74%, spc values of 32% and 77%, LR+ values of 1.4 and 3.2 and LR- values of 0.19 and 0.34, respectively.[11]

Diagnostic test study II

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

A study evaluating the validity of CRP for predicting renal damage compared with DMSA showed that CRP is correlated with the severity of renal injury by DMSA (P=0.032). For the prediction of kidney damage, CRP concentrations >10 mg/L had values for sns of 100% and 26% for spc, LR+ 1.4 and LR- 0.[11]	Diagnostic test study II
Two recent studies assessed the validity of CRP for the location of UTI vs DMSA; neither study provided data for the calculation of sns or spc. In the first study, CRP levels >20 mg/L showed values of 94% sns and 58% spc; LR+ 2.2 and LR- 0.1. In the second study, CRP levels >20 mg/L had values of 100% sns and 19% spc, LR+ 1.2 and LR- 0.[11]	Diagnostic test study III

In addition to the NICE CPG studies, 12 studies were found in paediatric patients with UTI evaluating the diagnostic validity of CRP at different cut-off points. One of them also evaluated the joint diagnostic validity of CRP and PCT. Finally, a meta-analysis evaluating the diagnostic value of PCT was found. Their findings are summarised below.

Two studies showed LR+ values >5: the first for CRP ≥70 mg/L and the second for CRP > 40 mg/L. The first study[170] had sns 83% (95% CI 80-86) and spc 88% (95% CI 85-91); LR+ 6.9 and LR- 0.19. The second study[171] had sns 80% (95% CI 66-90) and spc 91% (95% 77-97); LR+ 8.8 (95% CI 3-27) and LR- 0.22 (95% CI 0.11-0.4).	Diagnostic test studies II
Six studies had LR+ values <5 and LR- <0.2 for CRP levels >0.5 mg/L,[17] CRP levels ≥18.5 mg/L,[166] CRP levels ≥24 mg/L,[165] CRP levels >25 mg/L,[168] CRP levels ≥34 mg/L[172] and CRP levels ≥5 mg/L.[169]	Diagnostic test studies II[17,166,165,168] III[169,172]
Four studies[161-164] had LR+ values <5 and LR- >0.2 for varying levels of CRP (from ≥20 mg/L to >50 mg/L).	Diagnostic test studies III
A study performed a combined analysis on the diagnostic validity of the simultaneous presence of PCT ≥0.85 ng/mL and CRP ≥35 mg/L, compared against DMSA. The study gave sns of 78% (95% CI 57-91) and spc 100% (95% CI 88-100) for the diagnosis of APN.[166]	Diagnostic test studies II

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

A meta-analysis of 10 studies (n=627 children with UTI) aimed at determining the usefulness of PCT as a marker for ANP found that PCT levels >0.5-0.6 ng/mL were associated with a statistically significantly increased risk of ANP (OR 14.25, 95% CI 4.70-43.23).

SR of diagnostic test studies III

Three of the studies included in the meta-analysis at PCT concentrations ≥0.5-0.6 ng/mL gave LR+ >5-10 and/or LR- <0.1-0.2. However, the other studies included in this review did not give results as satisfactory at the same cut-off (PCT ≥0.5 ng/mL), as 2 studies had values of LR+ 2-5 and LR- 0.2 to 0.5; 2 other studies had LR+ values 2-5 and LR- <0.1-0.2; and one study had values of LR+ 6.6 and LR- 0.3.

Finally, 2 other studies included in the meta-analysis showed no usefulness for PCT in locating UTI.

Omitting the 2 recent studies, there was an increased risk of ANP (OR 26.7, 95% CI 10.3-69.4).[173]

9.4.3 Diagnostic accuracy of other blood and urine analysis parameters

The NICE CPG mentions a SR of several studies evaluating different analytical parameters with different cut-off points (ESR, leukocytosis, granulocytosis >52%, polymorphonuclear elastase-α1-antitrypsin complex, urine α1-microglobulin/creatinine ratio, urine β2-microglobulin/creatinine ratio, urine NAG, urine NAG/creatinine ratio, microscopic evaluation and detection of bacteria by immunofluorescent techniques) for the diagnosis of APN in children. The SR does not draw conclusions regarding the usefulness of these parameters, given the small number of studies for each of them, the various methodologies used and the different cut-off points adopted.[11]

SR of diagnostic test studies II

In addition, the NICE CPG identified a study evaluating different biochemical parameters in blood for the location of UTI in children. The study provided no data for the calculation of sns and spc. It showed that IL-1β levels >6.9 pg/mL, IL-6 >18 pg/mL and TNF-α >2.2 pg/ml give LR+ values of 2.4, 3.4 and 4.4, respectively, and LR- values of 0.05, 0.16 and 0.15, respectively.[11]

Diagnostic test study III

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

In addition to the aforementioned SR findings, 14 studies were found evaluating the validity of various analytical parameters in both blood and urine, compared with DMSA, for the diagnosis of APN in children. The results are summarised below.

Six studies[17,161,162,166,169,174] were found assessing the diagnostic validity of ESR at different cut-off points (>10-75 mm/h).

All studies show LR+ values <5 and only 2 studies showed values of LR- <0.2 for their respective cut-off points (ESR >10 mm/h)17 and (ESR >20 mm/h).[169]

Diagnostic test studies II[17,166]/ III[161,162,169,174]

Eleven studies[17,161,162,165-168,171,172,174,175] were found assessing the diagnostic validity of leucocytosis at different cut-off points (WBC >10,000-17,495/ mm^3).

Four studies found no differences in levels of leukocytosis among patients with a normal DMSA and patients with APN.[166,167,172,175] The remaining studies showed LR+ values <5 and LR- >0.2 for their respective cut-off points.[17,161,162,165,168,171,174]

Diagnostic test studies II[17,165,166,168,171]/ III[161,162,167,172,174,175]

Seven studies[161-163,165,171,172,174] were found evaluating the diagnostic validity of the presence of PMN for different cut-off points (PMN >4,890-14,990/ mm^3).

Two studies found no differences in PMN levels for patients with normal DMSA and patients with APN.[165,172]

Four studies showed LR+ values <5 and LR- >0.2 for their respective cut-off points.[161-163,171]

Only one study showed acceptable diagnostic values for levels of PMN >4,890/mm3, LR+ 7.2 (95% CI 1.15-45) and LR- 0.12 (95% CI 0.03-0.37).[174]

Diagnostic test studies II[165,171]/ III[161-163,172,174]

Three studies[168-170] were found evaluating the diagnostic validity of the presence of blood cytokines (IL-6 and IL-8).

For levels of IL-6 ≥4 pg/mL, 2 studies[169,170] showed LR+ 2.8 and 2.6 and LR- 0. For IL-6 levels ≥15 pg/mL, the 2 studies showed LR+ 4.7 and 4.2, respectively, and LR- 0.5.

For levels of IL-6 >22 pg/mL, 1 study[168] showed LR+ 5.2 (95% CI 2.5-11) and LR- 0.14 (95% CI 0.06-0.3). For IL-8 levels >12 pg/mL, this same study showed LR+ 3.7 (95% CI 1.9-6.8) and LR- 0.24 (95% CI 0.13-0.5).

Diagnostic test studies II[168,170]/ III[169]

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

Six studies[165,168,170,171,174,175] were found assessing the diagnostic validity of various cytokines (IL-6, IL-8, IL-1β, MIF) and other urinary markers.

Diagnostic test studies II[165,168,170,171]/ III[174,175]

A study[170] evaluating the presence of IL-6 in urine found LR+ 6.6 and LR- 0.64 for levels of IL-6 ≥15 pg/mL. A second study[168] found LR+ values of 4.5 (95% CI 2.2-8.7) and LR- 0.17 (95% CI 0.08-0.38) for IL-6/Cr levels >70 pg/mg. A third study[175] found no differences in levels of IL-6/Cr among patients with normal DMSA and patients with APN.

Two of the previous studies also evaluated the presence of IL-8 in urine and found, LR+ values of 4.9 (95% CI 2.4-10.5) and LR- 0.2 (95% CI 0.1-0.4) for IL-8/Cr levels >380 pg/mg.[168] A second study found no differences in levels of IL-8/Cr between patients with normal DMSA and patients with APN.[175]

One study evaluated the presence of IL-1β in urine and found LR+ values of 4 (95% CI 2.1-8.3) and LR- 0.15 (95% CI 0.07-0.35) for levels >150 pg/mg of IL-1β.[171]

One study evaluated the diagnostic validity of the cytokine MIF in urine and found significant differences between patients with APN and cystitis (P=0.002). For levels of MIF/Cr >4.9 pg/μmol, the study found sns values of 92% (95% CI 75-98) and spc of 100% (95% CI 68-98).[174]

Finally, a study evaluating the utility of different urinary markers (β2-microglobulin, α1-microglobulin, cystatin C, IgG and albumin) in the diagnosis of APN in children with a first episode of febrile UTI found no differences for any of the parameters between patients with APN and patients with normal DMSA.[165]

Also, during a review of grey literature, the abstract of a study evaluating kidney function in 53 paediatric patients was found (26 boys and 27 girls, mean age 10.3±16.7 months) with abnormalities by DMSA. There were 31.4% (16/51) of patients with VUR, and 30.6% (15/49) eventually developed renal scarring.

Case series III

The study found that 83% (44) of patients had reduced urine osmolality, the MA_u/creatinine ratio was high in 81.3% of cases (26/32), and the NAG_u/creatinine ratio was high in 63.9% of cases (23/36). One or more of these parameters was high in 90.6% of cases. There were no differences in renal function urine parameters between patients with and without VUR or with and without renal scarring. The authors concluded that when using sensitive functional urinary parameters, 90% of APN cases had impaired renal function. This may be useful in the topographic location of UTI in the absence of DMSA and to strengthen the diagnosis of APN in those centres where urine samples are collected by non-invasive techniques.[176]

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The GDG considered that the variability and inconsistency of results across the studies for clinical signs and symptoms in the diagnosis of APN made them unsatisfactory.

For fever, predictive values of LR+ <5 and LR- >0.2[11] were observed, although isolated studies had high specificity (LR+ 4.5-26.6)[11] or sensitivity (LR- <0.2)[11,168,169] in the presence of fever (T ≥38-38.5°C) in isolation or in combination with analytical parameters.

Other studies, however, found no differences in the presence of fever (T >38-38.5ºC) between patients with APN and those with a normal DMSA.[17,163-167]

Some studies showed an association between the duration of the fever before antibiotic treatment and the risk of acute kidney injury.[160,161]

There was also diagnostic variability found for analytical parameters commonly determined in blood (leukocytes, PMN, ESR and CRP). Therefore, either the results were mostly poor and insufficient (LR+ <5),[11,17,161–166,168-172,174] or there were no differences in the various analytical parameters evaluated between patients with APN and with normal DMSA.[167,175] However, there was improved LR- compared to isolated clinical variables, with LR- <0.2 for ESR values >10-20 mm/h,[17,169] CRP ≥0.5-70 mg/L,[11,17,165,166,168-170,172] or PMN >4,890/mm^3.[174] Also, there were some studies with a LR+ of 5-10 for values of PMN >4,890/mm^3 or CRP >40-70 mg/L.[170,171,174]

Some studies however had a higher accuracy in the diagnosis of APN with the use of PCT, with a spc of 100% (88-100%) for the joint presence of PCT >0.85 ng/mL and CRP >35 mg/L.[166]

For the isolated determination of blood PCT, the Mantadakis et al. SR showed a significant association between high levels of PCT >0.5-0.6 ng/mL and an increased risk of APN (OR 14.25, 95% CI 4.70-43.23), with values of LR+ >5-10 and/or LR- <0.1-0.2 in 3 of the studies included in the meta-analysis.[173]

For the other blood and urine parameters, excluding PCT, there were only a small number of studies with different methodologies and cut-off points that made evaluation of their validity difficult, although there is a potential role for interleukins: IL-6 ≥4 pg/mL in blood (LR+ 2.6-2.8, LR- <0.1),[169,170] IL-6 ≥15-22 pg/mL in blood (LR+ 3.4-5.2, LR- 0 14-0.5),[11,168-170] IL-6 ≥15 pg/mL in urine (LR+ 6.6 and LR- 0.64)[170] and/or IL-6/Cr ≥70 pg/mg in urine (LR+ 4.5, LR- 0.17).[168]

Only 1 recent study (available only in abstract)[176] evaluating the changes in urine osmolality was found within our search period for the determination of renal function to help in the diagnosis of APN. As it was the only study available, it was considered relevant for inclusion in the volume of evidence. However, the relationship between urinary concentrating ability and renal damage is well known, therefore the GDG considered including this parameter as a kidney damage marker in their recommendations.

In addition to the variability of results, the GDG also took into consideration the possibility of applying and generalising about some of the parameters evaluated, as many of them are available only in specialised research laboratories or are not performed in emergency department laboratories; although this may vary according to different hospitals (e.g., MIF, IL, NAG_u and proteins in urine).

Finally, the GDG considered the significance and clinical impact of the parameters analysed. Although the results of most studies are applicable in our setting, the GDG believes their practical value may be low, given the high pre-test probability of the selected cases: most patients attending hospital or emergency services; little effect on decision-making, with not being able to rule out the absence of renal parenchyma in all cases and at a higher cost with some recently used parameters.

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

Evidence summary

II[11,17,165,166] III[160-163,167]	The signs and symptoms (fever and its duration, vomiting, diarrhoea, abdominal pain, rejection of food, irritability) that are present in paediatric patients with suspected or confirmed UTI, regardless of age; in isolation, are not very accurate to confirm or rule out APN (LR+ <5, LR- >0.2).[11,17,160-163,165-167]
II[17,165,166,168,170,171] III[11,161-163,167,169,172,174,175,177]	Most analytical blood parameters (leukocytes, PMN, ESR, CRP, IL-6 and IL-8) that are present in paediatric patients with suspected or confirmed UTI, regardless of age; in isolation, are not very accurate to confirm APN (LR+ <5).[11,17,161-163,165-172,174,175,177]
III	The isolated presence of PCT ≥0.5-0.6 ng/mL seems a good marker for predicting APN (OR 14.25, 95% CI 4.7-43.23) in children (LR+ >5-10).[173]
II	The combined presence of PCT ≥0.85 ng/mL and CRP ≥35 mg/L seems a good marker for predicting APN in children (sns 78%, 95% CI 57-91) and (spc 100%, 95% CI 88-100).[166]
II[17,165,166,170] III[11,169,173]	In the context of UTI, APN is unlikely to be present if CRP <20 mg/L, ESR <10 mm/h, PCT <0.5 ng/mL or IL-6 in serum <4 pg/mL (LR- <0.1)[11,17,165,166,169,170,173]
II[11,165,168,170,171] III[175]	Most parameters analysed in urine (MA_u, NAG_u, low molecular weight proteins, IL-6, IL-8 and IL-1β) that are present in paediatric patients with suspected or confirmed UTI, regardless of age; in isolation, are not very accurate to confirm or rule out APN (LR+ <5, LR- ≥0,2),[11,165,168,170,171,175] except for IL-6 >15 pg/mL (LR+ 6.6).[170]
3	83% of paediatric patients with alterations in the acute phase by DMSA have reduced maximum urine osmolality.[176]

Recommendations

√	Suspect acute renal affectation (APN) in the presence of high fever ≥38.5°C and/or systemic involvement.
C	Suspect acute renal affectation (APN) with high acute phase reactants CRP and/or PCT, especially the latter.
C	Suspect acute renal affectation (APN) with IL-6 in urine >15 pg/mL.
√	Suspect acute renal affectation (APN) with a defect in renal concentrating ability, i.e. reduced maximum urine osmolality checked by an appropriate diagnostic test.
B	If there are no symptoms and/or clinical signs (fever, abdominal pain or malaise) with normal or slight increase in acute phase reactants (CRP <20 mg/L, PCT <0.5 ng/mL, ESR <10 mm/h and/or IL-6 in serum <4 pg/mL) or normal spontaneous osmolality, do not suspect renal parenchymal involvement.
√	Although analytical studies help in locating UTI, they are not routinely necessary for its management and treatment.

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10. Diagnostic imaging for UTI

Key question:

- What is the most effective imaging test for the diagnosis of structural abnormalities of the urinary tract and/or kidney damage in children with UTI?

Current management of paediatric urinary tract infection (UTI) in Spain typically involves imaging tests for urinary tract abnormalities that may predispose the patient to the new infections or complications with them. This practice reflects the recommendations of the majority of available clinical guidelines and protocols.[10] They recommend ultrasound, cystography or scintigraphy in different combinations, depending on the estimated risk, age and sex of the patient and the findings of previous examinations. However, most of these recommendations are based on the assumption that, in patients who are at risk of chronic parenchymal renal damage (mainly those with vesicoureteral reflux (VUR) or structural abnormalities that require surgical intervention) or in those who already have it, prophylactic treatment may prevent the onset or progression; thus preventing the development of hypertension or chronic renal failure. In addition, it may be that many of the urinary obstructive disorders are diagnosed in the prenatal period and not via the study of UTI, as was customary when there was no such diagnosis.

However, at present there is a debate emerging about the basis for that assumption.[178] Low-grade (I-III) VUR seems a more frequent finding than would be estimated, especially in infants, with little pathological implications, for both the risk of scarring and recurrence. Although high-grade (IV-V) VUR involves a higher risk, it is rare and often predates UTI, being often associated with kidney disease already present at birth. According to the Shaikh et al. SR, 24% (95% CI 20-28) of children with a first UTI have VUR, and 2.5% (95% CI 1.4-3.7) of children with first UTI have VUR (IV-V), which represents 10% of VUR after a first UTI.[45] Furthermore, the type of treatment for VUR appears not to change its evolution. Moreover, the effectiveness of antibiotic prophylaxis to prevent recurrence of UTI is not clear. So there are reasonable doubts that force us to reconsider the foundations of our current recommendations.[10]

Imaging tests are used in UTI to assess renal structure or the presence of urinary tract dilation (ultrasound) to detect VUR (cystography) or to identify renal parenchymal defects (DMSA scan). When judging the usefulness of these tests, their validity, the clinical utility of the diagnoses they provide, as well as their risk and cost all have to be considered.

To answer this question, studies from the NICE CPG[11] and later studies that were found are included.

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10.1 Diagnosis of APN

One SR included 18 studies from which the diagnostic accuracy of renal ultrasound was estimated against scintigraphy (DMSA in 14 studies) for locating APN. The studies included in the SR had a number of limitations, e.g. relating to the inadequate variety of patients, sample description, description of the reference standard and description of the index test.

SR of diagnostic test studies II

The results showed significantly different likelihood ratios ($P<0.0001$) between the studies included, with a final pooled LR+ of 3.1 (95% CI 2.3-4.3) and LR- 0.62 (95% CI 0.53-0.73).[11]

Another 2 studies to assess the validity of ultrasound in the acute phase vs. DMSA in the diagnosis of APN gave sns results of 49% and 9% and spc of 88% and 100%.[11]

Diagnostic test studies III

Two studies investigated the diagnostic accuracy of power Doppler ultrasound in the acute phase against DMSA in the detection of APN, finding results of sns 87% and 74%, and spc 92% and 94%, and therefore LR+ 10.9 and 12.3, and LR- 0.14 and 0.27, respectively.[11]

Diagnostic test studies III/Ib

Two later studies found better indicators of validity for power Doppler ultrasound than standard ultrasound in detecting APN compared with DMSA in the acute phase. They obtained LR+ 1.89 and LR-0.21,[179] and LR+ 4.87 and LR- 0.32,[180] respectively.

Diagnostic test studies III

Another 2 studies also evaluated the diagnostic accuracy of power Doppler ultrasound against DMSA for detecting ANP in the acute phase. The first study used power Doppler ultrasound and contrast,[181] while the second study used comprehensive ultrasound (power Doppler ultrasound with grey scale assessment).[182] The following results were found: LR+ 4.10 and LR-0.18, in one case, and LR+ 47.9 and LR-0.13 in the other case.

Diagnostic test studies III

10.2 Diagnosis of VUR

A SR included 11 studies from estimating the validity of ultrasound for the diagnosis of VUR compared with voiding cystourethrogram (VCUG). The following pooled estimates were obtained: LR+ 1.9 (95% CI 1.1-2.5) and LR- 0.76 (95% CI 0.63-0.93).[11]

SR of diagnostic test studies II

Other studies not included in the previous SR obtained similar results for the validity of ultrasound vs VCUG for diagnosing VUR: LR+ 2.16 and LR- 0.65,[183] and LR+ 1.05 and LR- 0.99.[184]

Diagnostic test studies II/III

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One study compared the validity of ureteric jet Doppler waveform with echo-enhanced voiding ultrasound for the diagnosis of VUR, giving LR+ values of 5.0 and LR- 0.14.[185]	Diagnostic test studies III
A SR of 14 studies evaluating the diagnostic validity of echo-enhanced cystography against VCUG as the reference standard in the diagnosis of VUR gave pooled estimates of LR+ 12.3 (95% CI 8.2-18.3) and LR- 0.17 (95% CI 0.11-0.27).[11]	SR of diagnostic test studies II
Another 2 studies, identified by the NICE CPG but not included in the previous SR, gave the following diagnostic accuracy values for echo-enhanced cystography against VCUG in diagnosing VUR: LR+ 1.66 and 36.50; LR- 0.16 and 0.28, respectively.[11]	Diagnostic test studies II/III
Another 2 studies also evaluated the diagnostic validity of echo-enhanced cystography against VCUG for VUR diagnosis, giving values LR+ 10.52 and LR- 0.10,[186] and LR+ 14.98 and LR- 0.06, respectively.[187]	Diagnostic test studies III
A subsequent study evaluated the diagnostic validity of echo-enhanced cystography with second generation contrast against the VCUG in diagnosing VUR. It gave values of sns 80% and spc 77% (LR+ 3.48 and LR-0.26). Considering the results from both tests as true positives, the sns of echo-enhanced cystography was 95% and the sns of the VCUG was 64%. In other words, echo-enhanced cystography detected more VUR conditions than VCUG.[188] A second study of 112 patients evaluated the usefulness of a second cycle without contrast in echo-enhanced cystography with contrast. It found that, after the first cycle, VUR was diagnosed in 39% of the sample (44 patients); performing a second infusion without contrast accounted for 12% more cases of VUR diagnosed. In other words, 8 of the 68 patients not diagnosed with VUR after the first cycle were diagnosed after the second.[189]	Diagnostic test studies III
A review summarised the results of 18 studies of the validity of echo-enhanced cystography with first generation contrast against VCUG. The review found values of sns between 57-100%, and spc values 85-100%. The review also compiled the results of 4 studies comparing the validity of echo-enhanced cystography with second generation contrast against VCUG or direct isotope cystogram (DIC), giving sns 85-100% and spc 70-97%.[190]	Diagnostic test studies review III
A study evaluating the correlation between DIC and VCUG in diagnosing VUR found a kappa coefficient of 0.60 (95% CI 0.40-0.80), indicating between moderate and substantial agreement according to the Landis and Koch scale (Annex 1, Table 16).[191]	Diagnostic test study III

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A study was performed to assess whether the results of a normal initial DMSA could be used as a screening method to detect severe VUR, and thus replace VCUG as the reference test. For DMSA in the acute phase detecting severe VUR, it found a sns of 100% (95% CI 54.1-100) and spc 75% (95% CI 68.3-82.6), giving LR+ 4.17 (95% CI 3.1-5.4) and LR- 0.[192] Another study found LR+ 2.06 and LR- 0.07.[193] None of these studies provides information on the clinical performance of the diagnoses made.

Diagnostic test study III

10.3 Diagnosis of renal damage

A SR included 6 studies comparing the validity of ultrasound against DMSA in the diagnosis of renal scarring. Three of the studies provided results in terms of renal units and found LR+ values of 1.3-35.9 and LR- 0.14-0.99. The other 3 studies provided results in terms of patients and obtained values of LR+ 2.6-27.4 and LR- 0.41-0.77.[11]

SR of diagnostic test studies II

The NICE CPG identified 3 further studies that also evaluated the validity of ultrasound (in the acute or delayed phase) versus DMSA (acute or delayed phase) in the diagnosis of renal scarring. These gave values of LR+ 1.51-5.9 and LR- 0.31-0.97.[11]

Diagnostic test studies II/III/III

Two later studies assessed the validity of ultrasound against deferred DMSA for detecting renal scarring. The first was with a small sample of patients (n=62) referred for delayed DMSA (more than 3 months after APN), with ultrasound performed 2 days after the DMSA. The ultrasound gave values of LR+ 16.0 and LR- 0.65 in the detection of renal scars.[194] The second study was with a sample of 476 patients with ultrasound and DMSA performed at least 8 weeks after diagnosis of UTI; it had results of LR+ 22.8 and LR- 0.78.[195]

Diagnostic test studies III

Another study in the diagnosis of renal damage with a small sample of patients (n=23) assessed the validity of power Doppler ultrasound performed within 14 days of diagnosis of UTI against DMSA at 6 months. It gave LR+ values of 14.5 and LR- 0.69.[196]

Diagnostic test study III

A SR included 2 studies assessing the diagnostic validity of MAG3 dynamic scintigraphy against DMSA in the diagnosis of renal scarring. LR+ values of 7.1 and 12.6, and LR- 0.15 and 0.21 were found.[11]

SR of diagnostic test studies II

A SR included 4 studies evaluating the diagnostic accuracy of intravenous urography (IVU) in diagnosing renal scarring compared with DMSA, and obtained values of LR+ 10-171.3, and LR- values 0.15-0.80.[11]

SR of diagnostic test studies II

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

Three studies compared the validity of MRI against DMSA in the diagnosis of renal scarring, giving LR+ values of 4.3-37.5, and LR- values 0.04-0.26.[11]

Diagnostic test studies II/II/Ib

Two studies compared the results of acute phase DMSA with DMSA results at follow-up. The first case gave sns 55.4%, spc 82.3%, LR+ 3.1 and LR- 0.54. The second study gave sns 85%, spc 78%, LR+ 3.9 and LR- 0.2.[11]

Diagnostic test studies III

Four studies evaluated the change in the probability of detecting permanent kidney damage in delayed DMSA in the presence of VUR.

Diagnostic test study III

The first study compared DIC against DMSA and gave sns 46.3% (95% CI 31.1-61.6%) and spc 88.2% (95% CI 79.5-97.1), LR+3.94 and LR- 0.61.[197]

3 other studies compared VCUG against delayed DMSA in the presence of VUR. They obtained a LR+ 1.78-2.57 and LR- 0.29-0.56 in renal damage detection.[198-200]

In addition, 3 other studies assessed the inverse relationship, i.e. the change in the probability of detecting VUR in the presence of abnormalities by DMSA. In the first study, the presence of an altered DMSA against DIC obtained values of LR+ 2.3 and LR- 0.35 in the detection of VUR.[197]

Diagnostic test study III

The other 2 studies compared DMSA against VCUG for the diagnosis of VUR. The first compared acute phase DMSA with VCUG a month after UTI and found LR+ of 1.38 (95% CI 1.19-1.85) and LR- 0.33 (95% CI 0-0.88).[60] The second study compared DMSA 6 months after infection with VCUG and got LR+ 2.37 (95% CI 1.42-3.96) and LR- 0.77 (95% CI 0.65-0.92).[201]

10.4 Diagnosis of abnormalities

A study in 250 patients with first UTI evaluated the correlation between pre-natal and post-infection ultrasound. Concordance was found in 96% of the 209 patients with both test results available. Overall, the predictive value of a normal pre-natal ultrasound for a normal or near normal post-natal equivalent was 96% (95% CI 93-99%).[202]

Diagnostic test study II

A small sample size study (n=43) was done to detect VUR in patients with a normal pre-natal ultrasound by evaluating the usefulness of post-infection ultrasound against VCUG 4-6 weeks after a first episode of UTI. It found LR+ values of 8.44 (95% CI 1.09-65.12) and LR- 0.59 (95% CI 0.32-1.09).[203]

Diagnostic test study III

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

The GDG found that the different study results were consistent, except for those related to the validity of ultrasound in the diagnosis of acute pyelonephritis or renal scarring, where some studies found a high sensitivity in contrast to most of the works.

The GDG took into account the possibility of applying and generalising the evidence when making recommendations. It considered that the validity estimates for most evaluated diagnostic tests may be applicable in our environment. However, the ability to reproduce these tests and make them widely available is not known; primarily ultrasound, because it implies a degree of subjectivity. The available information about echo-enhanced cystography suggests that this could be a suitable alternative diagnostic test for VCUG. Its availability and performance in each area still need to be assessed, however, before it can replace the current gold standard. This also applies to power Doppler ultrasound with grey scale assessment, with contrast or ureteric jet evaluation. Although these techniques seem to improve conventional ultrasound performance, their reproducibility and validity in our environment must be demonstrated. Similarly, the negative predictive value of the absence of pathologic images in pre-natal ultrasound as an alternative to post-infection ultrasound needs to be estimated in our environment.

Additional considerations taken into account by the GDG were related to the clinical impact of different diagnostic tests. Although there is sufficient information on the degree of validity of the main imaging tests (ultrasound, VCUG, DMSA, echo-enhanced cystography), there is no information on the clinical performance of diagnoses made from them. For example, only DMSA provides a reliable diagnosis of parenchymal affection in UTI; however, it has not been established whether this information being available improves patient management. Similarly, it is unclear whether the identification of VUR in a patient with UTI is useful as a follow-up or to improve prognosis. In the absence of experimental studies providing clinically important results about this, the usefulness of identifying VUR or parenchymal involvement can only be estimated indirectly from observational studies or the potential effectiveness of related interventions (e.g., the risk of renal progressive impairment or effective treatment of VUR).

Although the presence of certain radiographic findings is associated with increased detection of others, e.g. images of kidney damage and VUR, the clinical utility of these associations to indicate when to perform image testing is unclear. Thus, although the presence or absence of renal damage in DMSA may suggest performing a cystogram or not, in practice this prediction is not useful. This is because, in general, finding low grade VUR has little clinical relevance and high grade is very rare.

Also, the accessibility and cost of these tests needs to be considered. The different level of access to imaging tests should not be the criterion for suggesting them, but their validity and usefulness. The financial costs and risks associated with each test must also be taken into account. For example, the indication for VCUG must be weighed against the risks of urinary catheterisation and the radiological exposure involved (Annex 1, Table 15).

The GDG is aware of the difficulty of establishing the indications for imaging studies in a patient with a first UTI. There is enough evidence to choose the kind of test to rule out or diagnose various diseases, although, not enough to establish guidelines for all children with UTI. Most recommendations regarding indications for imaging are based on consensus or a low level of evidence. This will certainly not solve the uncertainty of the reader of this CPG, but may provide information about the current status of evidence and, in daily practice, may help in establishing a protocol or performance measures.

More than 5 years have passed since the publication of this Clinical Practice Guideline and it is likely that not all has been reviewed

Evidence summary

II	Conventional ultrasound is less accurate than acute phase DMSA for the diagnosis of APN (LR+ <5 and LR- >0.5).[11]
Ib[11] III[11,179-182]	Power Doppler ultrasound moderately improves on the performance of conventional ultrasound for the diagnosis of APN, at the expense of a better LR- (0.13-0.32).[11,179-182.]
II	Conventional ultrasound is less accurate than VCUG for the diagnosis of VUR (LR+ <2.5 and LR- >0.7).[11]
II[11] III[11,194,195]	Ultrasound is of limited use for the diagnosis of renal scarring, with very low LR- values of >0.20 in most studies, therefore a conventional ultrasound does not predict the absence of renal scarring in a DMSA.[11,194,195]
II[202]/III[203]	Although the existence of a normal foetal ultrasound makes it unlikely that a patient with UTI shows new findings on a post-infection ultrasound,[202.203] there is insufficient information to estimate the risk accurately.
II[11]/III[188]	Echo-enhanced cystography is accurate for the diagnosis of VUR (LR+ >10 and LR- <0.20),[11] and can even detect VUR that VCUG[188] cannot, and whose clinical significance is not established.
III	New contrasts improve the accuracy of echo-enhanced cystography in the diagnosis of VUR.[189]
III	VCUG and DIC show between moderate and substantial agreement in diagnosing VUR.[191]
III	The existence of a normal acute phase DMSA implies a low risk of high-grade or dilated VUR (LR- <0.10).[192]
II	MAG3 dynamic scintigraphy is sufficiently accurate (LR+ >5 and LR- ≤2) compared with DMSA for the diagnosis of renal scarring.[11]

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Recommendations

√	It is recommended to perform a urinary tract ultrasound after a first UTI if any of the following criteria apply to the patient: – Febrile UTI – No control over urination, and with no pre-natal or normal post-natal ultrasound. – Signs of urinary tract dysfunction. – Abdominal or bladder mass. – High creatinine levels. – UTI from a microorganism other than *E. coli*.
C	It is recommended to perform an ultrasound of the urinary tract in all children with recurrent UTI.
C	It is recommended to use techniques enhancing the ultrasound of the urinary tract, if available.
D	Do not perform routine DMSA in the acute phase for patients with UTI.
√	Consider selective use of DMSA in the acute phase, if available, if the result is important for the subsequent diagnosis of the patient (e.g., to decide treatment or complementary tests).
D	It is recommended to perform delayed DMSA scintigraphy (after 6 months) after a first febrile UTI if any of the following criteria apply to the patient: – Atypical evolution (persistence of fever >48 hours). – Signs of lower urinary tract dysfunction. – Abdominal or bladder mass. – High creatinine levels. – Septicaemia. – UTI from a microorganism other than E. coli. – Pathological findings in previous imaging studies (e.g., ultrasound, cystogram, DMSA).
√	Consider delayed DMSA scintigraphy (after 6 months) after a first febrile UTI if clinical, laboratory or radiological findings indicate a high likelihood of renal involvement.
C	It is recommended to perform DMSA scintigraphy on paediatric patients with recurrent febrile UTI.

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D	In general, it is not recommended to perform cystography (VCUG, radionuclide cystography or echo-enhanced cystography) on children after a first UTI, unless any of the following criteria apply to the patient: – Recurrent UTI. – Abnormalities in previous imaging studies (ultrasound or DMSA). – Signs of lower urinary tract dysfunction – Family history of VUR.
C	When performing a cystographic study in paediatric patients, it is recommended to use radionuclide cystography or echo-enhanced cystography, if available, instead of VCUG, unless lower urinary tract abnormalities are suspected.

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11. Predicting the risk of chronic kidney damage

Key question:

- Are there clinical, radiological or laboratory criteria for predicting the risk of chronic kidney damage after a first febrile UTI?

Febrile urinary tract infection may present in up to 60% acute parenchymal damage.[21,204,205] After acute pyelonephritis, the risk of permanent scarring is highly variable and is estimated to occur in 15-60% of cases.[206] Various associated factors have been proposed with the onset of permanent kidney damage, such as reduced age, male sex, delay in establishing treatment, persistent fever or marked elevation of acute phase reactants in the initial infection.[11,21] The presence of renal oedema in acute phase ultrasound, or dilated vesicoureteral reflux (VUR) in the voiding cystourethrogram (VCUG) have also been associated with an increased risk of permanent kidney damage.[207,208] Detected by DMSA, kidney damage also correlates with chronic renal failure factors, such as the presence of proteinuria, hypertension (HT) or decreased glomerular filtration.[209,210]

An attempt is made below to define the clinical, radiological and laboratory factors predicting the presence of permanent kidney damage detected by renal scintigraphy (DMSA) or intravenous urography (IVU).

The findings from 9 studies in the NICE CPG[11] are summarised below.

A population study in the UK showed a prevalence of renal scarring by DMSA after a first UTI of 4.7% in girls and 4.3% in boys. The logistic regression found no significant association with age or sex.[11] — Case series 3

A Swedish study with 596 patients under 16 years of age with first febrile UTI demonstrated differences in the prevalence of renal scarring by gender using IVU: 13% of boys had renal scarring compared to 4.5% of girls.[11] — Case series 3

One study linked the degree of VUR with the appearance of renal scarring detected by IVU in patients diagnosed with UTI (n=105, 23 boys and 82 girls); 52% of patients had VUR. The degree of affectation correlated significantly with the degree of VUR: 20% of patients with VUR grade I, 38% of patients with VUR grade II and 79% of patients with VUR grade III had renal scarring.[11] — Case series 3

One study evaluated the effect of the delay in diagnosing dilated VUR in the appearance of severe renal injury as measured by IVU (n=52, 24 boys and 28 girls). The ratio of moderate/severe damage according to the type of delay was 10/1 in the group without a delay in diagnosis, 11/13 in the group with a delay of up to 6 months and 6/11 for those where the delay exceeded 6 months, which was statistically significant.[11] — Case series 3

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Two studies analysed the presence of scarring after UTI, measured by IVU. The first study included 1,177 patients under age 10 with a first symptomatic UTI (952 girls and 225 boys). The study found that 5% of patients without reflux had renal scarring, which increased with the degree of reflux: 10% of patients with VUR grade I, 17% of patients with VUR grade II and 66% of patients with VUR grade ≥ 3, had renal scarring.[11] Case series 3

The second study had 252 patients aged between 6 and 24 months of age with first UTI, and found that 40% of children with VUR had renal scarring.[11]

A study in children of 3-4 years old with UTI and with normal ultrasound and normal DMSA, found after a follow-up period of 2 to 11 years, that 1.4% (5/355) had developed renal scarring, all of them were girls, and 80% of these girls had had recurrent UTI.[11] Case series 3

A study evaluating the prevalence of renal damage in 150 paediatric patients after a first UTI found, at 2 years of follow-up, a kidney scar prevalence of 13.3% (95% CI 8.3-19.8). The study found no association between persistent renal damage and the presence or severity of VUR (VUR III-V, P=0.34), recurrent infections (*P*=1.0), the need for hospitalisation (P=0.08) or duration of symptoms before treatment (*P*=0.10). It did find significant differences in persistent renal damage according to sex and age of the patients: being younger than 2 years old and being female showed an increased risk of persistent renal damage. However, when adjusting for patient age at the diagnosis of renal defect (median age 3.6 months in boys, range 0.75-31 months; median age 11.5 months in girls, range 1.7-59 months), the study found no differences in persistent renal damage among girls or boys (OR 3.11, 95% CI 0.61-15.86).[11] Case series 3

A study to determine differences in genetic polymorphisms of angiotensin converting enzyme and angiotensin II receptor type 1 enrolled 97 children with recurrent UTI and 100 controls. Compared with the controls, no association was found between genetic polymorphisms and the appearance of scars; with 30.9% of cases developing renal scarring. Patients with scars had a higher number of UTI recurrences (6.90±2.45 episodes) than patients without renal scarring (3.35±1.48 episodes, *P*<0.001) and were younger at the time of the presentation of the first UTI (2.61±1.52 years, compared to 3.52±2.17 years, *P*=0.04). No association was found with sex or with the presence of bacteria different to *E. coli*.[11] Case series 3

In addition to the studies included in the NICE guideline, the following studies examining the influence of different factors on the subsequent scarring were found. Factors such as the delay in the establishment of antibiotic treatment, patient age, sex, the presence of systemic symptoms, the presence and severity of VUR and analytical parameters in blood or urine were investigated. Also included are the results of studies evaluating the predictive ability of permanent renal damage from renal ultrasound performed at an early stage for a child with febrile UTI.

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A study involving 287 patients (age range 1 month to 7 years) with APN confirmed by DMSA evaluated if the delay in starting treatment (<1 day to >5 days) affected the appearance of renal scarring at 12 months, and found no differences between those starting treatment within 1 day and those after more than 5 days (OR 0.99, 95% CI 0.65-1.51).[211] Cohort study 2+

A study in infants with first febrile UTI (n=278, 153 boys and 125 girls, median age 3.5 months, range 0.5 to 12 months) evaluated at 6.5 months if the delay in the onset of treatment (median delay 2 days, range 1-8 days) had an effect on the occurrence of renal scarring after febrile UTI. The study found no significant differences in the incidence of renal scarring between patients starting treatment within 24 hours (46%) and those starting treatment later (54%).[27] Cohort study 2-

A study in infants with first febrile UTI (n=306, age 1-24 months) found a slight increase in the incidence of renal scarring at 6 months follow-up in those children with at least a 24h delay in starting treatment (11.9% of patients) compared with those who started treatment within 24 hours (9.1% of patients), although this was not statistically significant (P=0.29). Additionally, the study found significant differences in the incidence of renal scarring in patients with VUR (45% of patients) and patients without reflux (14.9% of patients; P<0.03), and a significant association between the degree of VUR and renal scar incidence (P=0.007).[212] Cohort study 2+

A study in children with first febrile UTI (n=227) examined various predictors of acute renal damage and renal scarring. The study found that in those patients with APN on initial DMSA (127 patients), the delay in starting treatment was significantly associated with increased risk of renal scarring at 6 months (OR 2.36, P=0.001).[160] Cohort study 2-

The objective of a study in children (n=335, age ≤14 years) with febrile UTI was to evaluate at 6 months if age influenced the development of renal scarring. It found patients older than 5 years of age had an increased risk of renal scarring (OR 3.35, 95% CI 1.04-10.78).[213] Cohort study 2-

A study in patients with APN (n=269, 147 girls and 122 boys, mean age 3.5±3.3 years, range 1 month to 14 years) analysed the influence of various factors on the onset of permanent kidney damage. The study found patients older than 5 years of age had an increased risk of renal scarring (OR 5.12, 95% CI 2.56-10.26). The study also identified the following as risk factors for renal scarring: infection by bacteria other than E. coli (OR 4.47, 95% CI 2.02-9.92), recurrent UTI (OR 2.09, 95% CI 1.24-3.5) and the presence of VUR (OR 2.36, 95% CI 1.42-3.94). The study found no differences in the incidence of renal scarring between boys and girls.[204] Cohort study 2+

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A study in children with VUR III-IV (n=203) found a higher incidence of new kidney damage by DMSA at 2 years in girls with recurrent febrile UTI compared to girls without recurrent febrile UTI (RR 8.53, 95% CI 2.84-25.58; *P*<0.05).[214]	RCT 1+
A study in 138 patients with UTI and primary VUR (53 boys, mean age 40.8±42.5 months and 85 girls, mean age 49.3±34.6 months) found the following as independent factors associated with the risk of renal scarring: male sex (OR 2.5, 95% CI 1.1-6.0), age ≥27 months (OR 4.2, 95% CI 1.7-10.6), and VUR grade IV-V (OR 12.4, 95% CI 4.6-33.4).[215]	Cohort study 2+
A study of 98 patients with primary VUR (46 boys, mean age 1.1±1.6 years; 52 girls, mean age 2.9±2.5 years) found the following as risk factors for renal scarring: VUR high grade (OR 14.5, 95% CI 4.9-42.2), age over 5 years (OR 12.6, 95% CI 2.7-58.8) and male sex (OR 6.5, 95% CI 2.0-20.7).[216]	Cohort study 2+
A study of 51 patients with kidney damage and 140 patients with UTI and no renal scarring assessed whether the presence or severity of systemic symptoms (fever, vomiting, malaise, anorexia) or the need for hospitalisation in the acute phase of infection, combined with the patient's age, were factors to help in predicting the risk of renal scarring. The study found that the presence of vomiting, anorexia or malaise correlated very weakly with the presence of renal scarring (R^2=0.03, P=0.02), while none of the other variables (sex, age, fever, hospitalisation) were associated with risk of renal scarring (*P*>0.5). By calculating the sensitivity and specificity and using proportionate reduction in uncertainty plots, the study showed that none of the considered variables were good predictors of renal scarring, such that the presence of fever showed a sns range of 38-67% and spc range of 79-55% according to patient age (>3 years, 6 months to 3 years, <6 months), the presence of vomiting, malaise and anorexia had values of sns of 43-78% and spc of 81-25% also according to the same age group; and finally, hospitalisation had sns values of 19-67% and spc 95-45% for these groups. The study therefore concluded that none of the variables was useful as a predictor of renal scarring in children under 3 years of age.[217]	Case control study 2+
A study in 218 patients with febrile UTI assessed the risk factors for renal scarring in patients with ALN (n=109) compared with patients with APN (n=109); and found an increased risk of renal scarring in patients with ALN (OR 13.56, 95% CI 6.53-28.19). The study found no association between patient sex, patient age or presence of VUR and increased risk of renal scarring.[218]	Case control study 2-

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A study in 72 children (age range 7 days to 3 years) with febrile UTI, evaluated the usefulness of PCT for predicting renal scarring in patients who develop APN. The study found significant differences in PCT levels between patients with renal scarring by DMSA at 12 months and those free of renal scarring (P=0.007). Similarly, the study found significant differences in PCT levels between patients with febrile UTI without renal involvement (median 0.49 ng/mL [IQR 0.12-1.00]), patients with APN without renal scarring (median 0.83 ng/mL [IQR 0.3-2.6]) and patients with APN and subsequent renal scarring (median 2.3 ng/mL [IQR 1-11.6]), showing an upward trend in the levels of PCT (P=0.006). For the diagnosis of renal scarring, PCT levels >1 ng/mL showed values of LR+ 2.17 (95% CI 1.75-2.40) and LR- 0.34 (95% CI 0.17-0.70).[219]

Diagnostic test study II

A study in 77 children with their first episode of febrile UTI (age range 1 month to 12 years) evaluated the usefulness of PCT and CRP in the diagnosis of APN with renal scarring. The study found significant differences in PCT and CRP levels between patients with and without renal damage in the acute phase, and also between patients with and without renal scarring (P<0.05). For the diagnosis of renal scarring, PCT levels ≥1ng/ml showed LR+ 2.4 and LR- 0.12; CRP levels of 20 mg/L showed LR+ 1.4 and LR- 0.22.[220]

Diagnostic test study II

A study in 100 children (age range 1 month to 13 years) with their first episode of febrile UTI evaluated the diagnostic accuracy of PCT and CRP in the diagnosis of acute renal disease and renal scarring. The study found significant differences in PCT and CRP levels between patients with and without acute affectation by DMSA at baseline (P<0.05), but only found significant differences in PCT levels between patients with and without renal scarring by DMSA at 6 months (P<0.05), but not for CRP levels (P=0.4).[221]

Diagnostic test study II

A study in 163 boys (median age 3.1 months, range 5 days to 19.9 months) and 140 girls (median age 8.5 months, range 5 days to 22.6 months) with first symptomatic UTI evaluated the relationship between the presence of various risk factors and permanent kidney damage. It found a significant association between the presence and degree of VUR, and renal abnormality by DMSA at 1 or 2 years of follow up. There was a progressive increase in the risk of renal scarring with increasing degree of VUR: VUR grade I (RR 1.20, 95% CI 0.43-3.35), VUR grade II (RR 2.17, 95% CI 1.33-3.56), VUR grade III (RR 2.50, 95% CI 1.55-4.01) and VUR grade IV-V (RR 4.61, 95% CI 3.23-6.57). The study also found a significant association between CRP peak levels at first UTI and renal abnormalities by DMSA at 1 or 2 years of follow up (P<0.001). By logistic regression, the study found that VUR was the only independent variable associated with the risk of renal scarring in boys (P<0.0001); whereas in girls the independent variables associated with renal scarring were CRP levels at first UTI (P<0.001) and presence of VUR (P<0.05).[222]

Cohort study 2+

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The objective of a study of 50 infants (<1 year of age) with dilated VUR and UTI, followed over a mean of 6.3 years (range 1-16), was to determine which parameter best correlated with decreased GFR (<80 mL/min/1.73m2) by including parameters such as the following in a multivariate multiple regression analysis: sex, pre-natal diagnosis, number of febrile UTI, serum creatinine >0.6 mg/dL, urea >200 mg/L, metabolic acidosis, proteinuria >40 mg/m2/h, hypertension, decreased size in multiple ultrasound measurements and number of renal scars by DMSA at 1 year. It found that only the initial rise in serum creatinine above 0.6 mg/dL showed a significant association with decreased renal function (P<0.001).[223]

Cohort study 2-

A study comparing the efficacy of 2 antibiotic treatment strategies in children with febrile UTI grouped the sample to analyse the influence of different factors on the occurrence of renal scarring. It found no influence by age, sex, duration of fever or delay in the start of treatment, although it did find an influence with the presence of VUR, high CRP and renal oedema by ultrasound. The multivariable regression analysis showed only VUR and renal oedema by ultrasound had a significant association, although renal oedema evaluated in isolation showed LR+ 2.86 (95% CI 1.01-8.06) and LR- 0.94 (95% CI 0.83-1.06).[207]

Cohort study 2-

A meta-analysis aimed at assessing the risk of renal scar according to ethnic differences in children diagnosed with APN by DMSA in the acute phase included a total of 23 studies (n=2,106 patients). Of these, 13 analysed the results in terms of patients, 7 in terms of renal units and 3 in terms of both. Of the original patients, only 1,408 had a second follow-up DMSA to determine renal scarring. The estimated total scarring after APN was 37.0% (95% CI 21.0-56.6) of the total renal units and 41.6% (95% CI 34.3-49.2) of the total patients.

Additionally, the SR showed the incidence of renal scarring according to the presence of VUR by subgroup analysis and noted that VUR tripled the risk of scarring, either in terms of patients (OR 2.8, 95% CI 1.9-4.2) or renal units (OR 3.7, 95% CI 1.3-11.1).[206]

Cohort study SR 2++

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Another 3 additional studies not included in the previous SR showed similar results regarding the association between VUR and the increased risk of renal scarring in paediatric patients with febrile UTI. Cohort studies 2+

The first study found that the presence of VUR was associated with a significantly increased risk of renal scarring (OR 9.37, 95% CI 4.48-19.64), but found no correlation between the severity of VUR grade and an increased risk of renal scarring (P=0.26).[224]

The second study evaluated the incidence of renal scarring in children with VUR grade III-V and observed a progressive increase in the incidence of renal scarring with increasing degree of VUR. Patients with VUR grade III had 7.4% of renal units affected; patients with VUR grade IV, 20.9%; and patients with VUR grade V, 43.2%.[225]

The third of the studies investigated the risk factors associated with different types of renal parenchymal damage in 549 paediatric patients with primary VUR (391 girls and 158 boys, median age at diagnosis of VUR, 19 months, IQR 9-38). By logistic regression, the study found the following as independent variables associated with renal damage by parenchymal contraction: VUR grade III-V (OR 9.7, 95% CI 4.1-23.0), age (>24 months) at the time of diagnosis of VUR (OR 3.0, 95% CI 1.6-5.1); unilateral reflux (OR 2.1, 95% CI 1.2-3.8) and male sex (OR 2.0, 95% CI 1.1-3.8). Independent variables associated with multifocal renal scarring were VUR grade III-V (OR 13.8, 95% CI 7.4-26.0) and age (>24 months) at diagnosis of VUR (OR 1.9, 95% CI 1.2-3.0). Finally, VUR grade III-V was an independent variable associated with unifocal renal scarring (OR 7.9, 95% CI 3.8-16.4).[208]

One study was aimed at assessing factors associated with the progression of renal damage in 3,646 children with first UTI who were followed during a mean period of 7 years. The factors found to be associated with progression of kidney damage included: the existence of previous renal scarring in both boys and girls; being in boys under 1 year of age, where the increased risk was more notable (OR 13.5, 95% CI 4.7-48.4); the presence of VUR, especially in girls under 1 year of age (OR 14.5, 95% CI 1.8-118); and recurrence of UTI, but only in girls: <1 year of age (OR 6.3, 95% CI 1.3-30.7), and ≥1 year of age (OR 2.7, 95% CI 1.7-4.2).[226] Cohort study 2-

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A meta-analysis was aimed at establishing the prevalence of renal damage in the acute phase (APN by DMSA within a period ≤15 days after the initial episode of UTI) and chronic renal damage (renal scarring by follow-up DMSA within a period >5 months - 2 years after the initial episode of UTI) in paediatric patients after a first UTI. It selected a total of 33 cohort studies including 4,891 patients (0-18 years old). The meta-analysis had a pooled prevalence of VUR in the total population with first UTI of 24% (95% CI 20-28), and a pooled prevalence of severe VUR IV-V of 2.5% (95% CI 1.4-3.7). From the results of 29 studies, the meta-analysis gave an overall prevalence of acute damage by DMSA consistent with APN of 57% (95% CI 50-64). Based on data from 10 studies comparing the risk of APN in patients with VUR (67%) against patients without VUR (49%), a significantly increased risk was found in the group of patients with VUR (RR 1.5, 95% CI 1.1-1.9). In relation to the presence of renal scarring the global prevalence was 15% (95% CI 11-18). Again, the presence and degree of VUR significantly increased the risk of renal scarring. The risk increased 2.6 times in the group of patients with VUR (41%) vs those without VUR (17%), (RR 2.6, 95% CI 1.7-3.9). Within the group of patients with VUR, those with with VUR grade III-V (53%) had a significantly increased risk of renal scarring when compared with those with VUR grades I-II (RR 2.1, 95% CI 1.4-3.2). Additionally, from the results of 4 studies, the meta-analysis estimated a prevalence of pre-existing renal damage or renal dysplasia by DMSA in the acute phase – and presumably unrelated to the UTI of the time – of 0.6% (95% CI 0-1). The results of other 4 studies show a prevalence of new lesions in areas not affected in the acute phase DMSA of 1.3% (95% CI 0.2-2.2). Finally, the results of 6 and 3 studies found that the annual incidence of recurrent UTI was 8% (95% CI 5-11) and the annual incidence of recurrent febrile UTI was 6% (95% CI 3-12).[45]

Cohort study SR 2++

There are 4 other studies examining the predictive ability of permanent renal damage from a renal ultrasound performed at an early stage in paediatric patients with febrile UTI.

A study of 45 children (age range 9 days to 9.8 years) with febrile UTI assessed the predictive value of renal ultrasound in the acute phase of UTI against DMSA at 6 months, for the diagnosis of posterior kidney scarring. The study found that ultrasound gave values of LR+ 1.5 (95% CI 0.9-2.5) and LR- 0.67 (95% CI 0.4-1.16). The simultaneous presence of high CRP levels (>70 mg/L) and alterations by ultrasound increased the diagnostic accuracy of renal ultrasound LR+ 2.78 (95% CI 1.17-6.6) and LR- 0.59 (95% CI 0.39-0.89).[227]

Diagnostic test study III

Two studies with 191 and 300 patients (<2 years old) with febrile UTI evaluated the predictive value of renal ultrasound in the acute phase of UTI against DMSA at 12 months for the diagnosis of posterior renal scarring. The ultrasound gave values of LR+ <5 and LR- >0.2 in both studies.[228,229]

Diagnostic test studies II

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One study of 23 patients (<4 years of age) with febrile UTI compared the predictive power of renal power Doppler ultrasound in the acute phase with DMSA at 6 months for the diagnosis of posterior renal scarring. The study gave values of LR+ 14.5 and LR- 0.69.[196]	Diagnostic test study III

In preparing the recommendations, the GDG looked at the results and considered that there were inconsistencies in many of the parameters analysed over different studies. Consistency was seen only in the increased risk of permanent kidney damage in children suffering from dilated VUR.[11,206,208,215,216,222,224]

Among the clinical parameters, the presentation and speed of starting treatment did not appear to be associated with an increased risk of scarring.[27,207,211,212,217]. The presence of recurrent infections showed an increased risk in some studies,[11,204,226] while in others this relationship was not shown.[223.230]

Several studies found an increased risk of scarring with increasing age,[204,208,213,215,216] while others found an increased risk of scarring with minor age, and several studies failed to demonstrate any clear association between age and increased risk of kidney damage.[11,207,217,218] The studies of higher methodological quality, based on multiple regression analysis, are those that found an association with older age, although it is clear that there is great inconsistency in the data.

Similar discrepancies appear with respect to sex as those occurring with age. Several studies show an increased risk of renal scarring in males,[11,215,216] especially if the infection is associated with VUR. While others found the greatest incidence with girls,[11] although most studies found no decisive influence.[11,56,204,207,217,223]

Some studies show a predictive value for high levels of acute phase reactants; however, it should be noted that both the PCT and CRP exhibit low discriminative ability with LR+ <5 and LR- >0.2.[207,219-222]

The presence of renal oedema in ultrasound performed in the acute phase has a low discriminative capacity,[227-229] although this ability is enhanced with a Doppler scan.[196]

While preparing this document, the Shaikh et al.[45] SR and meta-analysis was published and was included in the volume of evidence for being considered relevant. The SR includes the results of 12 studies which are also included in the Faust et al.[206] SR and meta-analysis.

Evidence summary

2+	The presence of systemic symptoms (anorexia, vomiting, discomfort) accompanying febrile UTI was not associated with an increased risk of permanent kidney damage.[217]
2+	An association between delayed initiation of antibiotic treatment and an increased risk of permanent kidney damage was not able to be demonstrated.[211,212]
2+	There are conflicting results regarding the sex of the patient as a predictor of renal scarring.[204,215-217]
2+	Older paediatric patients appear to be associated with an increased risk of renal scarring;[204,208,215,216] however, the results are not conclusive.[217.]
1+[214]/2+[204]	The existence of recurrent urinary tract infections increases the risk of permanent kidney damage.[204,214]

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II	An increase in acute phase reactants (PCT >1 ng/dL or CRP >20 mg/L) during febrile UTI has little ability to predict the onset of permanent kidney damage (LR+ <5, LR- >0.2).[219,220]
II[228,229]/III[227]	Conventional renal ultrasound performed early after a febrile UTI has little ability to predict the onset of permanent kidney damage (LR+ <5, LR- >0.2).[227-229]
2++	The presence of VUR increases the risk of permanent kidney damage (RR 2.6, 95% CI 1.7-3.9)45 and (OR 2.8, 95% CI 1.9-4.2).[206]
2++[45]/ 2+[208,222,225]	A greater degree of VUR increases the risk of renal scarring, and the difference is especially marked in dilated reflux.[45,208,222,225]

Recommendations

B	It is recommended to investigate renal injury in paediatric patients with VUR, as they present an increased risk of permanent injury.
B	It is recommended to investigate the presence of permanent renal damage in paediatric patients with recurrent febrile UTI.
B	An increase in acute phase reactants or renal ultrasound during febrile UTI, in isolation, should not be used as predictors of permanent kidney damage.
D	It is not recommended to investigate permanent renal damage by renal scintigraphy in paediatric patients with a first febrile UTI, based on the clinical presentation, delay in establishing treatment, patient's age or gender.

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12. Hospitalisation and referral criteria

12.1. Hospitalisation criteria for suspected UTI

Key question:

- What should be the hospitalisation criteria for children with suspected UTI?

Hospitalising a child with febrile urinary tract infection (UTI) has been the usual practice in recent decades, for two main reasons: to control serious infection complications and prevent permanent kidney damage. This was based on the assumption that early intravenous antibiotic treatment was advantageous in the rapid control of infection, decreasing the risk of acute complications and permanent renal parenchymal sequelae.

Hospitalising a child should be considered only when it is strictly necessary and when it provides a clear benefit to health. This is not just for economic considerations, but to minimise the psychological impact, reducing the disruption to family life and to prevent the risks of nosocomial infections associated with any hospitalisation in a paediatric ward. It is therefore logical to establish outpatient strategies to manage any condition if admission to a hospital is unlikely to provide a clear benefit for the child.

As discussed below, several clinical trials have recently shown that oral antibiotic treatment of a child with febrile urinary tract infection is as effective as intravenous in terms of clinical and bacteriological control of the infection in the acute phase and protection against the occurrence of renal scars.[212,231-233] As a result, there is increasingly less recommendation for hospital admission to control paediatric patients with febrile UTI[6,11,73,126] than before.

In order to define the hospitalisation criteria for paediatric patients with febrile urinary tract infection, 3 important aspects need to be considered: bacteraemia, renal functional impairment and poor therapeutic control.

Risk of bacteraemia

Urinary tract infection is bacterial in origin in most cases and there is a risk therefore of haematogenous spread, particularly in the case of infection of the renal parenchyma, which is highly vascularised. However, epidemiological studies show that this risk is low in childhood. A Finnish study showed an annual incidence of severe bacteraemia of urinary origin in children under 16 years of age without previous UTI of 1.5 new cases per 100,000 person - years, 88% of cases were individuals under one year, and 66% under 3 months. Boys were nearly twice more likely to be at risk than girls, although the excess risk decreased with age.[59] The estimated risk of bacteraemia during pyelonephritis may be 1/150 episodes,[59,234] but may reach 22% in those under 2 months of age, or 3% in under 36 months of age.[235] Therefore, infants are at an increased risk of bacteraemia, especially those under 2 months of age.[59,234-236]

Besides age, clinical presentation may suggest a serious bacterial complication. Thus, hospitalisation is recommended for any child with a "malaise" or "sickly appearance" as it involves an increased risk of bacteraemia. Besides the classic Yale scale for the management of children with fever without focus,[237] the NICE clinical practice guideline for managing a febrile child established a series of criteria for assessing the severity, based on various cohort studies: the presence of signs of dehydration, listlessness, low reactivity to stimuli, pale skin, poor peripheral perfusion

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or sickly appearance. Other high risk factors are irritability and vomiting or seizures. Any of these described situations warrants hospital monitoring of the patient, as there is an increased risk of sepsis.[238] The criteria used for managing febrile children can often be extended to children with urinary infection.[11]

Urinary tract abnormalities have been associated not only with an increased risk of permanent kidney damage after a urinary tract infection,[206] but with an increased risk of bacteraemia in the acute phase. In children with dilated VUR, the risk of bacteraemia during pyelonephritis is double that of children without dilated reflux.[59] And the risk of serious bacterial complications in patients with obstructive disease of the urinary tract can be 9 times as much.[11] However, the presence of VUR may also be important in the acute therapeutic approach to the infection to prevent scarring. In the Hoberman clinical trial, comparing the use of oral cefixime with intravenous cefotaxime for the treatment of pyelonephritis in paediatric patients, a subgroup analysis found that patients with VUR showed an increased risk of renal scarring if treatment was administered orally (RR 7.33, 95% CI 1.00-54.01), (NNT 3, 95% 2-12).[212] The problem is that, for many boys and girls with a first febrile urinary tract infection, it is not known if there is an associated malformation pathology. Some clinical and laboratory data can help define high-risk patients. Epidemiological studies in families with VUR have shown that 25-50% of siblings and 50-66% of children of patients with VUR also have reflux.[239] A large cohort study of children with VUR showed a good correlation between plasma CRP during acute pyelonephritis and the degree of reflux and subsequent scarring.[222] Therefore, very high levels of acute phase reactants can suggest the presence of high-grade reflux, but with little discriminative power. Also, the relationship between congenital pyelic dilatation and the presence of obstructive uropathy or high-grade reflux is known.[240] Therefore, children with a history of pyelic dilatation whose imaging studies are not completed should be considered patients at increased risk of febrile urinary tract infection.

Also, those children most vulnerable to severe infection due to immune system dysfunction should also be considered at high risk of bacteraemia after a febrile urinary tract infection: e.g., patients with primary or secondary immunodeficiency, cancer, diabetes or nephrotic syndrome.

Risk of renal functional impairment

During febrile urinary tract infection, special attention must be paid to those patients with impaired renal function, significant elevations of creatinine and electrolyte abnormalities. The presence of any of these alterations may be related to extensive renal parenchymal injury or to a normal extension injury in a patient with low renal functional reserve due to dysplasia, hypoplasia or chronic glomerulonephritis. In all these situations, it is best to admit the patient to hospital to treat these alterations, if required, and to deliver antibiotic therapy according to the degree of renal insufficiency present.

As well as the association between VUR and the increased risk of permanent kidney damage,[208,224,225] there are other situations that must be considered when deciding the management strategy of a child with febrile UTI. For example, high levels of creatinine during a febrile UTI in infants with VUR is shown to be a possible predictor for future chronic renal failure.[223]

Recurrent febrile UTI has been associated with an increased risk of permanent kidney damage in children with or without VUR. This should be considered therefore when recommending hospitalisation to better control such patients.[204,241,242]

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Risk of poor therapeutic control

Any patients who cannot be managed on an outpatient basis due to non-compliance with oral antibiotic treatment also require hospitalisation. Among them will be children with oral intake disabilities, those persistently vomiting and dehydrated patients requiring intravenous fluids. The social situation of the patient to ensure proper monitoring must also be carefully analysed. If this cannot be guaranteed, hospitalisation may be indicated to improve control.[11,73,126,243]

Clinical monitoring is recommended within 48 hours for all children with febrile urinary tract infection treated as an outpatient.[244] If no improvement is seen in this time, the therapeutic strategy should be reassessed by considering the resistance of bacteria in the urine, the possible presence of infectious complications and the patient's general condition.[11,244]

From the above information, by consensus the GEG recommends the following criteria to indicate hospitalisation for paediatric patients with febrile urinary tract infection.

√	A child with febrile urinary tract infection meeting any of the following criteria should be admitted to hospital: – Age less than 3 months old. – Affectation of the general condition, sickly appearance. – Vomiting or oral intolerance. – Dehydration, poor peripheral perfusion. – Urinary system malformations, VUR, obstructive uropathy, renal dysplasia, single kidney. – Poor care or trouble monitoring. – Primary or secondary immunodeficiency. – Electrolyte or renal function abnormalities.
√	A child with febrile urinary tract infection meeting any of the following criteria may be admitted to hospital, but can also be treated under supervision on an outpatient basis: – High fever (≥38.5°C) in children of 3-6 months of age. – Persistence of fever after 48 hours of treatment. – Risk factors of an unusual bacteria (recent antibiotic therapy, recent hospitalisation, catheterisation). – Family history of VUR or prenatal ultrasound with congenital hydronephrosis. – Recurrent febrile urinary tract infections. – Significant increase in acute phase reactants.
√	In all other cases, outpatient management of the patient is recommended.

Criteria adapted from the NICE CPG on the management and evaluation of febrile children.[238]

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12.2. Referral to a specialist

Key question:

- When should a child with UTI be referred from primary care to special care?

The consensus in the NICE CPG was to recommend paediatric nephrology monitoring if there was permanent bilateral renal parenchymal damage, abnormal renal function, hypertension and/or proteinuria.[11]

Other authors consider referral for patients with nephrourological abnormalities, recurrent APN, renal scarring, hypertension, family history of VUR or renal disease and bladder dysfunction syndrome not responding to general measures or associated with VUR and/or thoracolumbar region anomalies.[244,245]

In short, the specialist referral criteria for a child with UTI is based on the need for further tests unavailable in primary care, to confirm diagnosis, prescribe a specific treatment or monitoring of anomalies or complications.

Referral of a child with UTI to a specialist would be indicated if required to slow the progression of detected kidney disease or to require confirmation of renal damage in situations with increased risk of it being associated: e.g., structural or functional abnormalities of the urinary tract, atypical or recurrent UTI or patients younger than 2 years old.

Recommendations

√	Refer patients from primary care to specialist care if they meet any of the following criteria: – Febrile urinary tract infection and/or UTI in children under 2 years or in patients who cannot control urination and cannot be completely investigated in primary care. – Recurrent urinary tract infections. – Atypical UTI: fever >48 hours, unusual bacteria. – Structural abnormalities, single kidney and/or nephrourological functional abnormalities. – Permanent kidney damage confirmed by imaging studies or blood markers (urea, creatinine, cystatin C) or urine (proteinuria, maximum urinary osmolality). – Hypertension – Failure to thrive. – Family history of nephrourologic disease and/or CKD. – Anxious family and/or diagnostic confirmation.

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13. Treatment of the acute phase of UTI

13.1 Start of empirical treatment

Key question:

- When should antibiotic treatment for suspected febrile UTI start?

Antibiotic treatment of urinary tract infection (UTI) starts in most cases without knowing the bacteria responsible for the infection. One of the issues frequently raised in the consultation is when to start antibiotic treatment. One of the first studies was an animal study[246] which provided a clear relationship between the delay in onset of antibiotic treatment and the possibility of renal parenchymal damage. Subsequently, a study by Smellie et al.[247] investigated the severity of renal scarring as a function of delay in diagnosis and suggested a clear relationship between the delay in diagnosis/treatment of febrile UTI and renal scarring. While considering that the clinical improvement the patient obtains after starting antibiotic treatment is reason enough to avoid delays in treatment, it is important to know if the period between the beginning of clinical picture and early treatment may have implications for the complete resolution of the infection and the appearance of sequelae (renal scars).

One study evaluated the prevalence of renal damage in 150 paediatric patients in an emergency department diagnosed with first UTI (presence of fever unspecified). The study assessed the presence of renal scarring at 2 years. The final analysis was performed only on a total of 75 patients. In the 55 patients without renal scarring, median days delay to the start of treatment was 2 days (range 0-22 days), in 20 patients with renal scarring this median was 3.5 days (range 0-62 days), this difference was not significant (P=0.10).[11]

Case series 3

A study in 287 children related the presence of renal scarring after 12 months of the UTI episode to the time between the onset of fever and the onset of antibiotic treatment (within 3 days in all cases), and found no differences (OR 0.99, 95% CI 0.65-1.51). There were also no differences when evaluating the results according to disease severity, the level of hyperthermia or length of hospital stay.[211]

Cohort studies 2+

A study aimed at assessing oral antibiotic therapy against sequential intravenous treatment of febrile UTI in 306 infants aged between 1 and 24 months to analyse risk factors related to the presence of renal scars finds, at 6 months, an increased incidence of renal scarring in infants who received antibiotic treatment ≥24 hours after the onset of fever (11.9%) compared to those receiving antibiotic treatment before 24 hours (9.1%); this, however, was statistically not significant (P=0.29). A multivariate analysis of other predictor variables only related the presence of scars with the grade of VUR.[212]

Cohort studies 2+

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A study to evaluate the presence of different risk factors in the development of acute kidney injury and the development of renal scars in a sample of 227 children with febrile UTI found the presence of VUR (OR 2.32, *P*=0.034) and therapeutic delay time (5.11+3.17 days until the start of treatment in patients with acute injury compared to 2.67+1.93 days in patients without injury acute; OR 1.35, *P*=0.001) as associated risk factors for acute kidney injury.

In those patients who developed acute injury (127 patients), the study found risk factors associated with the development of renal scarring at 6 months to be the presence of VUR (OR 10.12, *P*=0.004) and the antibiotic therapeutic delay time (7.10+3.39 days until the start of treatment in patients with scarring compared to 3.54+1.82 days in patients without scars; OR 2.36, *P*=0.001).[160]

Cohort studies
2-

A study of infants with first febrile UTI (n=278, 153 boys and 125 girls; median age 3.5 months, range 0.5-12 months) assessed whether the delay in the start of treatment (median delay 2 days, range 1-8 days) correlated with the development of acute inflammatory changes and subsequent development of renal scarring. The study found that early and appropriate antibiotic treatment (within 24 hours of the onset of symptoms) decreased the likelihood of kidney affectation (DMSA) during the acute phase of infection (41% for affected patients treated within the first 24 hours, 59% if treated on the second day, 68% if treated on the third day, and 75% if treated on day four or later, *P*=0.000). However, it did not prevent scarring (DMSA 5-26 months after the acute phase, performed on only 76 of the 158 patients with acute phase affectation), as there were no significant differences in the incidence of renal scarring between patients starting treatment within 24 hours (46%) and those who started later (54%).[27]

Cohort studies
2-

A study aimed at comparing the efficacy of sequential therapy versus IV therapy in 548 children (2-58 months of age) with first febrile UTI also assessed whether the fact of starting antibiotic treatment within 48 hours from the onset of fever or later influenced the increased presence of renal scarring at 6-9 months. The study found no significant differences in the incidence of renal scarring between those who started treatment before 48 hours (47%) and those who started treatment later (53%).[207]

Cohort studies
2-

The GDG considered several additional considerations regarding the consistency of the evidence. Only the Oh et al.[160] study found an association between delay in starting antibiotic therapy and the incidence of renal scarring, while the other studies found no significant differences.[27,207,211,212,230] This could be due to a longer delay in starting treatment in this first study. The GDG believes that, even assuming that the time of starting antibiotic treatment has no effect on scarring, one must also consider the degree of patient affectation and the impact the disease may have on the patient during any delay in starting treatment.

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Evidence summary

2+	There were no significant differences in the incidence of renal scars in patients between those who received early antibiotic treatment (24h)[211,212] and those receiving it later.
2-	Patients with renal scars had a greater delay in the start of antibiotic treatment (7.10+3.39 vs 3.54+1.82 days; OR 2.36, *P*=0.001).[160]

Recommendations

√	It is recommended to start early antibiotic treatment at the first suspicion of febrile UTI, as delaying the onset of antibiotic therapy in febrile UTI cannot be justified on safety grounds.

13.2 Empirical therapy administration route

Key question:

- What is the most appropriate administration route for the antibiotic treatment of febrile UTI in infancy and childhood?

Febrile UTI is one of the most common bacterial infections in children.[248] Traditionally, orally administered (PO) antibiotic treatment has been recommended for lower UTI or UTI without fever, and intravenous (IV) for upper UTI or febrile UTI. In the latter case, the usual practice is first to administer antibiotics intravenously and then by PO for 7-14 days to clear the infection and prevent kidney damage. However, a RCT by Hoberman et al.[212] suggested that febrile UTI can be treated with PO antibiotics; this is discussed below.

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A SR of 23 studies including 3,295 patients from 0-16 years of age with APN aimed to assess the risks and benefits of different antibiotic regimens for the treatment of APN. It found 3 studies (total of 844 patients) comparing antibiotic administration by PO for 10-14 days with IV administration for 3 days or until the resolution of fever, followed by PO administration. No significant differences were found in the median time to clearance of fever (weighted mean difference 1.54, 95% CI -1.67 to 4.76); the rate of recurrence of symptomatic UTI at 6 months (RR 0.67, 95% CI 0.27-1.67); the rate of permanent renal damage by DMSA in relation to all patients with APN (RR 0.87, 95% CI 0.35-2.16); or the total number of patients with defects in the initial DMSA (RR 0.80, 95% CI 0.38-1.7). The SR from the data of one of the included studies performed a subgroup analysis and found no differences in the number of renal parenchymal disorders at 6 months by DMSA in patients with VUR (RR 1.88, 95% CI 0.83-4.24) nor in patients without VUR (RR 0.80, 95% CI 0.23-2.73). Although it noted that in patients with VUR grade III to V, persistent renal parenchymal disorders by DMSA at 6 months were more frequent in patients receiving antibiotic therapy by PO than patients who received initially IV antibiotics followed by PO (RR 13.6, 95% CI 1.00-54.01).[231] RCT SR 1+

The SR also included 5 studies (a total of 534 patients) comparing the administration of IV antibiotic treatment of short duration (3-4 days) followed by PO administration with long-term IV antibiotic treatment (7-14 days). No significant differences were found in the recurrence of UTI within the first 6 months (RR 1.15, 95% CI 0.52-2.51); the rate of permanent renal damage by DMSA (3-6 months) for all patients with APN (RR 1.13, 95% CI 0.86-1.49); nor in the relation to the total number of patients with defects in the initial DMSA (RR 1.10, 95% CI 0.84-1.45). Based on data from 2 studies, the SR included an analysis by subgroups and found no differences in the number of renal parenchymal disorders by DMSA (3-6 months) in patients with VUR (RR 0.99, 95 % 0.56-1.74), in patients without VUR (RR 1.19, 95% CI 0.81-1.76), in patients under 1 year of age (RR 1.46, 95% CI 0.71-3.01) and in patients older than 1 year of age (RR 0.89, 95% CI 0.59-1.34).

Finally, the SR included data from a study comparing an antibiotic regimen of a single intramuscular (im) dose followed by PO for 10 days against antibiotic PO administration at the same dose. No differences were found between groups for the persistence of bacteriuria after 48 hours (RR 0.77, 95% CI 0.19-3.20), persistence of clinical symptoms (RR 0.82, 95% CI 0.24-2.81) or total adverse events (RR 1.37, 95% CI 0.33-5.68). No child had UTI symptoms 1 month after treatment.[231]

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A study of 502 patients (aged 1 month to 6 years of age) with clinical diagnosis of the first episode of APN evaluated the safety and effectiveness of antibiotic treatment exclusively by PO (amoxicillin-clavulanate for 10 days) against initial intravenous antibiotic treatment (ceftriaxone for 3 days) followed by PO treatment (amoxicillin-clavulanate for 7 days) on renal scarring. The study found no significant differences in the rate of permanent renal damage by DMSA at 12 months (RD -4%, 95% CI -11.1 to 3.1).[232] RCT 1+

A study with 548 children (median age 15 months, range 3-191 months) with a first episode of APN evaluated the efficiency on renal scarring in DMSA at 6-9 months of IV antibiotic treatment of 8 days with ceftriaxone compared with a schedule of IV for 3 days with ceftriaxone followed by 5 days of treatment by PO according to the antibiogram. No significant differences between groups in relation to the presence of renal scars were found (RR 1.45, 95% CI 0.79-2.67).[207] RCT 1-

The GDG considered the applicability, consistency and relevance of the results when making recommendations. The studies included were conducted in developed countries, and included samples of patients diagnosed with febrile UTI able to be treated orally, excluding the most serious patients and patients with severe predisposing malformations. Therefore, the results are not applicable to risk groups such as children with known high grade VUR (IV-V).

All studies concluded that patients with febrile UTI could have PO treatment, excluding those more seriously affected and those with severe predisposing malformations. Therefore, the results are applicable to children with upper UTI only, with no underlying nephrourologic pathology and provided their clinical condition allows.

Finally, the GDG considered that PO antibiotic treatment of febrile UTI in infancy provides a significant financial saving for the health service (lower treatment cost, shorter hospitalisation), as well as no doubt improving the quality of life and social cost to the patient and families.

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Evidence summary

1+	In the treatment of febrile UTI, there were no significant differences for any of the variables analysed (mean time to defervescence, recurrence rate of symptomatic UTI, rate of permanent kidney damage) for exclusively PO antibiotic administration versus short-term IV then PO antibiotic administration.[231,232]
1+	In the treatment of febrile UTI, there were no significant differences for any of the variables analysed (recurrence rate of UTI, rate of permanent kidney damage) for short-term intravenous antibiotic administration then PO versus long-term IV.[231]

Recommendations

A	Oral administration is the recommended route of choice for antibiotic treatment of children with febrile UTI without known obstructive urological disease and no symptoms of a serious infection.
√	Intravenous antibiotic administration is recommended in children with suspected obstructive uropathy or high-grade VUR (IV-V), signs of septicaemia, uncontrollable vomiting or dehydration.
A	If antibiotic treatment is started intravenously, it is recommended to continue with oral administration when the patient's clinical condition allows it.
√	Clinically evaluate the patient after approximately 48 hours of antibiotic treatment by any route of administration.

13.3 Choice of empirical therapy

Key question:

- What is the most effective empirical antibiotic treatment for febrile UTI (APN) and afebrile UTI?

The choice of antibiotic treatment for UTI should be based on the urine culture and sensitivity results. However, if the symptoms or clinical status do not allow waiting for this information, it is important to know which antibiotic to use empirically in this initial period.

The NICE CPG analysed data from 3 randomised clinical trials regarding the empirical treatment of afebrile UTI. — RCTs 1+/1-/1-

The first compared cefixime PO versus TMP-SMX PO in children aged 6 months to 13 years of age with symptoms of UTI. There were no differences in any outcome variables between groups (leukocytosis, body temperature, urine analysis). — 1+

The other 2 RCTs compared TMP PO with TMP-SMX PO, and TMP-SMX PO with SMX PO. There were no differences between groups for any outcome variables (urine sterilisation and clinical response).[11] — 1-

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A SR of 6 studies compared different antibiotics with each other in the empirical treatment of APN. RCT SR 1+

Three studies involved a total of 108 children compared 3rd-generation cephalosporins (cefotaxime IV, cefetamet PO, ceftibuten PO) with amoxicillin-clavulanate or TMP-SMX. No significant differences were found for any of the variables analysed: persistence of bacteriuria after 48h of treatment (RR 5.5, 95% CI 0.3-101.3), recurrent UTI (RR 0.42, 95% CI 0.03-6.23), persistent fever >48 hours (RR 5.0, 95% CI 0.3-92.6), gastrointestinal adverse effects (RR 0.55, 95% CI 0.10-3.16).

One study, with a sample of 299 children, compared a 3rd-generation cephalosporin (ceftazidime IV) against a 4th generation cephalosporin (cefepime IV). Again, there were no significant differences in outcome variables analysed: persistent or recurrent bacteriuria with the same pathogen, recurrent UTI with same pathogen, clinical response and frequency of adverse effects.

Another study compared two 3rd-generation cephalosporins (ceftriaxone IV against cefotaxime IV) in 100 children over 24 months old. No significant differences were found for any of the outcome variables analysed: bacteriuria at the end of treatment, recurrent UTI 1 month after treatment and total adverse events. A subgroup analysis showed that there were no differences in outcomes of bacteriuria at the end of treatment and recurrent UTI 1 month after treatment in patients with and without urinary tract abnormalities.

A final study sample included 16 patients and compared 2 aminoglycosides (isepamicin IV versus amikacin IV). The study found no differences between groups for persistent bacteriuria at 48 hours after treatment and 7-30 days after treatment, nor in the mean time to resolution of fever.[231]

A review of the etiology of the UTI observed in different series of paediatric patients and the sensitivity of uropathogens isolated to different antibiotics consisted of 10 studies conducted in Spain. It showed that E. coli was the primary cause of UTI in childhood with a prevalence of 70-90% of cases in the most recent studies.2 The data in this review was completed and updated with subsequent national series (Chapter 6.1, Table 9), showing similar prevalence values for E. coli (70-80%).[65,67] Case series SR 3

The different national series in this guide (Chapter 6.1, Table 10) showed resistance to *E. coli*, in the range 50-80% for ampicillin, 7-15% for amoxicillin-clavulanate and 18-38% for TMP-SMX.

When making recommendations, the GDG considered the consistency, applicability and relevance of the results found. It was observed that all studies included obtained consistently good results in terms of efficacy for the individual antibiotics (sulfonamides, TMP-SMX, 3rd or 4th generation cephalosporins, amoxicillin-clavulanic acid and aminoglycosides). However, the GDG considered that the high degree of resistance of *E. coli* to sulphonamides and TMP-SMX in Spain puts their applicability in question. It believes that knowledge of the antibiotic resistance patterns for the main pathogens responsible for UTI in children (*E. coli*, *Proteus* and *Klebsiella*) throughout the country is especially important when starting empirical antibiotic treatment, to

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ensure it is effective and prevent the emergence of new antibiotic resistance. Therefore, the GDG concludes that all professionals should focus on the empirical treatment of UTI depending on the etiological and resistance data provided by their reference microbiology laboratory.

Evidence summary

1+	There were no significant differences in efficiency between the different individual antibiotics compared for the treatment of afebrile and febrile UTI.[11,231]
3	The main etiological agent of UTI in children in Spain is *E. coli*, with a prevalence of 70-90%, and with a resistance to ampicillin of between 50-80%, resistance to TMP-SMX in 18-38% of cases and resistance to amoxicillin clavulanate in 7-15 % of cases.[2]

Recommendations

√	The choice of empirical antibiotic treatment for UTI must be based on knowledge of local resistance.
√	At present in Spain, for empirical antibiotic treatment of UTI without fever seems appropriate to use amoxicillin-clavulanate, 1st or 2nd generation cephalosporins, phosphomycin, nitrofurantoin or TMP-SMX if the sensitivity information provided by local laboratory permits.
√	At present in Spain, for PO empirical antibiotic treatment of UTI with fever seems appropiate to use 3rd generation cephalosporins, and as an alternative amoxicillin-clavulanate or 2nd generation cephalosporins (if sensitivity is greater than 80-90% for *E. coli*).
√	At present in Spain, for IV empirical treatment of UTI with fever seems appropriate to use 3rd generation cephalosporins IV (cefotaxime, ceftriaxone) or as an alternative an aminoglycoside (gentamicin, tobramycin), amoxicillin-clavulanate IV or 2nd generation cephalosporins IV. Other 3rd generation cephalosporins, such as ceftazidime, and other antibiotics such as amikacin, carbapenems and quinolones should be reserved for special circumstances.
√	At present in Spain, for patients younger than 3 months open to the possibility of infection with enterococci, associate ampicillin to the recommended treatment base.

13.4 Aminoglycosides and single daily dose administration

Key question:

- How safe and effective is a daily dose of aminoglycosides when these antibiotics are required in the treatment of UTI?

Aminoglycosides are a group of antibiotics widely used in the treatment of bacterial infections including UTI. They have been traditionally administered in multiple dosing regimen, however, a number of studies in the last two decades have demonstrated they are also safe and effective in a single daily dose regimen.

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A SR of 3 RCTs, with a total of 495 children diagnosed with APN, compared parenteral administration of an aminoglycoside antibiotic (gentamicin or netilmicin) in a single daily dose to an 8-hour dosing regimen. RCT SR 1+

No significant differences were found between the different regimes for a number of different outcome variables analysed: persistent bacteriuria 1-3 days after initiation of treatment (RR 1.05, 95% CI 0.15-7.27), persistent bacteriuria 1 week after completion of therapy (RR 2.84, 95% CI 0.12-68.58), UTI recurrence 1 month after completion of therapy (RR 1.18, 95% CI 0.33-4.23), persistence of symptoms after 3 days of treatment (RR 1.98, 95% CI 0.37-10.53), mean time to defervescence (WMD 2.40 hours, 95% CI -7.90 to 12.70), number of patients with hearing loss (RR 2.83, 95% CI 0.33-24.56) and number of patients with renal dysfunction (RR 0.75, 95% CI 0.20-2.82).[231]

There was another meta-analysis that included 24 RCTs (3 of which were included in the previous SR) which evaluated the efficacy and toxicity of administering a single daily dose compared with multiple daily doses of different aminoglycosides (gentamicin, netilmicin, amikacin and tobramycin) in the treatment of various infections and clinical settings for children: cystic fibrosis, cancer, UTI, different infectious diseases, paediatric ICU and neonatal ICU. RCT SR 1+

The results of 10 and 7 RCTs were analysed for the efficacy of single daily dosing of aminoglycosides against multiple daily doses, while observing that there were no significant differences in terms of clinical failure (n=657 patients; RR 0.67, 95% CI 0.42-1.07) or microbiological failure (n =558; RR 0.51, 95% 0.22-1.18) by the fixed effects model.

Similarly, the results of 20 RCTs (n=1,878 patients) and 13 RCTs (n=842 patients) were analysed for nephrotoxicity and ototoxicity while observing there were no significant differences in any of the cases by the fixed effects model (RR 0.97, 95% CI 0.55-1.69) and (RR 1.06, 95% CI 0.51-2.19), respectively.[249.]

The GDG noted that the administration of a single daily dose of aminoglycosides in paediatric practice had similar efficacy and safety to other dosage regimens. However, when making recommendations, it also considered that the single dose regimen reduced treatment costs, simplified management and made it more comfortable for both patients and medical staff.

Evidence summary

1+	There were no differences in terms of safety and efficacy between the administration of a single daily dose of aminoglycosides and multiple daily doses in children.[231,249]

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Recommendation

A	It is recommended to administer aminoglycosides in a single daily dose when required for the treatment of febrile UTI in children.

13.5 Duration of antibiotic treatment

Key question:

- What is the most effective duration of antibiotic treatment in afebrile and febrile UTI?

The duration of antibiotic treatment for UTI is the subject of debate. The usual recommendation is for 10-14 days, but to reduce costs, promote compliance and reduce the emergence of resistance, shorter treatment regimens are suggested for lower UTI or cystitis.

A SR of 10 studies (n=652 patients, aged 3 months to 18 years of age with lower UTI confirmed by urine culture) of different antibiotic treatments (sulfonamides alone or in combination with betalactams and other antibiotics) was performed; with a short administration duration (3-4 days in 9 studies and 2 days in 1 study) being compared with a standard duration (7-14 days) of the same antibiotics, assessing persistence of symptoms, persistent bacteriuria, recurrent UTI, treatment adherence and resistance development. RCT SR 1+

The SR found no significant differences after treatment had finished in the number of patients with persistent bacteriuria from 0 to 10 days (RR 1.06, 95% CI 0.64-1.76), or in the number of recurrent UTIs during the follow-up period of 1-15 months after treatment (RR 0.95, 95% CI 0.70-1.29). No statistically significant differences in the rate of resistance in persistent bacteriuria (RR 0.57, 95% CI 0.32-1.01) or the rate of resistance in children with recurrent UTI (RR 0.39, 95% CI 0.12-1.29). There was no difference in compliance, and only 2 studies reported adverse effects.[250]

A SR was unable to identify eligible studies for comparing short-term antibiotic treatment with standard duration treatment for children with APN, and concluded that the optimal duration of treatment for children with APN remains unknown.[231] RCT SR 1+

Evidence summary

1+	A treatment duration of lower tract UTI of 2-4 days compared with 7-14 days found no significant differences in the frequency of bacteriuria 0-10 days after the end of treatment (RR 1.06, 95% CI 0.64-1.76), or the number of recurrences during 1-15 months of follow-up (RR 0.95, 95% CI 0.70-1.29). There is a tendency towards a lower number of children with resistant organisms in the short-term treatment.[250]

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1+	There are insufficient studies to demonstrate the most effective duration of treatment for APN.[231]

Recommendations

A	The recommended antibiotic treatment duration for afebrile UTI/cystitis is 3-4 days.
√	The recommended antibiotic treatment duration for febrile UTI/APN is a standard duration of 7-10 days.

13.6 Antibiotic treatment in lobar nephronia and renal abscess

Key question:

- What is the treatment of choice and its duration for lobar nephronia (acute focal nephritis) and renal abscess?

Acute lobar nephronia (ALN), also called acute focal bacterial nephritis (AFBN), and renal abscesses are uncommon forms of presentation of UTI. ALN, localised infection without abscess, is considered intermediate between APN and renal abscess. Both are diagnosed by imaging techniques, and they need to be distinguished from other processes such as renal tumours. When isolated, the pathogen most frequently responsible is E. coli, although other bacteria have also been isolated (*Pseudomona aeruginosa, Klebsiella, Enterococcus faecalis, Staphylococcus aureus, Proteus mirabilis*),[58,251,252] so the choice of antibiotic should be directed towards a broad spectrum of bacteria, taking into account the resistance in its environment.

However, the main interest in the treatment of these processes is to establish the route of administration and the optimal duration of treatment.

A RCT conducted in Taiwan included 80 patients diagnosed with ALN and compared treatment with IV antibiotics followed by 3 weeks PO (39 patients, age 4.16±4.22 years) with IV antibiotics followed by 2 weeks PO (41 patients, age 3.72±4.14 years). In both groups, changing from IV to PO was performed 2-3 days after cessation of fever. In both groups, the choice of antibiotic was according to the antibiogram.

The treatment failed (persistent bacteriuria with clinical or recurrent infection) in 7 patients in the group randomised to 2 weeks of treatment. This difference is statistically significant (ARR 17.1, 95% CI 5.6-28.6).[251]

RCT 1-

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A European series of 25 cases (mean age 4.5 years, range 0.25-17.5 years) diagnosed with ALN, analysed residual renal injury after IV treatment (3rd generation cephalosporin + gentamicin or ampicillin + gentamicin as an initial empirical therapy) for a mean of 12.6 days (range 9-16 days), followed by antibiotic prophylaxis (trimethoprim, nitrofurantoin, cefixime and cefaclor) for periods of 4 weeks to 6 months (mean 10 weeks). Three patients progressed to renal cyst formation and 2 developed renal scarring.[58] — Case series 3

A Taiwanese case series of 45 patients (median age 5.1 years, range 1 month to 16 years) diagnosed by CT with ALN and renal abscess (n=43 patients) or renal abscess (n=2 patients) analysed the results after administration of antibiotic therapy, initially IV then PO for 3-6 weeks, associated with percutaneous drainage, where necessary. After antibiotic treatment, 3 patients required percutaneous drainage; no case required open surgery or nephrectomy, and there was no abscess recurrence during follow-up. Twenty one out of 23 (91%) patients with DMSA performed 6-12 months after completion of the antibiotic treatment had renal scarring at the site of the abscess.[55] — Case series 3

A series of 127 patients (<15 years) diagnosed by CT with ALN from 2 hospitals in Taiwan analysed the correlation between clinical presentation and CT findings. There were 98 patients who received antibiotic treatment for 3 weeks and 29 patients treated for 2 weeks. ALN was classified according to CT findings: 94 patients were diagnosed with simple ALN (striatal regions or poorly defined wedge-shaped and less nephrographic density but more homogeneous) and 33 patients were diagnosed with complicated ALN (decreased heterogeneous density). There were 4 cases of treatment failure (recurrence of infection, persistent bacteriuria or absence of clinical improvement), all of whom had complicated ALN: 1 (of 24 patients) in the 3-week treatment group and 3 (of 9) in the 2-week group. There were no failure of treatment in any of the 94 patients with simple ALN[56] — Case series 3

Although the population studied was mostly Asian and belonged to a health, social and cultural environment different to the Spanish one, the GDG considered that the results could be applicable to our environment. The authors of most studies, including the single RCT as well as the case series, were consistent in proposing initial IV administration of antibiotics then PO after remission of fever.

Evidence summary

1-	Patients receiving antibiotic treatment for 2 weeks were more at risk of therapeutic failure (ARR 17.1, 95% CI 5.6-28.6) than those receiving the treatment for 3 weeks.[251]
3	All cases of treatment failure (recurrence of infection, persistent bacteriuria or absence of clinical improvement) were observed in patients diagnosed with complicated ALN[56]

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3	91% of patients diagnosed with renal abscess had renal scarring at the site of the abscess 6-12 months after completion of the antibiotic treatment.[55]
3	Most authors recommend the administration of broad spectrum antibiotics and use as initial treatment a combination of 3rd generation cephalosporin + aminoglycoside, administered IV.[58]

Recommendations

√	As treatment of choice for ALN and renal abscess it is recommended to use 2 antibiotics, chosen according to local sensitivities, initially administered intravenously then PO after clinical improvement.
D	The recommended antibiotic treatment duration for ALN and renal abscess is 2-3 weeks.

13.7 Symptomatic medication in UTI treatment

Key question:

- Does the use of symptomatic (anti-inflammatory) medication help improve symptoms or prevent kidney damage?

A study in Iran, assessed the role of treatment with dexamethasone in decreasing urinary levels of cytokines (IL-6 and IL-8) as an intermediate variable in the formation of renal scars in patients diagnosed with febrile UTI. A total of 34 patients (29 girls and 5 boys, mean age 3±2.8 years) received dexamethasone (0.15 mg/kg/6h) for 3 days with ceftriaxone, compared with a control group of 20 patients (17 girls and 3 boys, mean age 3.6±3.1 years) who received only antibiotic treatment with ceftriaxone. The study evaluated urinary concentrations of IL-6 and IL-8 at the time of diagnosis and 72 hours after initiation of treatment and found significant differences in the experimental group between the levels of IL-6 and IL-8 at the time of diagnosis and at 72 hours (P<0.001). The study also found significant differences in the decrease in urinary concentrations of IL-6 and IL-8 in the experimental group compared with the control (P<0.05). It concluded that the use of dexamethasone in combination with antibiotics may prevent renal scarring by reducing the inflammatory response. The study did not provide clinical or imaging data on the relationship between the decrease in urinary levels of IL-6 and IL-8 and the presence of permanent renal damage.[253]

Case control study 2-

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A primary care centre study in Germany compared the use of ibuprofen (400mg/8 hours) over the use of ciprofloxacin (250mg/12 hours) for 3 days in adult women (age range 18-85 years) with uncomplicated UTI to evaluate the efficacy of ibuprofen in the resolution of urinary symptoms on the 4th day after starting treatment. The study performed a per protocol analysis and found that 58.3% of patients who received ibuprofen were free of symptoms on the 4th day, compared with 51.5% of patients receiving ciprofloxacin (P=0.74). Patients who received ibuprofen reported fewer urinary symptoms on the 4th day than patients receiving ciprofloxacin. Due to a continuation or worsening of symptoms, 33% of patients receiving ibuprofen needed additional antibiotic treatment, compared with 18% of patients receiving ciprofloxacin (P=0.247). In neither case were significant differences found between the groups receiving ibuprofen and receiving ciprofloxacin.[254]

RCT 1-

In addition to these studies, three other studies were identified, but were excluded from the volume of the evidence for being either in-vitro[255] or animal sample[256,257] studies.

No studies were found of a suitable design, with good methodological quality, or had an appropriate study population or relevant come variables to be able to answer the question posed in this section.

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14. Prophylaxis for UTI

14.1 Antibiotic prophylaxis in children shown to have no structural or functional urinary tract abnormalities

Key question:

- Does antibiotic prophylaxis help to prevent further UTI and/or kidney damage in infants and paediatric patients without structural and/or functional abnormalities?

Urinary tract infection (UTI) is a common childhood disease that can be associated with long-term morbidity and also renal impairment that will affect 5% of children with a first ITU.[258] The observation that UTI and vesicoureteral reflux (VUR) are associated with kidney damage has led to cystograms being performed on patients with UTI to detect VUR, and establish a daily low dose of antibiotics for several years to prevent new UTI and renal damage. It is known that other patients without VUR are also at risk of UTI, and antibiotic prophylaxis has also been indicated for these. At present this clinical practice is under question.

The NICE CPG performed a meta-analysis to evaluate the efficacy of antibiotic prophylaxis in preventing recurrence of UTI and renal damage. This meta-analysis included 9 studies, and performed a subgroup analysis in children: patients with ABU; those with UTI but not VUR, or with a small portion of patients with VUR; and finally, a subgroup of patients with VUR.

RCT Meta-analysis 1+

The subgroup analysis showed that antibiotic prophylaxis did not reduce the risk of recurrence of symptomatic UTI (RR 1.04, 95% CI 0.64-1.68) or the incidence or progression of renal parenchymal damage (RR 1.11; 95% CI 0.54-2.28) in any of the subgroups. There was a significant reduction in the levels of ABU at the end of prophylaxis (RR 0.36, 95% CI 0.29-0.45), but this difference was not significant in the subgroup of patients with VUR (RR 0.84, 95% CI 0.45-1.58).[11]

An updated meta-analysis from the above assessed the efficacy of antibiotic prophylaxis in preventing the development of new renal scarring and a recurrence of symptomatic UTI in children. It also performed a subgroup analysis: patients with symptomatic UTI with and without VUR; patients with symptomatic UTI without VUR; patients with symptomatic UTI with VUR; and finally, patients with VUR.

RCT Meta-analysis 1+

The meta-analysis showed that antibiotic prophylaxis did not reduce the risk of incidence or progression of renal parenchymal damage in any of the subgroups (RR 1.15, 95% CI 0.75-1.78) or of recurrent symptomatic UTI in any of the subgroups analysed for this variable outcome (RR 0.96, 95% CI 0.69-1.32).[259]

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A study of 83 patients (≤6 years of age) with recurrent UTI showed that antibiotic prophylaxis was not associated with a decreased risk of recurrent UTI (HR 1.01, 95% CI 0.50-2.02), but was a risk factor for antimicrobial resistance (OR 7.50, 95% CI 1.60-35.17).[28]	Case control study 2+
A multi-centre study in Australia (PRIVENT study) evaluated the efficacy of antibiotic prophylaxis with low doses of TMP-SMX (2/10 mg/kg) to prevent the recurrence of symptomatic UTI in a sample of 576 children (mean age 14 months) with a history of at least one UTI followed for 12 months; 42% of the sample had VUR. The study found a statistically significant decrease in the number of symptomatic UTIs (HR 0.61, 95% CI 0.40-0.93; NNT 14, 95% CI 9-86). Among the secondary variables analysed, the study found statistically significant differences associated with a decreased risk of febrile UTI (HR 0.49, 95% CI 0.28-0.86; ARR 6%, 95% CI 1-11) and an increase of infections by TMP-SMX-resistant organisms (ARR 42%, 95% CI 22-61). There were no significant differences for the rest of the secondary variables: progression of kidney damage (ARR 4%, 95% CI -12 to 19), hospital admissions (ARR 2%, 95% CI -3 to 7), or adverse reactions (ARR 2%, 95% CI 0 to 5).[258]	RCT 1++

When making recommendations the GDG considered the applicability, consistency and impact of the results. The group considered that the samples of children from the different studies were similar to children in Spain and therefore the results are applicable, except for the Australian PRIVENT study, whose results are not applicable in our setting, given the significant resistance to TMP-SMX in our environment.[260]

There is some disagreement about the consistency of the results. The studies included in the meta-analyses[11,259] did not show any reduction in recurrent UTI or renal damage after prophylactic antibiotic treatment, and only showed a reduction in the prevalence of ABU.[11] However, the PRIVENT study[258] showed that 1 case of recurrent symptomatic UTI was prevented for every 14 patients treated with TMP-SMX, which represents a modest but significant reduction in the number of recurrent UTIs. As noted by Hoberman et al., this discrepancy may be due to the low statistical power of detecting clinically relevant differences in the various individual studies; the lack of blinding in some studies; the different classifications of these variables, given the different definitions of what was considered as UTI in the studies; or the use of inclusion criteria not representative of the entire affected population.[261]

Despite this, all studies were consistent in the lack of effect of antibiotic prophylaxis for the prevention of renal damage. This would suggest that it would be enough to treat each episode of UTI, as suggested by Craig et al. They concluded that, considering the low risk of new renal damage after a single UTI (5%), an absolute risk reduction of symptomatic UTI of 6% in patients receiving antibiotic prophylaxis represents a small impact on kidney damage, at best.[258] However, it should be emphasised that none of the studies included in the meta-analyses reviewed here,[11,259] including the PRIVENT study, had sufficient power to estimate the effect of antibiotic prophylaxis on kidney damage.

The GDG considered that at present there is wide clinical variability in the therapeutic management of children with urinary infection. Until now, it had been almost universally accepted that continuous antibiotic prophylaxis decreased recurrent UTI and renal scarring, which may lead to ESRD. If the current data does not show antibiotic prophylaxis benefitting patients in protecting the kidney and its future functioning, the implications for practice will be highly significant. One

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should also take into account the increase of bacterial resistance in the community and the possibility of rare but serious complications with the use of some drugs used for antibiotic prophylaxis.

Therefore, the GDG considered that, although prophylaxis may reduce the risk of UTI, this reduction has no effect on renal damage but leads to the emergence of resistant strains. It is therefore not appropriate to recommend antibiotic prophylaxis routinely in children with a first UTI and without structural or functional alterations being verified.

Evidence summary

1++	Low dose administration of TMP-SMX as a prophylactic treatment reduces the risk of recurrent symptomatic UTI in paediatric patients with at least one symptomatic UTI (HR 0.61, 95% CI 0.40-0.93; NNT 14, 95% CI 9-86).[258]
1++[258]/ 2+[28]	The administration of antibiotic prophylaxis is associated with an increased risk of infections from resistant organisms (ARR 42%, 95% CI 22-61[258]; OR 7.50, 95% CI 1.60-35.17[28]).
1++[258]/ 1+[259]	Antibiotic prophylaxis was not shown to reduce the risk of incidence or progression of kidney damage (ARR 4%, 95% CI -12 to 19[258]; RR 1.15, 95% CI 0.75-1.78[259]).
1+	The administration of antibiotic prophylaxis reduced the prevalence of ABU by the end of the treatment (RR 0.36, 95% CI 0.29-0.45), except in patients with VUR (RR 0.84, 95% CI 0.45-1.58). However, it did not reduce the recurrence of symptomatic UTI (RR 1.27, 95% 0.58-2.80) or the incidence of new renal damage or deterioration (RR 1.04, 95% CI 0.38-2.89) in the subgroup of patients suffering from ABU.[11]

Recommendations

A	Antibiotic prophylaxis should not be routinely given to children who have had a single UTI.
A	Antibiotic prophylaxis should not be given to children with ABU.
√	For children with recurrent UTI, it is recommended to evaluate the use of prophylactic antibiotics individually after appropriate study to rule out structural or functional abnormalities of the urinary tract, and taking into account the existence of resistant strains.

14.2 Choice of antibiotic and chemoprophylactic dose

Key question:

- When antibiotic prophylaxis is deemed necessary, what antibiotics and doses should be recommended?

The International Reflux Study and other randomised trials compared the combination of surgery and antibiotic prophylaxis with prophylaxis alone and found no difference in UTI recurrence rates and renal damage. These findings led to the adoption of prophylactic antibiotics as a treatment of choice in children with VUR.[30] It is known that other paediatric patients without VUR also have a higher risk of UTI and antibiotic prophylaxis was indicated for these children. At present, this

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clinical practice is being questioned. However, it may be indicated under certain circumstances and therefore it would be desirable to know which drugs to recommend and at what dosage for these cases.

A SR[26] was found aimed at determining the efficacy and adverse effects of prolonged prophylactic treatment for recurrence of UTI in children, where prolonged treatment was daily administration of antibiotics for at least 2 months. RCT SR

There were 2 studies within this SR that were relevant for the question posed at the beginning.

The first was a RCT of 130 children (126 girls and 4 boys), of whom 30 had VUR. The study compared nitrofurantoin (1-1.5 mg/kg) with trimethoprim (2-3 mg/kg) during a follow-up period of 6 months. The study found a statistically significant reduction of positive repeat urine culture with nitrofurantoin compared with trimethoprim (RR 0.48, 95% CI 0.25-0.92; RD -18%, 95% CI -34 to -3; NNT 5, 95% 3-33). Simultaneously, the study showed that the probability of prophylactic treatment discontinuation due to side effects (digestive disorders) was 3 times higher in the case of nitrofurantoin (RR 3.17, 95% CI 1.36-7.37; RD 22%, 95% CI 8-36; NNH 5, 95% CI 3-13). The study concluded that the side effects of nitrofurantoin could exceed its prophylactic effect, compared with trimethoprim, since the NNH was 5 (95% CI 3-13) and the NNT was 5 (95% CI 3-33). 1+

The second was 60 girls and compared nitrofurantoin (1 mg/kg) with cefixime (2 mg/kg) during a follow-up period of 6-12 months. The study found no significant differences between treatments in terms of positive repeat urine culture (RR 1.35, 95% CI 0.24-7.48). 1-

Additionally, a study in Iran was identified on a sample of 132 children (age 3 months to 12 years) comparing the efficacy of prophylactic antibiotic nitrofurantoin (1-2 mg/kg/day) against TMP-SMX (2 mg/kg/day of trimethoprim) administered as a single nightly dose over 6 months for the prevention of recurrent UTI (defined as positive culture in urine or urinary symptoms). The study also determined the resistance pattern in both groups. A recurrence rate of 36.2% was found in the nitrofurantoin group, compared with 63.8% in the TMP-SMX group (RR 0.57, 95% CI 0.35-0.92; ARR 19.7%, 95% CI 3.7-35.7; NNT 5, 95% CI 3-27). This greater protective effect of nitrofurantoin vs TMP-SMX was statistically significant only in the age group of 1-5 years (RR 0.44, 95% CI 0.20-0.94; ARR 23.1%, 95% CI 3.5-42.7; NNT 4, 95% CI 2-29). RCT 1-

In the patients taking nitrofurantoin, 37.5% of bacteria causing UTI were resistant to the prophylactic agent, while in the TMP-SMX group 56% of bacteria were resistant to the drug. In Iran, the empirical treatment of choice for various infections is TMP-SMX. The authors concluded that the high percentage of resistance to TMP-SMX may explain its lower efficacy in preventing recurrent UTI.[263]

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Finally, using a reverse search, 2 clinical trials comparing the efficacy of different antibiotics at prophylactic doses in preventing recurrent UTI were identified.

The first was a cross-over RCT which evaluated the efficacy of nitrofurantoin (1.5 mg/kg) against pivmecillinam (100 or 200mg, depending on patient age) in a single daily dose, over a period of 12 months and on a sample of 35 children with VUR or a history of recurrent UTI. The study concluded that there were significant differences in the incidence density of recurrent UTI between groups: 0.6 infections/patient year in those receiving pivmecillinam and 0.4 infections/patient year for nitrofurantoin. The study found differences in terms of tolerance and treatment compliance in relation to side effects: 8 nitrofurantoin treatments were discontinued and 1 with pivmecillinam.[264] RCT 1-

The second was a 3-arm RCT which evaluated the efficacy of TMP-SMX (1-2 mg/kg), cefprozil (5 mg/kg) and cefadroxil (5 mg/kg) in single daily doses over a period of 9 months. The antibiotic treatment was administered only during the first 3 months and on a sample of 80 patients with a history of recurrent UTI and normal urinary tract. The study found no differences between groups for recurrence of symptomatic UTI ($P > 0.05$). However, there were differences in ABU at 3 and 6 months: no cases of ABU in patients who received cefadroxil;7 and 0 cases, respectively, for patients receiving TMP-SMX; and 5 and 7 cases, respectively, in the cefprozil group ($P<0.05$). There were adverse effects due to the prophylaxis in 14%, 9% and 0% of patients from the TMP-SMX, cefprozil and cefadroxil group, respectively, although no patient stopped the treatment.[265] RCT 1-

When making recommendations, the GDG took into account the few studies of good methodological quality and the lack of equivalent comparisons.

Evidence summary

1+[262]/ 1-[263]	Nitrofurantoin was superior to trimethoprim[262] and TMP-SMX[263] as a prophylaxis in the prevention of positive repeat urine cultures and/or urinary symptoms.
1+	The risk of abandoning prophylactic treatment is higher in nitrofurantoin (RR 3.17, 95% CI 1.36-7.37) due to the side effects (NNH 5, 95% CI 3-13).[262]
1-	Nitrofurantoin was not superior to cefixime[262] or pivmecillinam[264] in the prevention of positive repeat urine culture or recurrent UTI.
1-	Cefadroxil was superior to cefprozil and TMP-SMX in preventing positive urine culture, but there were no differences among the 3 antibiotics for the prevention of recurrent UTI.[265]

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Recommendations

√	It is recommended to take into account local resistance patterns when proposing prophylactic treatment, and try to select antibiotics with a narrower spectrum of action to prevent the upper airway bacteria from developing resistance to them.
√	Taking into account the above recommendation, it is recommended to use TMP or trimethoprim-sulfamethoxazole in patients older than 2 months of age, and nitrofurantoin in patients older than 2-3 years; as the use of prophylactic antibiotics or antiseptics cannot be prioritised due to the lack of available evidence.
√	In children under 2 months of age, or in any situation where nitrofurantoin or TMP or trimethoprim-sulfamethoxazole cannot be used, it is recommended to use as prophylactic antibiotic amoxicillin or 1st or 2nd generation cephalosporins.
√	Recommended prophylactic doses are as follows: – Nitrofurantoin: 1-2 mg/kg/day. – TMP-SMX: 2-3 mg/kg/day (of trimethoprim). – Trimethoprim: 2-3 mg/kg/day. – Any other antibiotic: a third or a quarter of the usual recommended dose.

14.3 Antibiotic prophylaxis in children with structural and/or functional abnormalities

Key question:

- Is the use of prophylactic antibiotics effective in preventing further UTI or renal damage in children with structural and/or functional abnormalities of the urinary tract?

Until recently there was an established consensus on the need to provide antibiotic prophylaxis for paediatric patients with urinary tract obstruction or VUR-type abnormalities. Moreover, the approach of administering prophylactic antibiotics to children with functional disorders has focused primarily on the association of these abnormalities with VUR. There are recent studies evaluating the effect of antibiotic prophylaxis in the treatment of VUR and urinary tract obstructions; however, there are very few studies analysing the effect of antibiotic prophylaxis in patients with functional abnormalities of the urinary tract with or without associated VUR, especially when it is remembered that the relationship between VUR and functional abnormality is still not well-defined.

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A multicentre Swedish 3-arm RCT (prophylaxis group, endoscopic therapy group, observation group) evaluated the incidence of febrile UTI, new renal damage and resolution of VUR at the end of a 2-year follow-up period on a sample of 203 patients (128 girls and 75 boys) of 1-2 years old, with VUR grade III-IV (95.6% of cases detected after febrile UTI and 4.4% detected by pre-natal diagnosis). At baseline, 68.7% (88) and 31.3% (40) of girls and 50.6% (38) and 49.3% (37) of boys had VUR III and IV, respectively. Before starting the study, 65% (132) of the sample had been diagnosed with VUR grade III-IV before reaching 1 year of age, and had received antibiotic prophylaxis until the VCUG follow-up between 1 and 2 years of age. RCT 1+

At the end of the follow-up period, a higher incidence of recurrent febrile UTI was found in girls (32.8%) than boys (9.3%), $P<0.05$.

The study showed a lower incidence of recurrent febrile UTI in both girls receiving prophylaxis (8/43) and those receiving endoscopic treatment (10/43) compared to girls kept under observation (24/42), $P<0.05$. There were no significant differences among the boys, or between those girls who received antibiotic prophylaxis and those who received endoscopic treatment.

Prophylactic treatment in girls aged 1-2 years with VUR III-IV significantly decreased the risk of further febrile UTI (RR 0.33, 95% CI 0.17-0.64; ARR 38.5%, 95% CI 19.6-57.5; NNT 3, 95% CI 2-5).

Within the group of patients receiving antibiotic prophylaxis (69), 58 patients received trimethoprim, 6 patients received nitrofurantoin and 5 patients received cefadroxil.

An increase in resistance to trimethoprim was seen in the group of girls who received antibiotic prophylaxis compared with the group of girls kept under observation (RR 2.33, 95% CI 1.31-4.16), $P=0.038$. However, this increase in resistance was not seen in those girls who received prophylactic treatment when compared with those receiving endoscopic treatment ($P=0.70$).[266]

There was a higher incidence of new renal damage by DMSA at 2 years in girls (10%) than in boys (2.6%), even though at baseline the boys were those with more generalised renal damage (59% of boys vs 23% of girls).

The study found a significant reduction ($P<0.05$) in the risk of new renal scarring in girls receiving antibiotic prophylaxis compared with those under observation (ARR 19.0%, 95% CI 7.2-30.9; NNT 5, 95% CI 3-14).

There were no statistically significant differences among the boys, nor among the girls who received antibiotic prophylaxis compared with those who received endoscopic treatment ($P=0.055$), nor among this latter group compared to girls under observation ($P=0.547$).

The study found an increased incidence of new renal damage in girls with recurrent febrile UTI (22%) compared to those without recurrent febrile UTI (2.6%), (RR 8.53, 95% CI 2.84-25.58), $P<0.05$.[214]

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

The PRIVENT study assessed the effectiveness of antibiotic prophylaxis with TMP-SMX against placebo in preventing recurrence of symptomatic UTI in a sample of 576 children (mean age 14 months) with a history of at least 1 UTI and a follow-up period of twelve months. In the sample, 42% (243 patients) had primary VUR grades I-V. Of these, 47% (114) had VUR I-II and 53% (129) VUR III-V. In 17.2% (99) of the global sample the presence of VUR was unknown, and the remaining 40.6% of the sample (234) did not have VUR. The study found an absolute risk reduction of symptomatic UTI in favour of prophylactic treatment in all subgroups of patients with VUR. However, these figures were not statistically significant as the study was not powered to detect changes in these subgroups: patients with VUR grades I-II (ARR 5.4, 95% CI -6.4 to 17.2), patients with VUR III-V (ARR 6.8, 95% CI -6.3 to 19.8).[258]

RCT 1++

A study was found aimed at evaluating the effectiveness of antibiotic prophylaxis administered over a period of 2 years for preventing APN recurrence and renal scarring in a sample of 100 patients (48 boys and 52 girls) diagnosed with VUR grades II-IV after first febrile UTI (21 patients with VUR II, 46 patients with VUR III and 33 patients with VUR IV). Patients were randomised to receive TMP-SMX as antibiotic prophylaxis (50 patients, mean age 9±5.9 months) compared with the untreated control group (50 patients, mean age 8.3±5.4 months). At 2 years, there were no significant differences between the groups for APN recurrence (RR 1.2, 95% CI 0.68-2.11): 18 cases in the antibiotic prophylaxis group vs 15 cases in the control group; nor for the presence of renal scars (RR 1.22, 95% CI 0.75-1.98): 22 cases in the prophylaxis group and 18 cases in the control group.[267]

RCT 1+

A RCT assessing the effect of antibiotic prophylaxis (TMP-SMX or nitrofurantoin) on the incidence of recurrent UTI and renal parenchymal damage in a sample of 113 patients (91 girls, 22 boys) diagnosed with VUR I-III after a first febrile UTI (19 with VUR grade I, 57 with VUR grade II and 37 with VUR grade III). Patients were randomised into 2 groups: the prophylaxis group (55 patients, age: median 3 years, range 3 months-12 years) and the untreated control group (58 patients, age: median 2 years, range 3 months-9 years). At the end of the 1-year follow-up period, the study found the following: no significant difference in UTI recurrence (RR 1.05, 95% CI 0.54-2.07), with 13 cases in both groups; an increased risk of APN (RR 7.33, 95% CI 0.94-58.07), with 7 cases in the prophylaxis group and only 1 in the control group; and an increase in the risk of renal scarring by DMSA (RR 2.64, 95% CI 0.53-13.03), with 5 cases in the prophylaxis group and 2 cases in the control group; however, no differences were statistically significant.[268]

RCT 1+

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Another study evaluated the effectiveness of antibiotic prophylaxis to prevent recurrence of febrile UTI in 338 patients (234 girls and 104 boys) diagnosed with a first febrile UTI. Of these, 38% (128) had primary VUR grades I-III: 30 with VUR grade I, 58 with VUR II and 40 with VUR III. Patients were randomised to receive either antibiotic prophylaxis with TMP-SMX or amoxicillin-clavulanate (211 patients, mean age 14.7±15.5 months) or no treatment (127 patients, mean age 14.7±15.5 months). The study found no significant differences between these groups in preventing new febrile UTI with results as follows: total sample (ARR 2.34, 95% CI -3.8 to 8.4); patients with VUR (ARR 7.5, 95% CI -6.0 to 20.1); patients without VUR (ARR -0.2, 95% CI -5.5 to 5.1); patients stratified by VUR grade: VUR I (ARR 3.8, 95% CI -15.6 to 23.6), VUR II (ARR 1.0, 95% CI -14.1 to 16.1) and VUR III (ARR 19.8, 95% CI -10.8 to 50.4). RCT 1+

The study also found no significant difference in preventing new renal damage, whether new renal scarring (ARR 0.8, 95% CI -2.1 to 3.7) or new renal scarring at the site of the first APN (ARR 3.0, 95% CI -7.6 to 13.6) at the end of follow-up period of 12 months for the total sample.[269]

There was another study which also assessed the effectiveness of antibiotic prophylaxis after a first episode of febrile UTI in a sample of 225 patients (156 girls and 69 boys) diagnosed with VUR grades I-III (22 patients with VUR grade I, 147 patients with VUR II and 54 patients with VUR III). Patients were randomised to receive TMP-SMX (103 patients, mean age 12±8.1 months) or no treatment (122 patients, mean age 10.6±8, 4). At the end of the follow-up period of 18 months, there were no significant differences in UTI recurrence (RR 0.67, 95% CI 0.40-1.11) or febrile UTI (RR 0.81, 95% CI 0.42-1.56) for the whole sample, nor for females (P=0.8). However, the study found differences in the group of boys with VUR grade III (*P*=0.04), but not those with VUR grade I (*P*=0.36) or grade II (*P*=0.41). Additionally, the study showed an increased resistance of *E. coli* to TMP-SMX in the group receiving antibiotic prophylaxis (RR 1.92, 95% CI 1.51-2.45).[270] RCT 1-

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A retrospective study evaluated the incidence of UTI in 92 patients (72 boys and 20 girls) diagnosed with pre-natal hydronephrosis grades III and IV (21 patients with hydronephrosis grade III and 71 patients with hydronephrosis grade IV), of which 56 patients had post-natal diagnosis of ureteropelvic junction obstruction and 36 patients had ureteral obstruction. The mean follow-up from birth was 26.8 months (range 1-122 months). None of the patients in the sample had VUR or lower urinary tract obstruction. Most patients received no antibiotic prophylaxis maintenance, however, 27 patients (29.3%) received antibiotic prophylaxis for a median of 1.43 months while awaiting completion of the VCUG to rule out VUR. The study also evaluated the association of UTI with sex, degree of hydronephrosis, level of obstruction and circumcision status in males (41 boys circumcised, 24 uncircumcised, 7 unknown).

Cohort study 2-

Of the 92 patients, only 4 (4.3%, 95% CI 0.2-0.86) with grade IV hydronephrosis developed a febrile urinary tract infection (3 cases of febrile UTI in the patients with ureteral obstruction and 1 case of febrile UTI in the patients with ureteropelvic junction obstruction); with 3 of the 4 patients subsequently undergoing corrective surgery. The average age of the patient at the time of occurrence of the first UTI was 6.1 months (range 1-11 months). No significant association with sex, degree of hydronephrosis, obstruction level or state of circumcision in children was found. Given the low incidence of UTI during the follow-up period, and in the absence of antibiotic treatment, the authors concluded that antibiotic prophylaxis is not recommended in children with hydronephrosis grades III or IV diagnosed pre-natally, and secondary to upper urinary tract obstruction[271]

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Another similar study to that above evaluated the incidence of UTI during the first 12 months of life of 105 patients (82 boys and 23 girls) diagnosed with pre-natal hydronephrosis grade III-IV (47 patients with hydronephrosis grade III, 58 patients with hydronephrosis grade IV) and post-natal diagnosis of ureteropelvic junction obstruction in 75 patients and ureterovesical obstruction in 30 patients. None of the patients in the sample had VUR and, unlike the previous study, no patient had received prophylactic antibiotic treatment or had undergone circumcision.

Cohort study 2+

At the end of the follow-up period, 36.2% of patients (n=38) had developed UTI. Patients with ureterovesical obstruction had a higher incidence of UTI (15 cases out of 30 patients, 50%), compared to those with ureteropelvic junction obstruction (23 out of 75 patients, 30.7%), *P*=0.063. There were no significant differences found in the incidence of UTI by patient sex (*P*=0.874); nor for the degree of hydronephrosis, with 29.8% of cases in patients with hydronephrosis grade III and 41.4% of cases in patients with grade IV hydronephrosis (*P*=0.219).

There were 92.8% of cases (97) who had their first UTI in their first 6 months of life (mean age 2.6 months).

There were 73.3% of patients (77 cases, consisting of 53 patients with ureteropelvic junction obstruction and 24 patients with ureteral obstruction) who underwent corrective surgery at a mean age of 3.8 months.

There were also differences in the incidence of UTI within the group of patients undergoing surgery, depending on the level of obstruction, with 54.2% of cases in patients with ureterovesical obstruction compared to 24.5% of cases in patients with ureteropelvic junction obstruction (*P*=0.011).

Given the high incidence of UTI during the first 6 months of life, the authors concluded that infants with prenatal diagnosis of hydronephrosis grade III-IV caused by ureteropelvic junction obstruction, and especially those caused by ureterovesical obstruction, should be given antibiotic prophylaxis while waiting for this obstruction to be corrected.[272]

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A final study evaluated the incidence of UTI during the first year of life in 430 patients (351 boys and 79 girls) diagnosed with pre-natal hydronephrosis grade I-IV (161 patients with hydronephrosis grade I, 94 patients with hydronephrosis grade II; 79 patients with hydronephrosis grade III and 96 patients with hydronephrosis grade IV). No patient had VUR or had received prophylactic treatment. None of the boys had been circumcised.

Cohort study 2+

The study found an overall incidence of UTI of 19% (83) during the first year of life, with 84% of these patients (70) having UTI within the first 6 months of life (first episode of UTI at 4.1±2.7 months). The number of UTI episodes was 1.4±0.7 (range 1-4) during the first year.

The study found no significant differences in the incidence of UTI according to patient sex, but found significant differences according to the degree of hydronephrosis and the presence or absence of ureteropelvic junction and ureterovesical obstruction.

It was found that the more severe the degree of hydronephrosis, the higher the incidence of UTI: 4% of patients with hydronephrosis grade I, 14% with hydronephrosis grade II (OR 4.1, 95% CI 1.5-11.3; $P<0.001$); 33% with hydronephrosis grade III (OR 12.7, 95% CI 4.9-32.4; $P<0.001$); and 40% in patients with grade IV hydronephrosis (OR 16.9, 95% CI 6.7-42.1; $P<0.001$).

There was a higher incidence of UTI in patients with obstructive hydronephrosis (39%) than in patients with non-obstructive hydronephrosis (11%), (OR 5.2, 95% CI 3.1-8.6; $P<0.001$).

There was also a higher incidence (47% vs 13%) of UTI in patients with dilated pelvis and ureter (ureterohydronephrosis) than in patients with a dilated pelvis without ureteral dilatation (OR 6.0, 95% CI 3.5-10.3; $P<0.001$). Finally, within the patients with ureterohydronephrosis, those with ureterovesical obstruction also had a higher incidence of UTI (69% vs 35%) (OR 4.2, 95% CI 1.56-11.2; $P=0.004$).

The study concluded by recommending prophylaxis[273] for infants with severe hydronephrosis, hydronephrosis or ureterohydronephrosis due to obstruction, as they have a higher risk of UTI.

The GDG took note of the inconsistencies in the results when making the recommendations. For example, the Brandstrom et al. study[214,266] showed that antibiotic prophylaxis in 1-2 years old girls with VUR grade III-IV was effective in preventing recurrent febrile UTI and new renal damage, but found no similar effect for boys with VUR grade III-IV. It should be noted that the Brandstrom et al. study did not include a representative sample of the current situation in clinical practice, given that 62% of the sample received prophylactic antibiotic treatment prior to the study. The other studies[267-269] showed consistency regarding the lack of efficacy of antibiotic prophylaxis for the recurrence of febrile UTI in children affected by VUR. The difference between the results of these studies with those of Brandstrom et al. regarding the lack of efficacy of antibiotic prophylaxis in patients with VUR III[267-269] and VUR IV[267] is notable. The only consistent aspect seems to be the lack of efficacy of antibiotic prophylaxis in preventing UTI recurrence and renal damage in patients with VUR I- II[267-270] and in boys with VUR grades III- IV, although there are few patients with VUR grade IV.[214,266,267]

No RCTs assessing the effectiveness of antibiotic prophylaxis in children affected by other structural abnormalities were found, with only cohort studies assessing the risk of incidence of UTI in these patients. Among the 3 studies included here, the GDG considered the different inci-

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dence of UTI among patients in the Roth et al. study[271] (4.3%) and the Song et al.[272] study (36.2%) to be notable. The Roth et al. study[271] authors argued that this difference could be due to the use of antibiotic prophylaxis in 29.3% of their sample and the circumcision status of boys in their sample (63.0% circumcised). However, other notable differences between the 2 studies could be due to the fact that no criteria were established to define the terms of obstruction in the Roth et al. study,[271] with its diagnosis and interpretation being left to the discretion of the specialist. The fact that ultimately only 3 of 92 cases were corrected surgically suggests that the Roth et al. study[271] overdiagnosed cases of obstructive hydronephrosis, and in fact were very probably non-obstructive dilatations.

No studies evaluating the efficacy of antibiotic prophylaxis in patients with functional abnormalities were found.

Evidence summary

1+	Antibiotic prophylaxis reduces the risk of recurrent febrile UTI in girls aged 1-2 years with VUR III-IV, (ARR 38.5%, 95% CI 19.6-57.5) and new renal damage (ARR 19.0%, 95% CI 7.2-30.9).[214,266]
1+	Antibiotic prophylaxis was not shown to reduce the risk of further febrile UTI or new renal damage in children with VUR grades I-II.[267-269]
1+	Antibiotic prophylaxis was not shown to reduce the risk of further febrile UTI or new renal damage in boys with VUR gradeIII214,266-269 or in boys with VUR grade IV.[214,266,267]
2+	The incidence of UTI in patients with obstructive hydronephrosis grade III-IV without VUR who did not receive prophylactic antibiotic treatment was 36.2% in the first year of life, with a greater incidence (50%) in patients with ureterovesical than ureteropelvic junction obstruction (30.7%), P=0.063.[272]
2+	The presence of severe hydronephrosis increases the risk of UTI: hydronephrosis grade II (OR 4.1, 95% CI 1.5-11.3) grade III (OR 12.7, 95% CI 4.9-32, 4), grade IV (OR 16.9, 95% CI 6.7-42.1).[273]
2+	A dilated pelvis and ureter increase the risk of UTI with regard to renal pelvis dilatation in patients diagnosed pre-natally (OR 6.0, 95% CI 3.5-10.3), P<0.001.[273]
2+	Ureteropelvic junction obstruction increases the risk of UTI compared to non-obstructive dilatation of the pelvis in patients diagnosed pre-natally (OR 5.2, 95% CI 3.1-8.6), P<0.001.[273]
2+	Ureteral obstruction increases the risk of UTI compared to non-obstructive ureteral dilatation in patients diagnosed pre-natally (OR 4.2, 95% CI 1.56-11.2), P=0.004.[273]

Recommendations

B	It is recommended to use antibiotic prophylaxis in girls with VUR grades III-V for 1 year or until the degree of VUR is re-evaluated by cystographic examination.
√	It is recommended to use antibiotic prophylaxis in boys with VUR grades IV-V for 1 year or until the degree of VUR is re-evaluated by cystographic examination.
A	It is not recommended to use antibiotic prophylaxis neither in boys with VUR grades I-III nor in girls with VUR grades I-II.

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C	It is recommended to use antibiotic prophylaxis in paediatric patients with dilated urinary tract and suspected obstruction until the diagnosis is confirmed and proper treatment for the obstruction is given.
√	It is not recommended to use antibiotic prophylaxis for non-obstructive dilatations of the urinary tract.

14.4 Other preventive measures: uropathogenic strain vaccines, ascorbic acid, cranberry juice and probiotics

Key question:

- Are other measures effective in preventing UTI recurrence: e.g., uropathogenic strain vaccines, ascorbic acid, cranberry juice and probiotics?

Urinary tract infection (UTI) is a common childhood disease which often recurs and can cause long-term kidney damage (5% of boys and girls).[39,258] Therefore, various other non-drug treatments have been tried as an alternative to antibiotic treatment and prophylaxis.

Among these alternative interventions considered are immunisation against common bacteria that produce UTI, vitamin C (ascorbic acid) and natural products such as cranberry juice and probiotics.

Only 1 study was found regarding vaccines against uropathogenic strains conducted in quasi-random fashion on 20 girls between 5 and 12 years old with a history of 2 or more symptomatic UTI episodes. The study assessed the effect of vaccination with inactivated uropathogenic strains compared with antibiotics (as practised conventionally) on urine levels of secretory IgA and the incidence of UTI (defined as bacteriuria) over a follow-up period of 12 months. There were significant differences ($P<0.05$) between both groups regarding the number of positive urine cultures over this time: 58 in the antibiotic group versus 29 in the vaccinated group. There were also significant differences between the two groups at the end of the 12-month period in secretory IgA levels: 8 girls in the antibiotic group and 2 in the vaccinated group had levels of IgA <0.5 mg/L ($P< 0.01$)[274]

RCT 1-

A SR[275] was found which assessed the effectiveness of cranberry products in preventing UTI in susceptible populations. The SR included 10 studies, of which only 2 covered paediatric patients. Both are crossover studies performed on paediatric patients with neurogenic bladder undergoing intermittent catheterisation

RCT SR

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The first study was on a sample of 40 paediatric patients (mean age 9.3 years) who were randomised into 2 groups: one receiving cranberry juice 15 mL/kg/day (30% cranberry concentrate) for 6 months, while a second group received water for 6 months. There was a 47% loss due to taste (9 patients), calorific load (2 patients) and cost (1 patient). There were no statistically significant differences in the number of months with positive culture and symptomatic UTI (17% vs 17.1%) or the number of months with positive culture and asymptomatic UTI (24.1% vs 29%). 1-

The second study was on a sample of 15 paediatric patients (age range 2-18 years) who were randomised into a group drinking 300mL of cranberry juice/day (30% cranberry concentrate) for 3 months and a group drinking a placebo drink for 3 months. There were no significant differences between the experimental and control groups in the number of symptomatic UTI episodes (3 UTIs in 2 patients and 3 UTIs in 3 patients, respectively), or the number of asymptomatic urinary tract infections (75% vs 75%). 1+

There was also a 3-arm trial in girls with recurrent UTI, without uropathy or structural abnormalities of the urinary tract, evaluating the efficacy to prevent symptomatic UTI of cranberry juice (50mL of cranberry juice concentrate daily) in 28 girls and *Lactobacillus* in 27 girls, compared with no prophylaxis in 29 girls for 6 months. The study showed a statistically significant reduction in the recurrence of UTI for the randomised cranberry juice group of patients, compared with the no treatment group (RR 0.28, 95% CI 0.12-0.64), and a statistically no-significant reduction compared with the *Lactobacillus* group (RR 0.44, 95% CI 0.18-1.09)[276] RCT 1-

Finally, 2 studies were found regarding the use of probiotics as a prophylactic measure.

The above 3-arm study compared the efficacy of *Lactobacillus* administered to 27 girls as a drink (4 x 107cfu of *Lactobacillus*/100mL) for 5 days a month over a period of 6 months against no prophylactic treatment in 29 girls. The study found a statistically no-significant reduction in the recurrence of symptomatic UTI (RR 0.63, 95% CI 0.38-1.07).[276] RCT 1-

The second was a study in paediatric patients with persistent primary VUR (n=120) after prophylactic antibiotic administration of TMP-SMX for 1 year. They were randomised into 2 groups: one that continued receiving antibiotic prophylaxis with TMP-SMX (60 patients, mean age 19±12.1 months), and a second group (60 patients, mean age 21±11.4 months) that received 2 x 108 cfu of *Lactobacillus acidophilus*/day for a follow-up period of 1-year. After this period, there were no differences found in the recurrence of symptomatic UTI between the groups (18.3% of recurrences in the probiotic group vs 21.6% in the antibiotic group, *P*=0.926).[277] RCT 1-

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No studies were found for the use of vitamin C or ascorbic acid as a prophylactic measure for the treatment of UTI in children.

When making its recommendations, the GDG considered that the results of the study using vaccines for uropathogenic strains would be difficult to apply in practice, as the outcomes evaluated were surrogate outcomes (sIgA levels in urine) and of little clinical relevance (positive urine cultures). Similarly, the results of the 2 SR[275] studies were not directly applicable to our population, as they were paediatric patients undergoing intermittent bladder catheterisation for neurogenic bladder, which could in turn explain the inconsistent results in the Ferrara et al.[276]study, whose sample consisted of girls without structural abnormalities with a history of recurrent UTI.

The results of the probiotic studies found[276,277] were a little inconsistent, which may be explained by the use of different controls, no prophylaxis in one case[276] and TMP-SMX at low dose in the other[277]. They may also be due to the difference in the constitution of the sample: girls without uropathy or urinary tract disorders in the Ferrara et al. study[276] and paediatric patients with VUR in the Lee et al. study.[277]

Finally, the GDG considered that, given the paucity in numbers and good methodological quality of the studies, there was insufficient scientific evidence to support a recommendation for the use of any of these preventive measures; it being necessary to recommend more research (Chapter 21).

Evidence summary

1+	Cranberry juice (30% cranberry concentrate) does not reduce the risk of symptomatic UTI in paediatric patients with neurogenic bladder subjected to intermittent catheterisation.[275]
1-	Daily administration of cranberry juice concentrate, compared to no prophylaxis, reduced the risk of recurrent UTI in girls with a history of recurrent UTI, and without uropathy and urinary tract disorders.[276]
1-	There was no significant reduction observed in the risk of recurrent UTI with the administration of Lactobacillus, compared to no prophylaxis, in girls with a history of recurrent UTI, and without uropathy and urinary tract disorders.[276]
1-	Daily administration of *Lactobacillus acidophilus* was not inferior to the administration of prophylactic antibiotics in preventing recurrent symptomatic UTI in paediatric patients with persistent primary VUR.[277]

Recommendations

√	There was insufficient scientific evidence to support a recommendation for the use of any of the following preventive measures: vaccines with uropathogenic strains, ascorbic acid, cranberry juice or probiotics.

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15. Prevention of UTI and lifestyle modifications

Key questions:

- Does improving poor voiding habits help prevent UTI recurrence?
- Does improving constipation help prevent UTI recurrence?
- Does increasing fluid intake help prevent UTI recurrence?

In recent years there has been great emphasis on functional abnormalities of the lower urinary tract, reflected by the presence of poor voiding habits as risk factors for recurrence of urinary tract infection (UTI).[278] It has also been shown that such abnormalities may be associated with bowel movement disorders, such that constipation and/or encopresis could increase the risk of recurrent UTI.[279]

Therefore, improving or normalising such dysfunctions could lead to prevention of UTI and its consequences, such as kidney damage and morbidity associated with UTI. Another intervention that may promote prevention could be increasing fluid intake, which may promote more regular evacuation of the bladder and prevent bacterial multiplication.[280]

Below is evidence taken from the NICE CPG[11] as well as additional studies that were found.

A study conducted in Switzerland evaluated the presence of various risk factors (family history of UTI, infrequent voiding, low fluid intake, functional constipation, inadequate anogenital hygiene and bathroom habits) in 90 girls (median age 8.4 years, range 3.9-16 years) with a history of recurrent UTI (≥3 UTIs) compared with 45 girls without a history of UTI (median age 7.3 years, range 4-14 years). The study found significant differences in the risk factors in girls with recurrent UTI compared to those girls without urinary infection: family history of UTI (42% vs 11%, $P<0.001$), infrequent voiding of urine (54% vs 24%, $P<0.001$), low fluid intake (53% vs 16%, $P<0.001$) and functional constipation (30% vs 13%, $P<0, 05$). However, no differences related to inadequate anogenital hygiene or bathroom habits were found comparing the cases (14%) and controls (13%).[11]

Case-control study 2 +

A study in the Philippines evaluated the association between bathroom habits and cleanliness (washing frequency: daily versus less than once a day, cleaning after urination, cleaning after defecation; cleaning direction, use of soap during cleaning) as well as voiding habits (frequency of urination: less than 5 times a day, or more than 5 times a day; retention of urine during the day; permission to urinate in school) with the risk of UTI in 23 children with UTI, compared to 23 children with no history of UTI (age range 6-12 years). The study found no association between any of the variables and the increased risk of UTI.[11]

Case-control study 2 -

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A US study compared the prevalence of dysfunctional elimination syndrome (DES) in a cohort of children diagnosed with UTI before 2 years of age (115 girls and 8 boys, mean age 7.3 years, range 4.3-10.6 years) compared to a cohort of children with no history of UTI (120 girls and 5 boys, mean age 7 years, range 4.3-10.6 years) to establish whether UTI encourages the development of DES. The study found no differences in the prevalence of DES among girls and boys with UTI (22%) and without UTI (21%), *P*=0.82. Within the UTI cohort, there was no difference in the prevalence of DES among those with VUR (18%) and those without VUR (25%), *P*=0.52. The study also evaluated the prevalence of various risk factors (encopresis, DES, VUR) in the subgroup of patients with recurrent UTI (n=31) and found that encopresis was the only statistically significant risk factor associated with recurrent UTI: encopresis (OR 2.5, 95% CI 1.1-5.4; *P*=0.03), DES (OR 2.2, 95% CI 0.99-5.0; *P*=0.05), VUR (OR 2.2, 95% CI 0.90-5.0; *P*=0.07).[11]

Cohort study 2+

A retrospective US study analysed the incidence of recurrent UTI and associated risk factors in patients diagnosed with first UTI before 6 months of age without radiographic abnormalities at the time of diagnosis (n=84, 52 girls and 32 boys; mean age 4.8 years, range 2.3-7.2 years), during a mean follow-up period of 4.4 years (range 1.9-7.0 years). None of the patients received prophylactic antibiotics after the radiological study.

A total of 16 patients (19%) had recurrences. No risk factor studied by univariate analysis (*P*>0.05) was significantly related with the onset of recurrence. These included age at which toilet training was taught (before or after 2 years), daytime urinary continence and history of constipation (less than 3 bowel movements per week).[122]

Cohort study 2-

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A Belgian study investigated the possible relationship between recurrent UTI and possible risk factors; among them, learning to control the bowels. It questioned 4,332 families with school age children (2,215 boys and 2,117 girls, mean age 11.5±0.56 years). The study found that the prevalence of a single UTI in girls and boys was 13% and 4.4%, respectively, and recurrent UTI, 5% and 1% respectively; these differences were statistically significant (18% vs 5.4%, $P<0.001$). Regarding the rest of variables studied they found a higher prevalence of recurrent UTI in children with daytime urinary incontinence (with or without enuresis; $P<0.001$); in children with 10 or more voids per day ($P<0.02$); and in children with nocturia at least once a week ($P<0.001$).

Cross-sectional study 3

Regarding the learning to control the bowels they found that it was earlier (before 18 months of age) in the group of children without UTI than in the group with recurrent UTI ($P<0.05$). Teaching methods and reactions to voiding failures were different between families, such that, for example, families of children with recurrent UTI were forcing children to stay longer on the toilet ($P<0.001$), encouraging pushing ($P<0.001$) or opening the water tap ($P<0.001$).

Among children with recurrent UTI, they found that 9.1% had encopresis, compared to 2.5% without recurrent UTI.[11]

A Danish study investigated the relationship between voiding habits, the prevalence of daytime urinary leakage and the presence of UTI in children (median age 7 years, range 6-9 years) in 1,557 families by questionnaire. It found a prevalence of UTI of 9.4% in girls and 2.8% in boys.

Cross-sectional study 3

For girls, the symptoms suggestive of voiding difficulties were more frequent in those with previous UTI than those with no history of UTI: bedwetting (25.3% vs 12.4%, $P<0.002$); daytime urinary incontinence (29.3% vs 12.9%, $P<0.0002$); not reaching the bathroom (40% vs 27.9%, $P<0.03$); prolonged voiding (33.3% vs 17.8%, $P<0.002$); poor urine flow (29.3% vs 15.8%, $P<0.003$); ability to void again (32% vs 17.3%, $P<0.002$); manual compression of the abdomen (17.3% vs 7.3%, $P<0.003$); and encopresis (13.3% vs 6.0%, $P<0.03$). By logistic regression, the symptoms that correlated with UTI in girls were squatting (OR 4.6, 95% CI 1.6-13.1) and encopresis (OR 6.1, 95% CI 1.3-28.4).

Due to the small number of boys with UTI, conclusions about voiding habits and UTI could not be drawn.

There were no significant differences in the frequency of daily urination for those with and without UTI.[11]

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A Swiss study evaluated the role of family history, infrequent voiding, low fluid intake, constipation and poor hygiene or bathroom habits in a sample of 141 girls (median age 6.5 years, range 3.9-18 years) with a history of recurrent UTI (≥3 episodes of symptomatic UTI). There was a total of 212 functional and behavioural abnormalities in 86% (121) of the girls: infrequent voiding (45%), low fluid intake (43%), constipation (21%), poor hygiene (19%), dysfunctional emptying (18%) and overactive bladder (5%). A total of 66 girls had more than 1 anomaly concurrently.[11]	Case series 3
A Canadian study in girls (n=47, mean age 8.2±2.5 years) of functional constipation (with a large faecal reservoir), bladder instability (uninhibited bladder contractions) and recurrent UTI without anatomical abnormalities of the urinary tract found that treatment of functional constipation using enemas prevented recurrence in 93.6% of cases. Among girls affected by enuresis (68%), enema treatment led to the end of enuresis in 69% and improvement in 22% of girls.. Similarly, enema treatment resolved 95% of the cases among the 45% of the girls who suffered from encopresis.[281]	Case series 3
Another Canadian study described the presence of uninhibited bladder contractions and rectal dilatation in 16 girls and 1 boy (mean age 6.24±2.2 years) with a history of recurrent UTI and VUR. Clinically, 10 patients had enuresis and 5 also had encopresis. Rectal manometry confirmed the existence of functional constipation in all patients.[282]	Case series 3
A US study in 143 patients (105 girls and 38 boys) with a history of UTI and primary VUR under antibiotic treatment until resolution of VUR (surgical or spontaneous), described the prevalence and influence of the bladder or gastrointestinal dysfunction in their history and treatment. It found that 46% of patients had DES (bladder instability, infrequent voiding and constipation), with constipation as the most common symptom (50%), followed by bladder instability (27%) and infrequent bladder emptying (23%). Of the total sample, 49% (70) suffered recurrent UTI during follow up, and 77% (54) of these had DES, compared with the remaining 23% (16) who did not (P<0.00001). Among patients who did not experience recurrent UTI (73), 16% (12) had DES, compared to 84% (61) who did not (P<0.00001). The presence of DES thus increased the risk of recurrent UTI in patients with VUR (OR 17.15, 95% CI 7.45-39.47).[283]	Cohort study 2-

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A questionnaire-based study in Australia of UTI risk factors at the population level from a sample of 2,856 schoolchildren (1,503 boys and 1,353 girls, mean age 7.3 years, range 4.8-12.8 years) was performed. Case-control study 2 +

In the total sample, the prevalence of enuresis was 18.3%; daytime urinary incontinence was 17.3%; encopresis 10.3%; and constipation 5.7%.

The prevalence of problems associated with voiding was: 67.4% urgency, 40.1% retention, 32% frequency and 9.2% leakage.

Of all the patients with a history of UTI at some point, according to the families (n=362), only in 191 cases a urine culture record could be obtained, from which UTI was confirmed in 103 cases (3.6%).

The study found the following as independent variables associated with UTI: renal structure abnormality history (OR 15.7, 95% CI 8.1-30.4); daytime urinary incontinence (OR 2.6, 95% CI 1.6-4.5); female sex (OR 2.4, 95% CI 1.5-3.8); and encopresis (OR 1.9, 95% CI 1.1-3.4). The study found no association between constipation and UTI.

The risk of UTI in boys with daytime urinary incontinence (OR 8.6, 95% CI 3.9-19.1) was higher than in girls with urinary incontinence (OR 2.1, 95% CI 1.2-3, 6). Similarly in older children with kidney problems: over 6 years (OR 25.2, 95% CI 9.0-70.0) and over 8 years of age (OR 30.7, 95% CI 10.5-90.1), the risk of UTI was higher than in those of a younger age (4-6 years old) with kidney problems.[284]

A Swedish study evaluated the residual volume of urine as a possible risk factor in the pathogenesis of lower tract UTI in 29 girls and 10 boys with cystitis (median age 5 years, range 1-14 years), compared with a control of 35 girls and 20 boys (median age 5 years, range 1-12 years). The study found significant differences in residual urine volume ($P<0.01$). During the acute episode of cystitis, 61% of cases had residues ≥5mL urine compared to 25% of controls, and 24% of cases had ≤2 mL residues compared with 62% of controls.[285] Case-control study 2 -

A Turkish study evaluated the frequency of nocturnal enuresis, UTI and symptoms of bladder instability in 22 girls and 16 boys (mean age: 5.3±4.25 years) with chronic functional constipation, compared with 16 boys and 15 girls as controls (mean age: 6.8±3.8 years). Significant differences were found regarding the frequency of UTI and urinary urgency. Both situations are more frequent in the group with constipation than in the control group: 42.1% and 26.9% vs 19.4% and 4% ($P<0.05$), respectively. No significant differences were found between groups for frequency of urinary incontinence (19.2% vs 0%, $P=0.051$) and nocturnal enuresis (23.1% vs 8%, $P> 0.05$).[286] Case-control study 2 -

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A US study of 176 boys and 58 girls (mean age: 9±3 years) with functional constipation and encopresis determined the frequency of UTI and urinary incontinence before and after treatment for constipation over an average 15-month follow-up. The study found an overall incidence of UTI episodes 11% higher in the case of girls (33%) than in boys (3%), $P<0.001$. There was an overall prevalence of 46% urinary incontinence (29% daytime incontinence, 34% nocturnal incontinence and 17% daytime and nocturnal incontinence), without any significant differences in sex or age ($P> 0.05$). Treatment of constipation led to its resolution in 52% of cases (121). In all cases resolved, there was a significant decrease in the prevalence of urinary incontinence day and night, 23% and 34% before treatment and 2% and 12% after treatment ($P<0.05$), respectively. In all resolved cases without structural abnormalities of the urinary tract, there was no case of recurrent UTI during follow-up.[287]

Case series 3

A Dutch study evaluated the treatment of constipation by colonic enemas in 44 girls and 6 boys (mean age 9.6 years, range 6.5-12 years) with constipation, voiding dysfunction and a history of recurrent UTI, who had not responded to previous treatment with oral laxatives and biofeedback. None had anatomical abnormalities of the urinary tract and all received antibiotic prophylaxis. After enema treatment, there was no recurrence of UTI in 84% of cases during a follow-up period of 6 months.[288]

Case series 3

A Canadian study of 29 girls and 16 boys (range 6 months-14 years) with a history of UTI and abnormal bowel habits (hard stools with difficulty in expulsion, no daily bowel movements, rectal bleeding due to anal fissures, prolonged use of laxatives and/or suppositories, large stools and encopresis) found that after initial treatment for improvement of constipation, it resolved in 80% of cases. During the first year of monitoring, there was recurrent UTI in only 20% of cases, which were the ones that had not responded to the initial constipation treatment. After further corrective treatment, there was recurrent UTI at 3 years in only 2 cases with new onset of constipation.[289]

Case series 3

When making the recommendations, the GDG considered the consistency of the results, which showed an association between constipation, encopresis, low fluid intake or DES and UTI, especially among the higher level evidence-based studies.[11,284] A certain consistency in the results was seen in the lack of association between anogenital hygiene and the presence of UTI.[11]

The GDG considered the preventive measures necessary to improve voiding habits, adequate fluid intake or correction of constipation were shown to be clinically harmless and inexpensive, and could be included in so-called lifestyle changes or healthy habits acquisition.

Evidence summary

2+	Girls with recurrent UTI had a higher prevalence of infrequent voiding (54% vs 24%, $P<0.001$), low fluid intake (53% vs 16%, $P<0.001$) and functional constipation (30% vs 13%, $P<0.05$) than girls who had never had UTI.[11]

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2+	No association was seen between inadequate anogenital hygiene and/or inappropriate bathroom habits with the presence of recurrent UTI.[11]
2+	DES is associated with an increased risk of recurrent UTI (OR 2.2, 95% CI 0.99-5.0, *P*=0.05).[11]
2+	Encopresis is associated with an increased risk of UTI (OR 1.9, 95% CI 1.1-3.4)[284] or recurrent UTI (OR 2.5, 95% CI 1.1-5.4).[11]
2+	Daytime urinary incontinence is associated with an increased risk of UTI (OR 2.6, 95% CI 1.6-4.5).[284]
3	A correction in constipation for children with functional constipation and/or encopresis with no urinary tract abnormalities prevents or reduces the occurrence of future UTI recurrence[281,287-289]

Recommendations

C	Preventive measures aimed at reducing recurrences of UTI should be tailored according to the pattern of urinary tract dysfunction or urinary habits of the patient, and directed to achieve adequate fluid intake.
D	It is recommended to investigate and address any constipation in children with UTI and/or signs of lower urinary tract dysfunction to prevent recurrence of UTI.

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16. UTI prognosis

16.1 Risk of UTI recurrence in children

Key question:

- What is the risk of recurrent UTI in children with no known structural or functional abnormalities of the urinary tract with a first UTI, and what follow-up is required?

After the first manifestation of a urinary tract infection (UTI), various epidemiological studies report that recurrence is common and affects more than 30% of patients.[13,47]

However, these studies usually include patients with a normal urinary tract and those with structural abnormalities, such as obstructive processes (posterior urethral valves, hydronephrosis, ureterohydronephrosis, etc)[290] or vesicoureteral reflux (VUR) of greater or lesser degree.

At present, the natural history of the first episode of UTI in children with a normal urinary tract is not well understood and there are few data on the risk of recurrences with these patients. Neither is it known what factors are likely to cause such recurrences nor whether their appearance encourages the formation of renal scars.

Below are 6 retrospective observational studies that provide information about the natural history of UTI, the incidence of recurrence and risk factors.

Case series 3

A case series in Spain from a sample of 134 girls older than 1 month with UTI and a normal urinary tract described the clinical course over a mean follow-up period of 3.4 years (range 1-7 years) of those girls who developed more than 3 UTI episodes in 1 year (n=39, mean age at first bacteriological diagnosis, 4.8 years, range 1-7 years). All girls received antibiotic prophylaxis (TMP-SMX or nitrofurantoin) for some time during follow-up.

Of all the girls with a normal urinary tract, 55 developed recurrent UTI (41%).

Within the group of girls with more than 3 UTI episodes, it was seen that the number of recurrences decreased with age from 3.8 per girl/year during the 1st year to 1.5 per girl/year in the 5th year.

The percentage of girls with ABU ranged from 25% during the 1st year to 14.3% in the 6th. Nitrofurantoin prophylaxis significantly decreased the number of recurrences ($P \leq 0.05$). Only 1 out of 39 girls (2.9%) developed VUR and unilateral scar lesion at follow-up.[291]

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A US case series described the natural history and risk factors of recurrent UTI in a sample of 78 patients (57 girls and 21 boys) with a normal urinary tract diagnosed with febrile UTI (mean age at diagnosis in girls: 31 months, range 1 month to 10 years; mean age at diagnosis in boys: 21 months, range 1 month to 14 years) over a mean follow-up period of 3.5 years (range 1-7 years). There were 25 patients with recurrences (19.5%), and these were more frequent in girls (22, 45%) than in boys (3, 14%), P=0.02. The 3 boys with recurrence had not been circumcised, and 2 of them were under 1 year of age. For girls, those under 1 year of age had a 39% UTI recurrence rate; those between 2 and 5 years had 24% recurrence; those aged 5 years or over had a 58% recurrent rate, all had symptoms of DES.[292]

Case series 3

A study in Argentina used urodynamics to analyse findings in 100 patients (98 paediatric and 2 adults) with recurrent UTI and normal urinary tract. Various types of transient bladder dysfunction were detected as causing the recurrences in 27% of the patients (22 girls and 5 boys): acute urinary retention (19%), functional stenosis (26%), intermittent pattern (52%) and tubulisation of the trigone (7%).[293]

Case series 3

A retrospective study in the USA monitored the incidence of recurrent UTI and associated risk factors over 4.4 years in patients diagnosed with first UTI before 6 months of age, without radiographic abnormalities at the time of diagnosis (n=84, 52 girls and 32 boys). None of the patients received prophylactic antibiotics after the radiological study.

Recurrence was seen in 16 patients (19%). No risk factors were found to relate significantly to the recurrence (P> 0.05) by univariate analysis. These included the following: age, sex, constipation, recurrent fevers, family history, breastfeeding and circumcision.[122]

Cohort study 2-

A retrospective study in Finland analysed the incidence of recurrent UTI and associated risk factors in a sample of 262 patients (134 girls and 128 uncircumcised boys) diagnosed with first UTI before 12 months of age (mean age at the time of diagnosis: 0.33±0.23 years in boys, 0.48±0.25 years in girls). None of the patients received antibiotic prophylaxis. During a follow-up period of 3 years, 34% of patients had recurrent UTI, with no significant differences between sexes (35% of girls and 32% of boys, P>0.05). The appearance of recurrences occurred within the first year of evolution in 92% of cases.

Of all the patients who underwent VCUG (121 patients), the study identified VUR in 46%, with significant differences in the incidence of recurrent UTI according to the degree of VUR. No significant differences in the number of recurrences among patients without VUR (37%) and patients with VUR grades I-II (39%) were found; however, there were significant differences between patients with no VUR or VUR grades I-II and patients with VUR grades III-V (75%), P<0.05, with the latter having shorter periods free of recurrence.[99]

Cohort study 2-

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A retrospective study conducted in South Korea investigated the incidence of recurrent UTI and related risk factors using multivariate logistic regression on a sample of 190 patients (158 uncircumcised boys and 32 girls) with a normal urinary tract who were diagnosed with first UTI before 12 months of age (mean age at diagnosis 3.9±2.5 months in boys, 4.7±2.5 months in girls) during a 1-year follow-up period.

Cohort study 2+

There is a recurrence incidence of 21.1%, without significant differences between the sexes (P>0.05). The following risk factors correlated significantly with recurrences in boys: age ≤ 6 months (OR 72.7, 95% CI 10.3-489; P<0.001); presence of non-retractable foreskin (OR 8.8, 95% CI 3.2-24.5; P<0.001) and episodes of APN (OR 4.6, 95% CI 1.6-13; P<0.003). None of the studied risk factors correlated with recurrences in girls (age ≤6 months, vaginal reflux, episodes of APN).[124]

Few studies were found evaluating the recurrence of UTI specifically in children with a normal urinary tract. When making the recommendations, the GDG took into consideration the variation of the samples in the studies in relation to age, sex, different definitions of recurrent UTI and different follow-up periods.

All studies reviewed were consistent regarding the children having frequent recurrences. One study[99] noted that these recurrences occurred mostly during the first 12 months of follow up in young children.

Two studies agreed that uncircumcised boys have a higher risk of recurrence in the first 12 months of life.[124,292]

On the other hand, there were 3 studies that contradicted each other: 2 of them[99,124] found no differences in UTI recurrence between boys and girls, while another did.[292] This may be due to the age of the patients in each study being different or because the number of children in the studies was small.

In one study, patients without reflux had the same recurrence rate (37%) as patients with reflux I-II (39%), P>0.05).[99]

One study differed from the rest by not finding any risk factors associated with recurrence of UTI.[122] The authors, however, explained that this finding was due to the small size sample.

In conclusion, all the studies agreed that recurrence in children with a normal urinary tract was common. However, there was little consistency in any other aspect discussed.

Evidence summary

2-[122]/ 2+[124]/ 3[291,292]	The incidence of recurrent UTI in children with a normal urinary tract was between 19-41% in different studies.[122,124,291,292]
2-	The incidence of recurrent UTI in children under 12 months of age diagnosed with first UTI was 34%.[99]
2+	In boys under 12 months of age with a normal urinary tract diagnosed with first UTI, the presence of a non-retractable foreskin (OR 8.8, 95% CI 3.2-24.5) and age ≤6 months (OR 72.7, 95% CI 10.3-489) increased the risk of recurrent UTI.[124]

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2-	Patients with mild VUR (grades I and II) with a first UTI had a similar recurrence rate to patients with a normal urinary tract (39% and 37%, respectively, $P>0.05$).[99]
2-	For patients under 12 months of age diagnosed with a first UTI, 92% of recurrences occurred within the first year.[99]
3	In girls with a normal urinary tract, the number of recurrences of UTI decreased with age.[291]
3	27% of patients with recurrent UTI and a normal urinary tract had temporary bladder dysfunction to explain the recurrence of UTI.[293]
3	58% of girls aged ≥5 years old with a normal urinary tract and recurrent UTI had symptoms consistent with DES.[292]

Recommendations

C	Following a first UTI, monitor patients with a normal urinary tract, especially boys under 12 months of age with a non-retractable foreskin, during the first year of evolution, as they have frequent recurrences.
D	Investigate voiding and bowel habits in children with UTI for their possible association with recurrent UTI.

16.2 Prevalence of chronic kidney damage in children with UTI

Chronic renal damage or renal scarring (RS) is defined as the presence of irreversible focal or diffuse renal markings in the renal parenchyma.

The term *renal scarring* applies to acquired, or post-natal, abnormalities as well as primary or congenital abnormalities; both may or may not be associated with VUR.

In acquired renal damage, associated with a bacterial infection, renal scarring is a consequence of the inflammatory and immune response triggered to eradicate the bacteria causing the urinary tract infection localised in the renal parenchyma.[294] However, in primary renal damage, the renal scarring seems to be the result of a congenital abnormality of nephrogenesis.[295]

DMSA renal scintigraphy is considered the imaging "gold standard" or reference standard for diagnosis. RS is defined as the presence of scarring or the overall contraction of the kidney, where a renal scar is the defect in the renal contour with a reduced tracer uptake on the scan performed at least 6 months after the acute phase of urinary tract infection.[296]

Establishing the true prevalence of renal scarring after a urinary tract infection is not straightforward, due to a number of factors, including the following: the imaging technique performed for diagnosis, which has changed over the years from intravenous urography (IVU) to DMSA; the selection criteria of the research population; and the inability to distinguish congenital RS from acquired RS by the imaging techniques.

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16.2.1 Renal scarring in children

To assess the prevalence of renal scarring in the population, the NICE CPG[11] analysed 3 population studies among others and estimated the frequency of renal scarring in the population.

The first study, published in 1974 and performed in Sweden, with 596 patients under 16 years of age with first febrile UTI, showed a prevalence of 13% renal scarring in boys and 4.5% in girls.[13] Given that the study found a cumulative incidence of UTI of 3% in girls and 1.1% in boys, the NICE CPG estimated the population frequency of renal scars to be 0.14% for both sexes.[11]

The second, published in 1997 and performed in the UK, found a prevalence of renal scarring by DMSA after a first UTI of 4.7% in girls and 4.3% in boys.[39] Given that the cumulative incidence of UTI was 11.3% in girls and 3.6% in boys, the NICE CPG estimated the population frequency of renal scarring to be 0.53% in girls and 0.16% in boys.[11]

Finally, the third study, published in 2001 and in Sweden, evaluated the incidence of renal scarring (detected by IVU) after UTI in children under 16 years old living in a health area in Stockholm County during 1990-95. The study showed a renal scarring incidence of 9.3 persons per 100,000 persons per year, with a range of 7.5-11 persons per 100,000 person per year.[297] Using these data, the NICE CPG estimated the frequency of renal scarring in females to be 0.18% and 0.11% in males.[11]

16.2.2 Renal scarring and urinary tract infection

Renal scarring after urinary tract infection

A prospective study of 271 children of 0-14 years old with a first episode of UTI assessed the level of infection at the start and after 2 years by IVU. It did not detect any child with a renal parenchymal reduction initially, while 2 years later it detected renal scars in 12 of 252 children (5%). All these 12 children were among the 164 children who had been diagnosed with upper UTI, with none (0%) in the 88 children with lower UTI or asymptomatic bacteriuria.[298]

A SR of studies conducted between 1966-94 included series of at least 30 children with symptomatic UTI and with imaging studies performed, and excluded those studies in children selected for having urologic abnormalities or studies on adults. It assessed whether routine imaging studies, performed on children after their first UTI, managed to prevent the development of renal scarring, hypertension or renal failure. Based on the data from 4 prospective studies that describe radiological findings in both IVU and DMSA, the SR authors estimated that 5-15% of children with a first UTI have renal scarring on the IVU or DMSA performed 1-2 years after the first apparent UTI episode.[20]

Renal scarring already present in the first episode of UTI

Scar lesions seen in UTI imaging studies are not always secondary to it, they may have been there before the infection process.

One study evaluated the properties of the primary renal scars detected in the initial study, and those detected a year after, referred to as secondary. The study included children from 0-15 years of age diagnosed with a first episode of UTI and excluded those diagnosed with neurogenic bladder, and previously known abnormalities. IVU was performed on 545 of 652 children with febrile UTI, and 208 of 569 children with afebrile UTI. Renal scarring was detected in 74 children (21 boys and 53 girls), and was classified as primary in 34 and acquired in 40. The primary scars were significantly more frequent in boys than girls: 86% vs 30% (P<0.001). The age of onset of

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the first UTI was lower in boys than in girls: 0.25 years (range 0.03-8.9 years) and 2.8 years (range 0.1-10.5 years), respectively ($P<0.01$).[299]

Renal scarring after febrile UTI

Performing DMSA renal scintigraphy during the acute phase of febrile UTI and subsequent controls revealed that 50-80% of patients had acute inflammation of the renal parenchyma.[300] It also showed that renal scarring developed in the same place as the acute inflammation. In most cases, the inflammatory changes this produces are reversible and do not lead to scar formation.[301] Also, not observing scars when being analysed by DMSA is normal for children in the acute phase of infection.[21] Therefore, children with renal parenchymal inflammation during UTI are those at risk of acquired RS.

A meta-analysis of 28 studies analysed 23 patient cohorts, which included children diagnosed with a first episode of APN by DMSA, who were then analysed at least 3 months after the initial episode, and excluded those patients who had a recurrence of the urinary infection, found a total renal scar frequency of 41.6% of patients (range 26-62%) and 37% of renal units.[206]

A subsequent prospective study was consistent with the previous meta-analysis data. This study included 316 children (223 girls and 93 boys) with a first febrile UTI and excluded those with previously known urinary tract anomalies. It detected acute affectation by DMSA in 187 (59%) of the children; 123 of these children were analysed again by DMSA at 6 months, whereupon, renal scarring was detected in 43 of them (35%).[213]

Renal scarring after febrile UTI in children without VUR

No specific studies were found in the literature to investigate this condition. While many of the studies excluded those children with previously known structural and/or functional abnormalities, they all included patients with VUR.

To evaluate the incidence of renal scarring in this group of children, 3 studies were assessed that: included children with VUR, but expressed their data separately; excluded children with structural abnormalities; and excluded or provided data on the incidence of new UTI episodes in the interval between the UTI episode and the DMSA scan.

The first study included 218 children aged from 3 months to 18 years diagnosed with APN by DMSA which assessed the role of VUR in the frequency and severity of UTI and in renal scarring. It showed that 6 (5.7%) of the 105 patients without VUR had renal scarring at 6 months after the APN episode.[268]

The second study included 389 children with a first episode of febrile UTI and analysed any differences in the frequency of acute renal damage and renal scarring according to the presence and degree of VUR by DMSA. It showed that 95 of 296 children without VUR had renal affectation in the acute phase of UTI; however, only 15 (5%) had renal scarring 6 months after the febrile UTI episode.[224]

The third study, of 316 children aged 1-14 years with a first febrile UTI, investigated the association between age and the presence of APN and renal scarring by DMSA. It showed that 127 of the 208 children without VUR had renal affectation in the acute phase, but only 23 (11%) children in the DMSA performed 6 months after the initial episode, and without any new episodes of UTI being reported during this time.[213]

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16.2.3 Risk factors for renal scarring

Risk factors traditionally associated with renal scarring are VUR, age, treatment delay and recurrent UTI.

VUR

Renal scarring observed after an episode of APN is often detected in children without demonstrating the presence of VUR.

A series of studies over the years in children diagnosed with APN using DMSA showed that 50% (range 25-75%) of children with renal scarring 6 months after infection did not have VUR.[21,222,224,230,268,302-306] These data support the idea that UTI itself, rather than VUR, is the prerequisite for the formation of renal scars.

A SR and meta-analysis which investigated if the diagnosis of VUR in paediatric patients hospitalised with UTI was able to predict renal damage by DMSA showed that VUR is a weak risk marker of renal damage.[307]

However, if in addition to analysing the features of children who develop RS, those children diagnosed with VUR are analysed, it can also be seen that RS is more common among children with VUR than those without VUR.

In these series of studies, renal scarring occurred in 35% of children with VUR (range 6-60%) and 17% of those without VUR (range 5-34%).[21,222,224,230,268,302-305] In 4 of these studies there was no difference or significant correlation between VUR and renal scarring.[230,268,305,306] While in 5 of the 6 that did find a significant association between VUR and the formation of renal scars, it was related to the grade of VUR,[21,222,224,302-304] and especially with VUR grade III or above.[302,304]

One study aimed at evaluating the impact of VUR in renal scarring after an episode of APN compared the findings of refluxing and non-refluxing renal units in patients with unilateral VUR included 48 children. The DMSA performed 6 months after the initial episode found renal scarring in 23 (47.9%) of 48 refluxing units and in 7 (14.6%) of non-refluxing units (OR 5.39, 95% CI 2.02-14.38; $P<0.01$). They concluded that VUR increased the risk of kidney scarring after an episode of APN.[308]

The aforementioned meta-analysis also analysed the influence of VUR in renal scarring. Information about the incidence of renal scarring after urinary tract infection and its relation to the presence or absence of VUR was provided in 8 of the 28 studies included. Children with VUR were more likely than those without VUR to develop renal scarring after an episode of APN (OR 2.8, 95% CI 1.9-4.2). Also, refluxing renal units had a greater risk of developing renal scars after an episode of APN (OR 3.7, 95% CI 1.3-11.1).[206]

Another meta-analysis reviewed the correlation between the severity of VUR and permanent kidney damage. It included 19 studies published between 1992 and 2006 that assessed the prevalence or incidence of renal damage in children with VUR with and without previous urinary tract infection, excluding children with nephrourological abnormalities other than VUR. The overall RR for renal damage was significantly greater in children with VUR than in the controls, observed by DMSA and IVU (3.7 and 2.8, respectively). However, in severe VUR, the RR of congenital kidney damage was 5.6 times higher than in the controls; by contrast, the overall RR for acute renal damage in children with VUR was comparable with the controls.[309]

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Age

Current data do not seem to confirm that children under 1 year are at increased risk of renal scarring.

Two prospective studies were conducted to evaluate the relationship between age, APN and renal scarring. The first study, conducted in Switzerland, found that renal scars were more frequent in the group of children from 1 to 5 years old than those under 1 year ($P<0.0001$).[310] In the second study, carried out in Italy, children under 1 year had a lower risk of renal scarring, with a linear relationship between scarring and age ($P=0.0598$).[213]

Other studies, which also include the assessment of renal scarring and its relationship with age, either find no relationship[21,303,304] or find that renal scars are more common in older children.[204,230,302,305]

Treatment delay

A prospective, randomised, comparative study investigating the association between renal scarring by DMSA after the first episode of APN and the time when treatment is started, found that a progressive delay in starting therapy (from less than 1 day to 5 days or more) was not associated with a significantly increased risk of developing renal scars, further suggesting that early treatment does not help to prevent this condition.[211]

Another 2 studies found no significant relationship between scar formation and the duration of fever before starting treatment.[21,302]

The first study of 76 children from 0 to 15.9 years of age with a clinical diagnosis of APN was to determine the incidence of renal scarring after an episode of APN and establish any correlation with risk factors such as VUR, age, treatment delay and recurrent urinary tract infection. It found renal scarring in 28 children, but did not find any significant differences in the duration of the disease, expressed as the number of days with fever: 3.2 days in children who developed scars, 3.1 in those without scars.[302]

The second study, conducted in 309 children aged 1-24 months, was to assess the value of routine imaging studies performed after a first episode of febrile UTI. It found no significant relationship between the formation of scars and the duration of fever before the start of treatment (≤24 hours or >24 hours, $P=0.29$) or duration of fever after starting treatment (≤36 hours or >36 hours, $P=0.30$)[21]

Recurrent urinary tract infection

A prospective multi-centre study included 269 children diagnosed with APN by DMSA, of whom 152 had their first episode of UTI and 117 had recurrent UTI. Of those with the first episode of UTI, 55.9% of children developed renal scars, while of those with recurrent UTI 72.6% had scarring ($P=0.004$).[204]

Another prospective study of 76 children diagnosed with APN found that 13 (17%) had recurrent UTI (9 APN). All children with recurrent APN developed renal scars.[302]

To summarise, renal scarring is observed in 5-15% of children after a urinary tract infection; 50-80% of children with febrile urinary tract infection have acute inflammation of the renal parenchyma and, of these, about 40% develop renal scars.

Renal scarring is detected in children without VUR; however, VUR and especially severe VUR is a risk factor for its development.

Recurrent UTI and age are also risk factors for developing renal scars, with a seemingly linear relationship between age and the development of renal scarring.

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16.3 Risk of renal morbidity in children with renal damage after UTI

Renal scarring in children with UTI may lead to hypertension (HT) and chronic kidney disease (CKD) in the medium to long term, with the presence of proteinuria considered an indicator of renal damage.

16.3.1 Hypertension

The incidence of hypertension in children is less than 2%, and is estimated at 10% for children with RS; although figures between 0 and 38% are quoted, depending on the study.[11,30]

Renal scarring compared with no renal scarring

In a cohort study of children with UTI, followed from 16 to 26 years old, 9% of patients with renal scarring and 6% of the controls without scarring developed hypertension. After comparing ABPM findings between the 53 children with renal scarring and the 45 with no scarring, no differences were found between groups, nor when comparing children with severe or bilateral renal scarring with controls.[299] In a systematic review, the risk of developing hypertension was similar in patients and the control group in 4 studies.[311]

HT and primary or congenital renal scarring

A retrospective study of 146 children diagnosed with VUR (with and without renal scarring) with a mean age of 5 years and mean follow-up of 9.6 years found no case of hypertension, after excluding those diagnosed with renal dysplasia-hypoplasia. The study suggests that hypertension develops only if there is associated renal dysplasia.[312]

HT and severity or extent of renal scarring

A study in 30 women diagnosed with renal scarring in childhood and followed for 27 years gave the following results: 7 developed hypertension (3 had bilateral and 4 had unilateral renal scarring, 3 of them severe).[209] A second case-control study of 111 women diagnosed with UTI in childhood, followed for 15 years, found that 3 of the 54 women with renal scarring (5.5%) developed hypertension and those with severe renal scarring had systolic BP higher than women without scars ($P<0.05$).[313]

HT risk markers

The CPG on Management of VUR[30] analysed plasma renin and the ABPM findings as potential risk markers for developing hypertension. It concluded that there was no correlation between plasma renin levels and BP,[314] and that the ABPM results performed in children with renal scarring and normal casual BP in cross-sectional studies showed changes in various parameters.[315-318] However, no studies evaluating the usefulness of the ABPM as a prognostic factor for developing hypertension were found.

16.3.2 Chronic kidney disease

The 2008 data from the Spanish Registry of Paediatric Chronic Kidney Disease (REPIR) reported that 63 children in Spain had started the dialysis/transplantation programme. In 17 (27%), the

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cause was renal scarring without obstruction, which was congenital in 11 (17.4%) and acquired in 6 (9.5%). The 2001 annual report of the North American Paediatric Renal Transplant Cooperative Study (NAPRTCS) referred to the following as cause of CKD (defined as CrCl<75 mL/min/1.73m^2): reflux nephropathy in 8.7% of cases and renal aplasia/dysplasia/hypoplasia in 18%.[319]

A retrospective study analysed the reason for entering a dialysis/transplant programme over 10 years. Of the 102 paediatric patients registered, only 1 case attributed UTI as a significant cause of renal damage.[320]

CKD and severity or extent of renal scarring

A study of 30 women diagnosed with renal scarring in childhood, and followed for 27 years, showed that 2 developed CKD (one with bilateral renal scarring without HT and other unilateral renal scarring with HT) and 3 developed ESRD (all with bilateral renal scarring).[209] Another study involving 111 women diagnosed with UTI in childhood (54 with renal scarring), and followed for 15 years, showed that mild CKD developed in 4 of 19 women with severe renal scarring and 2 of the 57 without renal scarring. In this study, the glomerular filtration rate (GFR) correlated with the total kidney area (P<0.001, r=0.578).[313]

Proteinuria and CKD

The presence of microalbuminuria is considered an indicator of kidney damage and the earliest manifestation of glomerular hyperplasia and focal segmental glomerulosclerosis detected in children with renal scarring.[321]

Two aforementioned studies[209,313] also evaluated the presence of albuminuria. In the first, albuminuria was significantly greater in patients with bilateral renal scarring compared to controls (P<0.05).[209] However, in the other, albumin excretion was low, no differences were found between groups with and without renal scarring and no correlation was found with the GF values.[313]

Risk markers for CKD

The CPG on the Management of VUR[30] analysed the presence of microalbuminuria and GFR at diagnosis as markers to predict progression to CKD and ESRD.

One study found that the presence of alpha-1-microglobulin in urine showed high specificity and sensitivity for detecting children with progressive renal dysfunction.[322]

One study determined that plasma creatinine values (PCr >0.6 mg/dL) at the time of diagnosis of VUR and renal scarring in the first year of life was the most significant predictor of progression to CKD.[223]

Another study determined that CrCl values below 40mL/min/1.73m^2 at the time of diagnosis was the most significant predictor of progression to ESRD.[323]

To summarise, although the natural history of UTI is not well known and many studies have been conducted in children with VUR, the risk of developing HT and/or CKD after an episode of UTI, in the absence of urinary tract abnormalities, does not seem to be generally very high.

Developing both HT and CKD seems to be related to the extent or severity of the scarring and the presence of renal dysplasia/hypoplasia.

Currently, there are no markers for predicting the development of HT. The presence of alpha-1-microglobulin may be useful for detecting children with progressive renal dysfunction; in children under 1 year, PCr >0.6 mg/dL at the time of diagnosis appears to be the most significant prognostic factor for progression to CKD; while CrCl values below 40 mL/min/1.73m^2 at the time of diagnosis are the most significant predictor of progression to ESRD.

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17. Monitoring UTI in children

17.1 Urine culture and/or systematic urine analysis

Key questions:

- Should a culture and/or systematic analysis of urine be performed in asymptomatic patients during or after antibiotic UTI treatment?
- Should a culture and/or systematic analysis of urine be performed in asymptomatic patients with structural and/or functional abnormalities?

Routine urine analyses after antibiotic treatment, or periodically during follow-up, have been widely recommended as part of the monitoring for asymptomatic healthy children with a history of urinary tract infection (UTI), whether or not prophylactic treatment was given.[3,24] The reason for this intervention is to detect the presence of bacteria in the urine and to evaluate its eradication. Given these considerations, one must ask whether the detection and treatment of asymptomatic bacteriuria (ABU) is effective in protecting against kidney damage or new UTI episodes in asymptomatic patients, whether or not prophylactic treatment is given.

On the other hand many authors recommend a new urine culture analysis if clinical response is not favourable, i.e., if fever persists for more than 48 hours after the start of antibiotic treatment, in order to detect possible complications and/or bacterial resistance.[73]

As seen previously (Chapter 14.1), the NICE CPG provides evidence of the ineffectiveness of antibiotic prophylaxis in paediatric patients with ABU for the prevention of recurrent UTI or the progression or incidence of new renal damage. The NICE CPG performed a meta-analysis by subgroups from 4 studies involving school-age girls with ABU detected by screening, with or without VUR. From a total of 321 girls with ABU, the meta-analysis showed that antibiotic prophylaxis does not reduce the recurrence of symptomatic UTI (RR 1.27, 95% CI 0.58-2.80). Similarly, and with 391 girls, antibiotic prophylaxis did not reduce the incidence of new kidney damage or kidney damage progression (RR 1.04, 95% CI 0.38-2.89). Finally, out of 529 girls, the meta-analysis found a significant reduction only in the levels of bacteriuria at the end of prophylaxis (RR 0.27, 95% CI 0.20-0.37).[11]

RCT SR 1+

In addition to the studies included in the NICE CPG,[11] the CPG on Management of patients with VUR[30] includes another 3 studies summarised below.

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The first was a retrospective study evaluating the clinical course of 26 asymptomatic girls (age/years: mean 8.9, range 3.3-14.8) with established renal damage and ABU, of which 16 (61%) had VUR. The monitoring period ran until 16 years of age. None of the girls received initial antibiotic treatment for ABU; and 54% of the sample (14) received no antibiotic treatment whatsoever, while 64% (9) of these continued with bacteriuria without developing symptoms of APN or cystitis during a median period of 3.1 years (range 1.2-8.6 years). The remaining 36% (5) recovered spontaneously from the ABU. Case series 3

A total of 46% of the sample (12) received antibiotic treatment for different reasons, and 3 cases of APN developed, compared with no cases in the girls who received no antibiotic treatment. This represents an increased absolute risk of APN of 25% (95% CI 0.5-49.5). No abnormality was found in 20 patients from a renal urography.

The authors concluded that the presence of ABU had no long-term detrimental effect on kidney development.[30]

The second was a prospective study evaluating the incidence of symptomatic UTI and renal damage in a sample of 25 girls with ABU of less than 6 months old until they reached 6 years of age. None of the girls in the sample received antibiotic prophylaxis. The diagnosis of renal scarring was made by intravenous urography. At the end of follow-up period, the study found recurrence of UTI in 9 children (it is unclear whether this was symptomatic UTI or ABU) and renal scarring in 3 girls, who had suffered recurrent UTI during the follow-up period, with evidence of VUR and probable urination abnormalities.[30] Case series 3

The third and final study, included in the CPG on Management of VUR, prospectively evaluated the incidence of renal damage in a sample of 50 patients (36 boys and 14 girls) younger than 1 year of age with ABU detected by screening who were monitored for a period of 6 years. The renal abnormalities found were: 1 girl with obstructive hydronephrosis, 1 girl with a double collecting system, 4 boys and 1 girl with VUR and 1 boy with minimal urethral valve obstruction. None of the patients received antibiotic treatment for ABU, but received antibiotic treatment for other infections. The diagnosis of renal scarring was made by intravenous urography. No new renal damage was found at follow-up in any of the 36 patients who had undergone intravenous urography. Only 2 girls developed UTI (1 affected with a double excretory system) and 1 boy (with urethral valve affectation).[30] Case series 3

Additionally, 4 retrospective studies were found analysing the need for urine culture and/or systematic analysis during antibiotic treatment applied generally and/or when presenting prolonged fever (>48 hours), establishing the prevalence of positive urine culture during monitoring, with the results summarised below.

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Three retrospective studies in the United States[325-327] analysed the need for urine culture and/or systematic analysis during antibiotic treatment applied generally and/or when presenting prolonged fever (>48 hours) in a total of 907 patients (619 patients ≤18 years[325,326] and 288 patients ≤2 years of age[327]), hospitalised for febrile UTI with or without VUR. Most of them did not have a positive urine culture after starting appropriate antibiotic treatment (follow-up urine culture <72h after hospital admission[326]), (follow-up urine culture at 48h [IQR, 38-65h] after hospital admission[327]). Only one of the studies found any prevalence of positive urine culture: 0.3% (95% CI 0-1.7) 2 days after starting antibiotic therapy.[325] The authors of these 3 studies concluded there was no need for a follow-up urine culture if the antibiotic sensitivity was already known, even for the presence of VUR, children under 2 years old and/or persistence of fever >48 hours, which was observed in 32% of the cases in one study[326] and 11% of cases in another.[327]

Case series 3

A study in Thailand was performed to determine the prevalence of positive urine culture after antibiotic therapy in paediatric patients under 15 years of age admitted for diagnosis of UTI (n=449, total episodes of UTI=533) and to evaluate risk factors associated with positive urine culture. It found a prevalence of 9.2% positive urine culture at follow-up (49 episodes), despite appropriate antibiotic treatment in 83.3% of cases, with 5% of the positive urine cultures having etiological agent mutating to another strain and 4% remaining the same. The positive urine cultures were due in 38% (19) of the cases to *Enteroccoco* strains spp., 16% (8) due to *Pseudomonas aeruginos*a and 24.5% (12) due to *E. coli*.

Case series 3

Of the total sample, 25.1% had VUR, 10.1% had other urinary tract abnormalities (neurogenic bladder, hydronephrosis, posterior urethral valve and bladder exstrophy) and 12.2% had other concomitant conditions.

Of all the positive urine cultures, 24.5% appeared in patients with VUR, 22.4% were in patients with other urinary tract abnormalities, 8% in patients with other pathologies and the remaining 36.7% in patients with no other concomitant pathology.

Using multivariate regression, the study found as microbial persistence risk factors the following: age ≤1 year (OR 2.7, 95% CI 1.4-5.5), presence of *Enterococcus* spp. (OR 4.5, 95% CI 1.08-19.5), persistence of fever of ≥72 h (OR 2.4, 95% CI 1.0-5.4), inappropriate antibiotic treatment (OR 3.2, 95% CI 1.2-8.0) and presence of uropathy other than VUR (OR 2.8, 95% CI 1.1-7.0). Among the risk factors not related to the persistence of positive urine culture were the following: sex, presence of VUR, infection with *P. aeruginosa*, the presence of other diseases not related to uropathy and recurrent UTI (P>0.05).[328]

When preparing the recommendations, the GDG considered the consistency of the results of the various intervention studies showing that antibiotic treatment of ABU had no effect on the prevention of recurrent UTI or prevention against renal damage.[11]

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Apart from the Anantasit et al. study,[328] the studies were conducted in health environments similar to ours, and in most cases the prevalence results showed the follow-up urine culture to be negative after starting antibiotic treatment.[325-327]

The GDG considered that the results would be applicable in the Spanish health service in both hospitals and primary care. The studies[325-328] were inpatient parenteral treatments and, except in specific circumstances, their efficacy was similar to oral or sequential treatment regarding bacteriological eradication and recurrence of UTI, except for the Anantasit et al. study.[328] Similar results may not, however, apply to patients with multi-resistant bacterial infections.

The results of the Anantasit et al. study,[328] performed in Taiwan, were not considered to be applicable in our environment, mainly due to differences in the study samples, the very different health systems and paediatric population.

Only 3 case series, included in the CPG on Management of patients with VUR, were found to have consistent and applicable results for asymptomatic patients with structural and/or functional abnormalities. These series include a very small number of patients with urinary tract abnormalities and valid conclusions cannot be drawn from them, due to significant methodological limitations. Finally, the expert opinion used by the authors of this CPG concluded that it was not recommendable to perform control urine cultures in paediatric patients with asymptomatic VUR.[30]

Finally, the GDG considered the negative impact of repeated urine cultures during treatment, as they may prolong hospital stay, are uncomfortable for patients and increase costs. In view of the evidence regarding follow-up included in this guide, the GDG believed that it best to avoid the practice of performing routine urine cultures in asymptomatic patients, thereby preventing unnecessary inconvenience for the patient and family.

Evidence summary

1+	The treatment of asymptomatic bacteriuria does not decrease the risk of UTI nor renal damage.[11]
3	In patients ≤18 years of age with UTI, in normal circumstances and after initiation of appropriate antibiotic treatment, according to the antibiogram, bacteriological eradication is the expected trend, even in children under 2 years and/or in the presence of VUR.[325-327]
3	Persistence of fever for more than 48 hours after initiation of antibiotic therapy is quite frequent and does not necessarily imply a lack of response.[326,327]
3	Patients <15 years of age with a diagnosis of UTI had a prevalence of 9.2% for a positive urine culture at follow-up, despite appropriate antibiotic therapy in 83.3% of cases.[328]
4	It is not recommended to perform control urine culture on paediatric patients with asymptomatic VUR.[30]

Recommendations

D	It is not recommended to perform urine culture and/or systematic analysis during antibiotic treatment in children with UTI if the clinical course is favourable.
D	It is not recommended to perform regular culture and/or systematic analyses of urine in asymptomatic children after UTI.
D	It is not recommended to perform regular culture and/or systematic analyses of urine in asymptomatic children with structural and/or functional abnormalities.

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17.2 Information for families or carers to help in the diagnosis of UTI

Key question:

- What information should be provided to the families and carers of patients who have had a first UTI?

UTI is a fairly common disease and therefore warnings and advice must be given to families, carers and patients themselves, according to their age, as is done for other common infectious diseases. The purpose of this question is to establish what information should family members receive after diagnosis and treatment, and what information about signs and symptoms can help them recognise any future recurrences of UTI, thereby enabling a rapid diagnosis so as not to delay the implementation of appropriate treatment.

A questionnaire-based study of family members (with open and closed questions) conducted in the UK analysed understanding of UTI in 52 families of children (under 2 years old) affected by it, and their perception of any possible delay in diagnosis; as well as assessing the usefulness of the information provided. Case series 3

The proportion of families who felt that they had received sufficient information on the need to test for UTI was 87%. Among them, 83% felt that the explanation had been helpful. Only 52% of families reported having received information leaflets, with 100% considering them useful; while 80% of families reported receiving sufficient information on the possibility of future recurrences of UTI. Some 70% of families reported receiving information on how to collect the urine sample, with 95% considering it a great help. In addition, 54% of households expressed difficulties in urine collection, especially when using the collection bag; they referred to the discomfort and difficulties in holding the bag properly. The clean catch method was preferred by 40% of families surveyed, while 37% preferred the urine collection bag, and 23% preferred sterile pads for the collection.

The proportion of families who reported that they knew what to do if there was a new UTI episode was 89%.

Analysing the qualitative content of the study identified some important points. These included the delay perceived by some families from the time the child begins to feel unwell to the time a urine collection was required to be taken by the family (37% of patients were asked for a urine culture at the first visit and 31% on the second visit). Most families demanded more information and more detailed advice. The families in the survey stated that the experience of the first episode made them understand the importance of early diagnosis and they would be in a better position to help diagnose UTI in the future. Also, some families expressed frustration with organisational aspects of the health system, such as the limitations of primary care services during weekends and the various hospital appointments required to perform different diagnostic procedures. Finally, they also expressed their frustration with the differing information they received from various health professionals.[41]

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Another study, also in the UK, evaluated the urine collection preferences of 44 families (clean catch, bag or pad) for their boys (median age 4 months, range 1-18 months). The families' preference was pads, bags and clean catch, in that order. On the positive side, the families reported that the use of pads and bags was easy, hygienic and fast; with the pads reported as being comfortable. On the negative side, the families reported that the bags were uncomfortable or unpleasant for the child and produced local irritation. Also, some families reported the difficulty of extracting the urine from the pads. For clean catch, most families reported that it was the most complicated method to use, and they were spending more time collecting the urine, due to the perception of having to hold the child still. However, the median time for the collection of urine was 25 minutes in all 3 methods.[11]

Case series 3

A Dutch study used a semi-structured interview to explore the knowledge and awareness of families (n=20) about their children (18 girls and 4 boys, age ≤12 years) being recently diagnosed (less than a year) for UTI by the primary care physician.

Qualitative study

The families were aware their child may have had UTI when their children showed symptoms typical of UTI. However, if the symptoms were atypical (abdominal pain, vomiting, high fever, malaise), the possibility of them indicating UTI did not occur to most families. Nevertheless, the majority of these families kept in touch with the primary care physician, since the behaviour of their child was different from normal. A quarter of families felt that the delay in diagnosis was due to the primary care physician not always recognising UTI, even when symptoms were typical, or even in some cases advising that there was nothing to worry about. There were differences among the families about whether UTI in children was recognisable as such: some families felt that it would not be if the symptoms were atypical, while others considered this very unlikely, expecting they would observe changes in behaviour, in urination for example.

Most families were concerned while the diagnosis was not known, and expressed peace of mind once it was known to be UTI. Most families did not consider UTI to be a serious condition, although some families were concerned about the future, mentioning possible renal failure as one of those concerns.

Also, families showed dissatisfaction with the lack of communication about prognosis. In general, they stated they receive very little information about the consequences of UTI not diagnosed in time. They felt that this was because the doctors were not sensitive to the problem. They considered they received more information from the Internet or from leaflets than they received from health professionals.

Families felt that information on the main identification signs and symptoms of UTI could be improved via brochures, posters or health education via the various health centres, libraries and schools. They recognised the Internet as an important source of information. On the other hand, some families felt that people only looked for information if they themselves were affected by the problem. Others thought the information might alarm the general population, and most families did not think a media health education campaign would help raise awareness of UTI in children. Nor did they consider that general level screening was a good method for identifying children with UTI.

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The authors concluded that families did not know about the atypical symptoms of UTI and its possible consequences. Families did not consider screening or educational campaigns via the media to be helpful measures; they preferred to be offered more information at the time of diagnosis. The authors believed that better understanding by the families of atypical symptoms and the serious consequences of UTI could help an earlier diagnosis and better treatment adherence.[329]

When making its recommendations, the GDG considered the results of the studies included here to be applicable to the Spanish national health service, as the health care settings are similar. One difference, however, is that paediatric patients are cared by general practitioners in primary care in both the UK and Holland; this could explain the perception of some families that UTI diagnosis was delayed by the primary care physician in the study by Harmsen et al.[329]

The GDG also considered the relevance and impact of accurate information given to families of patients in the management of UTI: it would lead to better understanding, adherence to treatment, and probably to a faster diagnosis of any recurrence.

Evidence summary

3	83% of families felt the explanation given on the need to perform a test for UTI was helpful.[11]
3	100% of the families considered the information leaflets to be useful.[11]
3	95% of families felt the information on how to collect the urine sample was helpful.[11]
3	80% of families felt that the information received about the possibility of UTI recurring was adequate.[11]
Qualitative study	Families identified the possibility of UTI in their children by the presence of typical symptoms, but not for atypical symptoms.[329]
Qualitative study	Families mentioned a lack of communication about prognosis and claimed to have received very little information on the consequences that UTI may have if left undiagnosed over a significant period.[329]
Qualitative study	Families preferred receiving more information about UTI at the time of diagnosis, rather than via health campaigns and/or by establishing screening systems.[329]

Recommendations

Q	If UTI is suspected or diagnosed, it is recommended to inform the family, carers or patient (depending on age) about the need for early antibiotic treatment and the importance of completing it.
Q	It is recommended to warn of the possibility of recurrence and advise about appropriate preventive hygiene measures. Give guidance for recognising UTI symptoms (fever of unknown origin and urinary symptoms), and the need to seek medical advice if they appear.

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D	It is recommended to give instructions on the collection of the urine sample and its preservation until the time of the test.
Q	It is recommended to inform about the prognosis, especially the risk of kidney damage and about the reasons for clinical monitoring and/or long-term treatment when required.
Q	It is recommended to inform about the scans to be performed, the reasons for them and what they consist of.

17.3 Monitoring children with permanent kidney damage after UTI

Key question:

- What monitoring is required for children with permanent renal damage after UTI?

Children with renal parenchymal damage need to be monitored for complications that can develop, such as hypertension, proteinuria, impaired renal function, complications during pregnancy and recurrent episodes of pyelonephritis with renal damage progression.[330]

Given these considerations, the presence of these complications and appropriate strategies for their early detection in each case was evaluated in children with renal scarring after UTI.

A cohort study retrospectively analysed hypertension in 319 patients with RN for 76 months (6-411 months). There was an increased risk of HT in cases of renal impairment (OR 5; 95% CI 1.7-15), although no difference according to severity.[331]

Cohort study 2+

No studies were found in the literature analysing whether plasma renin levels predicted the early detection of HT in children with permanent kidney damage, with or without VUR. The results of studies involving 108 patients followed for 15-22 years found no significant correlation between BP values and plasma renin values.[314,332]

Cohort study 2-

Furthermore, regarding the use of ABPM, no studies were found analysing whether its abnormalities predicted the development of HT, CKD or ESRD, although 5 cross-sectional studies (4 of which are included in the CPG on Management of patients with VUR[30,333]) show elevated nocturnal systolic and diastolic ABP in children with severe RN, despite the use of different reference values to define normality. However, another cohort study, in this case at high risk of bias[332], did not find these alterations in patients with renal damage after UTI.

Cross-sectional studies 3

Cohort studies 2-

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There are few studies in children analysing the predictive value of proteinuria or creatinine levels and glomerular filtration objectified at the time of diagnosis of permanent renal damage for the prediction of CKD and/or ESRD. Although the presence of microalbuminuria (MAu) is an indicator of kidney damage, and is considered the earliest clinical manifestation of glomerular hypertrophy and focal segmental glomerulosclerosis detected in children with RN, in 1 study included in the CPG on the Management of patients with VUR, only the presence of alpha-1-microglobulin in urine (as opposed to other parameters such as MAu, NAGu and beta-2-microglobulin) showed high specificity (100%) and sensitivity (78%) for detecting children with progressive renal dysfunction, measured as a percentage of uptake on DMSA scintigraphy in 28 children with RN followed for 10 years.[30]

Cohort studies 2-

However, another cohort study, also included in the CPG on Management of patients with VUR, retrospectively analysed this association in 343 patients diagnosed with primary VUR who went into renal failure (GFR <70 mL/min/1.73m^2), showing that the risk of developing ESRD is 4 times higher if the values of baseline creatinine clearance are <40 mL/min/1.73m^2, and that only patients with a urinary protein/creatinine ratio >0.8 had a significantly higher risk of developing ESRD.[30] A study with a high risk of bias and lower level of evidence found no differences in GFR or microalbuminuria after 25 years (17-34 years) follow-up in 57 patients with permanent kidney damage after UTI (54% with RRF <40 % by DMSA), when compared with a control group without renal damage.[332]

Cohort studies 2+

Cohort studies 2-

Another cohort study included in the CPG on the Management of patients with VUR retrospectively analysed a series of variables (sex, prenatal diagnosis, number of episodes of febrile UTI, urea levels, metabolic acidosis, proteinuria, diuresis, hypertension, ultrasound renal length and renal scars) to find risk factors predicting progression to CKD (GFR <80 mL/min/1.73m^2) in 50 children with severe primary bilateral VUR diagnosed in the first year of life, and followed for 6.3 years (1-16 years). They found that a plasma creatinine level >0.6 mg/dL in the first determination was the most significant risk factor for development of CKD, with an OR of 125 (P<0.001). The other study variables were not significant.[30]

Cohort studies 2+

A cohort study retrospectively analysed the association of complications with the extent of kidney damage in 120 patients with RN followed for 79 months (13-411 months). It found a higher rate of CKD (GFR <75 mL/min/1.73m^2) with bilateral affectation (ARI 16%, 95% CI 2-30; RR 2.5, 95% CI 1.1-5.8), although no another gradation of renal affectation was performed according to severity.[331]

Cohort studies 2+

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Another study using Kaplan-Meier plots in 318 patients with RN after a follow-up of 72 months (13-110 months) established the risk of HT at age 21 depending on the severity of renal damage: 0% (95% CI 0-6), no kidney damage; 15% (95% CI 5-25) if there was unilateral damage; and 45% (95% CI 16-74) if there was bilateral damage.[334] — Cohort studies 2+

In another study, included in the CPG on Management of patients with VUR, 84 children with RN were followed for 10-35 years: 14 patients developed HT, 11 of whom had bilateral nephropathy, however, there was no evidence of accuracy or strength of association.[30] — Case series 3

Finally, another cross-sectional study of patients with a history of VUR and bilateral scarring showed significantly lower values of maximum urine osmolality and GFR and high levels of creatinine and microalbuminuria, with respect to those with normal renal parenchyma.[335] On the other hand, 2 other cohort studies, with a high risk of bias, found no differences according to the severity of the scarring in patients with renal damage after UTI.[332,336] — Case series 3; Cohort studies 2-

There are few studies that evaluate both evolution of renal damage during adolescence and/or development of complications in pregnancy, as discussed in the CPG on the Management of patients with VUR.[30]

One study determined the urinary concentration of albumin and alpha-1-microglobulin during adolescence and suggested that kidney damage progressed during this period, especially in men. It suggested that this could be due to oestrogen acting as a protective factor in women.[30] — Cohort study 2-

In one study in pregnant women, HT was significantly more frequent in women with RN (with or without VUR) than in the control group (RR 3.3 vs 1.8; $P<0.01$).[30] — Cohort study 2+

Another 3 studies examined outcomes in pregnant women diagnosed with RN.

One of them showed that APN episodes were significantly more common among women with scarring than in controls, although some women received prophylaxis. HT and pre-eclampsia were associated with the presence of renal scarring, but there were no differences in the duration of the pregnancy, mode of delivery, abortions and birth weight in the control group. In another study, APN episodes were significantly more common in pregnancies of women with a prior history of APN and/or persistence of VUR. In a recent study, there were no significant differences in episodes of UTI and APN and the presence of scarring or its severity; although women with a history of UTI before pregnancy received prophylaxis. However, bilateral scarring increased the risk of pre-eclampsia (RR 4.1), but not other complications. A serum creatinine (PCr) level before pregnancy >1.24 mg/dL was the factor most often associated with maternal and foetal complications.[30] — Cohort study 2+

Implementation: 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

The GDG believes that the body of evidence is not sufficiently accurate to answer the question regarding the best monitoring practice for paediatric patients with chronic kidney damage or scarring, whether associated or not with VUR. Furthermore, it must be remembered that most studies reviewed did not differentiate between renal damage cases after UTI and those after both UTI and VUR. Similarly, congenital damage associated with or without UTI were also not differentiated. Therefore, the GDG made its recommendations upon the renal damage found, which is the most important factor, and the one that ultimately conditions the prognosis for these patients.

The recommendations are fully applicable to the Spanish national health service, both in primary and specialised care, as the determinations and investigations are simple and available to any centre.

Having markers for renal damage progression in these patients would be of great importance, as therapeutic measures could be tried to slow or halt the progression to chronic kidney disease.

Evidence summary

2+	The risk of HT is higher in children with RN than in those without permanent renal damage (OR 5, 95% CI 1.7-15).[331]
2-	No correlation was found between plasma renin levels and BP.[314,332]
3	The ABPM results on children with permanent kidney damage associated with VUR and normal casual blood pressure from cross-sectional studies show changes in various parameters; however, no studies were found evaluating the usefulness of this as a prognostic factor for the development of HT, CKD or ESRD.[30,333]
2-	No changes in ABPM in patients with permanent renal damage were detected after UTI.[332]
2-	The presence of alpha-1-microglobulin in urine is highly specific and sensitive for detecting children with RN with progressive renal dysfunction.[30]
2+	Plasma creatinine values (PCr) >0.6 mg/dL in children diagnosed with severe primary VUR in the first year of life are the most significant predictor of progression to CKD.[30]
2+	CrCl values at diagnosis less than 40 mL/min/1.73m^2 and moderate proteinuria (urinary protein/creatinine ratio >0.8) are the most significant predictors of progression to ESRD in children with primary VUR.[30]
2-	No changes in GFR or MA_u are found in patients with permanent kidney damage detected after UTI.[336]
2+[331,334]/ 3[30,335]	The occurrence of complications, such as HT and CKD, and alterations in renal function are more common in children with RN with severe bilateral renal damage.[30,331,334,335]
2-	The extent of kidney damage does not influence the occurrence of complications.[332,336]
2-	Glomerular damage progresses during adolescence predominantly in men with RN.[30]
2+	The number of episodes of APN, which represent the most common cause of maternal morbidity in pregnant women with RN, are not related to any other maternal complications nor to foetal morbidity or mortality.[30]
2+	There were no differences in episodes of UTI and APN during pregnancy and the presence of scarring or its severity.[30]

More than 5 years have passed since the publication of this Clinical Practice Guideline and its validity has not been reviewed

2+	In different studies, the presence of RN increased the risk of HT during pregnancy (RR 3.3 and RR 4.1).[30]
2+	High levels of plasma creatinine (PCr) >1.24 mg/dL and HT at the beginning of pregnancy are the biggest risk factors for pregnancy complications in women with RN.30

Recommendations

√	It is recommended to determine BP, PCr, glomerular filtration rate, proteinuria, microalbuminuria, alpha-1-microglobulin and maximum osmolality urine as markers of kidney damage and/or indicators of progression
√	In children with permanent, bilateral and severe (Goldraich type 3-4) kidney damage, it is recommended to test with a dipstick and determine the BP every 6 months, or annually for children with unilateral or mild affectation (Goldraich type 1-2).
√	Follow the centre protocol for monitoring patients with impaired renal function. In case of impaired renal function it is recommended to follow the patient according to the centre protocol.
√	It is not recommended to routinely use ABPM in children with permanent kidney damage and no alteration in renal function, as its prognostic value is not clearly demonstrated.
√	Do not routinely use plasma renin levels as a prognostic marker for HT in children with permanent kidney damage.
√	Boys with permanent kidney damage require further monitoring of renal function and BP in adolescence.
√	Give pregnant adolescents with renal disease regular check-ups for the early detection of bacteriuria and foetal/maternal complications (e.g., BP abnormalities, impaired renal function, intra-uterine growth retardation, foetal loss or premature birth).

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18. UTI and catheterisation in children

Urinary or bladder catheterisation circumvents the natural defence mechanisms of the body. There are risks associated with its use, which increase when the catheter is kept attached for long periods of time; urinary tract infection associated with a catheter or probe is the most common complication.[337]

The proportion of patients undergoing this procedure varies according to the different medical specialties, from 12-40%.[337] There are also variations in the proportion of patients catheterised for short periods of time in hospitals, either to monitor the amount of urine during an acute episode or after surgery for treatment of urinary retention or diagnostic reasons, with figures of between 15-25% of all patients admitted being catheterised.[338]

Most studies of catheter-associated urinary tract infections (CAUTI) are in adults, with little specific information about children. The Tenke et al. review stated that 40% of nosocomial infections are urinary in origin and about 80% of patients with nosocomial UTI underwent permanent urethral catheterisation.[32] In the UK, it is estimated that 20% of all nosocomial infections are urinary tract infections.[337]

The EPINE report 2009 (Study of Prevalence of Nosocomial Infections in Spain) stated that 22% of all nosocomial infections were urinary tract infections. Based on the results of 278 hospitals in the country, among the indicators from health care interventions it was estimated that 18.5% (95% CI 18.1-18.8) of patients admitted to hospital had a urinary catheter (either open or closed), and 80% (95% CI 79.3-80.8) of catheterised patients had closed urinary catheters.[339]

The EPINE 2009 report estimated that 3.88% of the total patients admitted had an open urinary catheter and 15.15% had closed catheters; with a prevalence of nosocomial UTI of 3.2% among those with an open catheter and 4.1% among patients with closed catheters.

The EPINE 2009 report gave figures for the prevalence of nosocomial UTI according to different hospital services and according to different age groups, but did not relate the prevalence of nosocomial UTI to urinary catheterisation in paediatric patients. It reported a prevalence of nosocomial UTI in Spanish hospitals for patients of 1-15 years old of 0.53%.[339]

The Fuster et al. study analysed the emergence of nosocomial infections in the paediatric intensive care unit of a Spanish hospital during 2000-2004, and found a mean nosocomial UTI incidence per daily use of closed urinary catheter of 2.63‰, with a wide variation from year to year. The authors reviewed different epidemiological series in paediatric intensive care units and found a very wide variability in results, with cumulative incidences of patients infected with nosocomial UTI associated with urinary catheter closed of 1.8 to 10.4‰.[340]

The Langley et al. study, performed in a tertiary paediatric hospital in Canada, found the cumulative incidence of nosocomial urinary tract infection in children under 16 years of age during the years 1991-97 to be 2.4%; with a decreasing density of incidence over the years, from 0.9 to 0.6 per 1000 patients/day at the study end. The study also found that only half of patients who suffered nosocomial UTI had been previously catheterised (of the intermittent or indwelling type during the previous 7 days).[341]

The literature on urinary catheters should be reviewed carefully, because many of the published studies used the term catheter-associated bacteriuria without providing any information on the proportion that were asymptomatic. In addition, other studies use the term catheter-associated urinary tract infection to include catheter-associated bacteriuria aswell, and even asymptomatic bacteriuria.[342]

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After a single insertion of a urinary catheter, it is estimated that 1-5% of patients develop bacteriuria[32] and that the risk of developing bacteriuria due to having a urinary catheter maintained over time increases to 3-6% per day of its use.[343]

18.1 Antibiotic prophylaxis in catheterised children

Catheters still need to be used in paediatric urology, despite the problems associated with their use. Given the relationship of catheters with the subsequent occurrence of UTI or ABU, antibiotic prophylaxis may need to be administered before catheterisation. Since catheterisation can be performed in three modes (indwelling, single sampling or intermittent), the effectiveness of prophylactic treatment in these situations is discussed below.

18.1.1 Antibiotic prophylaxis in children with indwelling catheters

Key question:

- Is the use of prophylactic antibiotics effective in preventing a new UTI and renal damage in asymptomatic children with an indwelling catheter?

There were 2 quasi-random clinical trials found evaluating the efficacy of antibiotic prophylaxis in boys under temporary catheterisation after corrective surgery for hypospadias.

The first trial evaluated the efficacy of postoperative antibiotic prophylaxis with cephalexin in preventing bacteriuria and surgical complications in 101 boys (mean age 2.3 years, range 11 months to 6.5 years) catheterised after hypospadias surgery by plate tubulisation during a monitoring period of 6 months against a control group with no treatment. Patients received antibiotic prophylaxis after surgery from the first day and up to 2 days after catheter removal (removal of the catheter after 8.6 and 8.3 days in the prophylaxis and control groups, respectively). The study showed a significant reduction in bacteriuria (RR 0.41, 95% CI 0.23-0.75; NNT 3, 95% CI 2-8) and complicated UTI, defined as positive urine culture and fever >38.5°C (RR 0.24, 95% CI 0.07-0.78; NNT 5, 95% CI 3-20) in the group receiving antibiotic prophylaxis. There were no significant differences between groups with respect to the incidence of complications after surgery.[344] RCT 1-

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The second was a clinical trial evaluating the incidence of bacteriuria after antibiotic prophylaxis with sulfamethoxazole, compared to no treatment, in 78 boys (age range 2-12 years) with either a urethral (28 patients) or transperineal (50 patients) catheter for 10 days after undergoing corrective surgery for hypospadias (84 operations). The treated group (41 patients) received antibiotic prophylaxis after surgery from the first day and up to 3 days after catheter removal. RCT 1-

The study showed a significant reduction in bacteriuria in the group of patients receiving antibiotic prophylaxis compared to the control group (RR 0.26, 95% CI 0.08-0.88, $P<0.05$; NNT 5, 95% CI 3-29), despite the higher incidence of VUR in the group of children receiving prophylaxis (9 out of 41 children compared to 2 out of 37). There were 4 children in the control group and 0 in the treatment group who developed febrile UTI with a temperature >38.5°C. The most frequently found bacteria was *E. coli* (2 out of 3 cases and 6 out of 10 cases in the treatment and control group, respectively).[345]

When making the recommendations, the GDG took into consideration the limited applicability of the results of the studies found, as they were only applicable to boys with hypospadias.

Evidence summary

1-	The use of antibiotic prophylaxis was effective in preventing febrile UTI and bacteriuria in boys with a temporary urinary catheter after hypospadias repair.[344,345]

Recommendations

√	It is recommended to use prophylactic antibiotics to prevent UTI in children with a temporary urinary catheter after hypospadias repair urethral surgery.
√	It is recommended to use prophylactic antibiotics to prevent UTI in children with a temporary urinary catheter after vesicourethral surgery.
√	It is not recommended to use antibiotic prophylaxis in children with a temporary urinary catheter for non-surgical reasons.

More than 5 years have passed since the publication of this Clinical Practice Guideline, and its validity has not been reviewed

18.1.2 Antibiotic prophylaxis in children under intermittent catheterisation

Key question:

- Is prophylactic treatment recommended for children requiring clean intermittent catheterisation for voiding problems?

A SR was found to determine the best long-term use guidelines (regarding insertion route and use of prophylactic antibiotics) for catheters in terms of effectiveness, complications, quality of life and cost-effectiveness in adults and children (long-term was defined as more than 14 days for both intermittent and indwelling catheterisation). RCT SR 1-

The SR compared the administration of continuous prophylactic antibiotics to clinically indicated antibiotics (in case of pain or fever) in 2 crossover trials in paediatric patients undergoing intermittent catheterisation, by calculating the rate of symptomatic UTI per week of catheter use.

Both studies evaluated the effectiveness of prophylactic doses of nitrofurantoin against placebo in paediatric patients with neuropathic bladder who used intermittent catheterisation at home. One study (n=56) had 4 cases of UTI in 430 weeks of using the catheter during the period of antibiotic prophylaxis compared with 2 cases of UTI in 389 weeks during the placebo period. The second study found no statistically significant decrease in the density of incidence of UTI in patients who received antibiotic prophylaxis (DI 0.50, 95% CI 0.17-1.44).

The SR concluded that the results from the 2 studies were inconsistent for paediatric patients with intermittent catheterisation, and the data are too few to predict whether antibiotic prophylaxis reduces urinary tract infections.[346]

A study of 85 patients with neuropathic bladder in a paediatric hospital assessed whether antibiotic prophylaxis was necessary for performing clean intermittent catheterisation. Patients were randomised into 2 groups: the first continuing with antibiotic prophylaxis (31 patients) and the second group stopping treatment (22 patients). There was a loss of 33% in the sample (28 patients) due to families rejecting the randomisation. At the end of the 4-month follow-up, the study found an increased risk of UTI in patients receiving prophylaxis compared with patients who had stopped antibiotic prophylaxis, due to developing resistance (RR 4.73, 95% CI 1.60-13.98). All pathogens were resistant to the prophylaxis antibiotic.[347] RCT 1-

Evidence summary

1-	There was insufficient credible evidence for antibiotic prophylaxis reducing the rate of recurrent UTI in children under a intermittent catheterisation regime.[346]

Recommendations

√	It is not recommended to use antibiotic prophylaxis in paediatric patients under a clean intermittent catheterisation regimen.

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18.1.3 Antibiotic prophylaxis in children catheterised for single sampling or endoscopic procedures

Key question:

- Is the use of antibiotic prophylaxis recommended in children undergoing catheterisation for single sampling (VCUG, CEUS, isotope VCUG, urine collection) or endoscopic procedures (cystoscopy, ureteroscopy, nephrostomy)?

Given the few studies found for assessing the incidence of UTI in paediatric patients requiring catheterisation for diagnostic or exploratory tests, the results of studies found in adult patients are included.

In addition to the volume of evidence, the consensus recommendation of the NICE CPG[11] is also included.

One study showed the incidence of bacteriuria, pyuria and bacteraemia in adult outpatients (n=75, mean age 57±13 years, range 27-81 years) attending the urology department for a cystoscopy. None of the patients had received previous antibiotic treatment. It was found that 48 hours after the procedure 16% of patients (12) had pyuria, but only 8% (6) had pyuria and bacteriuria; the other 8% (6) had pyuria without bacteriuria. Of the 6 patients with bacteriuria, only 2 had symptoms of dysuria and none developed fever.

Prior to the cystoscopy, 5 patients had pyuria, 4 of whom developed bacteriuria after 48 hours. The study found that the association between pyuria prior to the diagnostic test and bacteriuria at 48 hours was statistically significant ($P<0.05$). None of the patients developed bacteraemia.[348]

Case series 3

A multicentre study evaluated the effect of prophylactic antibiotics administered before the completion of urethrocystoscopy in a total of 2,172 outpatients over 16 years of age. They were randomised into 2 groups: one receiving prophylaxis (1,115 patients) of 1g IM ceftriaxone and a control group (1,057 patients) which received no antibiotic treatment.

It found that 10.2% of patients (108) in the control group developed symptomatic bacteriuria, compared with 2.5% of patients (28) in the prophylaxis group (RR 0.25, 95% CI 0.16-0.37; ARR 7.7%, 95% CI 5.7-9.8; NNT 13, 95% CI 10-18). The most common manifestation of this bacteriuria was voiding syndrome, affecting 85% of cases (92) in the control group and 82% of cases (23) in the prophylaxis group; followed by pyelonephritis, affecting 13% of cases (11) in the control group and 3.6% of cases (1) in the prophylaxis group.

There were no significant differences between the groups in the incidence of asymptomatic bacteriuria or in the incidence of irritative syndrome with sterile urine ($P>0.05$).[349]

RCT 1-

More than 5 years have passed since the publication of this Clinical Practice Guidelines and its validity has not been reviewed

A meta-analysis was found evaluating the safety and effectiveness of antibiotic prophylaxis against placebo or nothing in reducing the risk of UTI (demonstrated by bacteriuria) in patients undergoing urodynamic studies (invasive cystometry). RCT SR 1-

The meta-analysis included 8 RCTs with a total of 995 adult patients (age range 18-82 years), and found that the risk of bacteriuria in patients receiving antibiotic prophylaxis was reduced (OR 0.39, 95% CI 0.24-0.61).

From the control groups of the 8 included studies, the authors of this SR calculated an incidence of bacteriuria of 13.7% in adult patients undergoing urodynamic studies. This gave a NNT of 13, i.e. the number of adult patients undergoing urodynamic studies required to be treated with antibiotic prophylaxis to prevent 1 case of bacteriuria.[350]

An Israeli retrospective study evaluated the incidence of symptomatic UTI in children (n=421) after undergoing VCUG. They were given prophylactic antibiotics (cephalexin 20 mg/kg/day) from the day before the VCUG until visiting the outpatient paediatric nephrology department 7-10 days later. Cohort study 2-

VCUG was performed in 349 patients (274 girls and 75 boys, mean age 1.9±2.2 years) after febrile UTI and to 72 patients (13 girls and 59 boys, mean age 0.5±0.9 years) to study hydronephrosis.

There were 172 cases of VUR detected after performing VCUG (44% of patients in the febrile UTI group and 25% of patients in the hydronephrosis group).

Of the total 421 patients, 7 (1.7%) developed symptoms suggestive of febrile UTI 1-3 days after the VCUG. The 7 cases were in the febrile UTI group of patients and all had VUR grades II-IV. Of these 7 cases, 5 were confirmed by urine culture; with 1 case of *E. coli* (patient did not follow prophylactic treatment) and 4 cases of *P. aeruginosa*. These 4 latter cases occurred in patients with a VUR grade ≥III, and were equivalent to 6.8% (4/59) of the total.

Multivariate logistic regression found VUR (OR 2.52, 95% CI 2.24-2.83) and the degree of VUR >III (OR 2.32, 95% CI 2.05-2.62) to be risk factors associated with the development of UTI after VCUG. The authors concluded that the incidence of UTI after VCUG in children receiving antibiotic prophylaxis was low, and that the use of prophylactic anti-pseudomonas may be indicated in patients with a high degree of VUR who undergo VCUG monitoring.[351]

The NICE CPG contained no evidence to address this question; however, it recommends antibiotic prophylaxis for 3 days for all children who undergo a VCUG (the day before the test, the day of the test and the following day).[11] Expert opinion 4

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A prospective study conducted in the UK was found assessing the incidence of UTI in children undergoing VCUG (n=107, median age 7 months, range 1 month to 11.6 years). Most (75.7%) of the sample received antibiotic prophylaxis compared to the rest (24.3%) who received no prophylaxis. A urine culture sample was collected at the time of performing VCUG. Some days later (median of 4 days, range 1-45 days), a dipstick urine analysis was performed in primary care, and samples testing positive were sent for urine culture. There were 2 positive urine culture samples out of the 30 submitted, with just 1 of the cases being a new infection. Neither of the 2 patients had received antibiotic prophylaxis prior to VCUG.[352]

Case series 3

The GDG noted the limited applicability to children of the adult study results, as well as the lack of studies with a control group to assess the incidence of UTI in paediatric patients undergoing diagnostic or endoscopic testing who required intermittent urinary catheterisation, without prior administration of antibiotic prophylaxis. Therefore, only 2 studies were relevant to our population, and are therefore of little use for making recommendations.[351,352]

Evidence summary

1-	Administration of antibiotic prophylaxis in adult patients undergoing urodynamic studies or urethrocystoscopy reduced the risk of bacteriuria.[349,350]
2-	The incidence of febrile UTI in paediatric patients undergoing VCUG receiving antibiotic prophylaxis was 1.7%.[351]
4	Antibiotic prophylaxis over 3 days is recommended for paediatric patients undergoing VCUG.[11]

Recommendations

√	It is not recommended to give routine antibiotic prophylaxis to children prior to diagnostic procedures requiring a single catheterisation (cystoscopy, VCUG, CEUS, urodynamics, urine sampling).
√	Antibiotic prophylaxis may be considered when there is a risk from related illnesses (e.g., heart disease), recurrent UTI, atypical UTI, suspected VUR grade IV-V or abnormalities.

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18.2 Catheter care

Urinary catheterisation and patient management is traditionally the responsibility of nurses.337 It is estimated that nurses carry out urinary catheterisation approximately 50% of the time.[353]

This section is intended to address the uncertainty about certain care and maintenance procedures for the urinary catheter in its various forms.

18.2.1 Short-term catheterisation

Key questions:

- What is the best material or type of catheter to reduce UTI associated with short-term catheterisation?
- Does the size of the indwelling catheter affect the risk of CAUTI?
- Does cleaning the urethral meatus prior to inserting the catheter reduce the incidence of CAUTI?
- Does routine care of the urethral meatus in patients under indwelling catheterisation reduce the incidence of CAUTI?

Evidence from 3 CPGs and 3 SRs[31,33,34,343,354,355] regarding indwelling catheterisation is provided below.

The most commonly used indwelling catheters are the following:[354]

- Latex catheter impregnated with polytetrafluoroethylene (Polytef particles). Designed to limit the absorption of water by the catheter wall and reduce the surface resistance to insertion.
- Hydrogel-coated latex catheter, which allows limited absorption of water and a reduction in surface resistance to insertion.
- Silicone-coated latex catheter, which limits the absorption of water and reduces the friction between surfaces and exposure to the latex.
- Silicone catheter, with similar properties to those above and prevents hypersensitivity to latex.

No statistically significant reduction of ABU was found when comparing the most frequent types of catheters used.[31]	Observational studies 3
The type of material used on patients catheterised for periods of up to one week does not appear to modify the incidence of CAUTI.[31]	Observational studies 3
In adult patients (>65 years of age) under long-term catheterisation, the catheters are prone to clogging with scale-type deposits, which are reduced when using silicon catheters. No differences were observed between different catheter materials for patients considered not prone to clogging.[33,356]	RCT 1-

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The Schumm et al. SR identified 3 RCTs comparing different types of standard catheters (without antibiotic and/or antiseptic material) in adults hospitalised and catheterised for short periods of time (≤14 days) for a reduction in ABU or bacteriuria. No study found any significant differences for any of the outcomes of interest: ABU (silicone vs latex catheter: RR 1.07, 95% CI 0.23-5.01; silicone vs hydrogel catheter: RR 0.82, 95% CI 0.46-1.47); bacteriuria (hydrophilic polymer coated latex catheter vs latex catheter: RR 0.94, 95% CI 0.66-1.34; hydrophilic polymer coated latex catheter vs PVC catheter: RR 0.87, 95% CI 0.63-1.19; PVC vs latex catheter: RR 1.09 95% CI 0.81-1.45).[343]	RCT SR 1-
The same Schumm et al. SR identified 3 RCTs comparing different types of standard catheters (without antibiotic and/or antiseptic material) in adults hospitalised and catheterised for short periods of time (≤14 days) for urethral side effects. The studies found that patients with a silicone catheter had less of a burning sensation in the urethra (silicone vs non-silicone: RR 0.28, 95% CI 0.13-0.60); had fewer cases of urethritis (silicone vs latex: RR 0.09, 95% CI 0.01-0.68); and a lower risk of urethral reaction (silicone vs hydrogel coated latex: WMD -16.00, 95% CI -18.84 to -13.16; silicone vs silicone latex: WMD -16.00, 95% CI -18.96 to -13.04).[343]	RCT SR 1-
It was observed that the use of silicone Foley catheters with balloons have a greater tendency to cause pain and damage to the patient when deflated and withdrawn than latex catheters.[34]	Observational studies 3

Various documents discussing the use of catheters coated with silver alloys, silver oxide or antimicrobial agents for adult patients undergoing indwelling catheterisation were found while preparing this section. It seems that using catheters coated with silver alloy for periods up to 14 days is associated with a lower incidence of bacteriuria than catheters of silicone, latex or other materials. The cost-benefit ratio of these devices has not been established, although it appears that a significant reduction in the total number of infections would be cost effective for the use of silver alloy catheters.[31] Catheters impregnated with antiseptic or coated with antibiotics can prevent or significantly delay the onset of CAUTI, when compared with silicone or latex catheters in their various guises.[31] Catheters maintained for a short period (up to 14 days), coated with a silver alloy reduce the risk of bacteriuria and CAUTI in catheterised patients. Those impregnated with antimicrobials (minocycline + rifampicin or nitrofurantoin) reduce the risk of bacteriuria and CAUTI during the first 7 days, although not for 14 days.[354] In Spain, the use of urinary catheters coated with silver in its various forms or with antibiotics is exceptional, and so these were not taken into account when making recommendations.

Additionally, 2 in-vitro studies were found, which were therefore not included in the volume of evidence, suggesting that the material of the catheter is a factor to be taken into account in the formation of biofilm and that silicone promotes the formation of biofilm by uropathogenic strains.[357,358]

Evidence was taken from 2 CPGs[31,34] regarding the influence of catheter size on the risk of CAUTI. A review[354] attempted to investigate this effect, but failed to identify documentation on the appropriateness of one size catheter over another.

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Despite not having any quality studies, the 2 CPGs consider that, in adults, smaller size Foley-type catheters with a 10 mL balloon minimise urethral trauma, mucosal irritation and residual urine in the bladder, which are all predisposing factors for CAUTI.[31,34] They therefore recommend selecting smaller gauge catheters that allows for the free flow of urine, while bearing in mind that hospitalised patients undergoing urological surgery may require larger gauge catheters with a larger balloon to minimise any blockage due to blood clots.[31]

Expert opinion 4

The following evidence was gathered regarding the care of the urethral meatus before inserting the catheter, and for routine care afterwards.

There were 3 CPGs that recommended the health professional always insert the catheter using the aseptic technique, both in hospitals[31]and in outpatient care.[34] Sterile equipment should be used when performed in a hospital setting[33] despite the finding of a SR.[359] This SR identified 1 RCT evaluating the incidence of bacteriuria in adult catheterised patients about to undergo surgery while inserting the catheter using the sterile technique (sterile gloves, sterile gown, strict aseptic technique, surgical hand washing, meatal cleansing with antiseptic, sterile lubricant, no-touch technique, sterile catheterisation pack) and the non-sterile, clean technique (non-sterile gloves, no coat, hand washing with soap and water, cleaning the meatus only if dirty to the naked eye and only with tap water, non-sterile lubricant, no catheterisation pack). There were no differences found between the groups (P>0.10) 3 days after surgery.

Expert opinion 4

RCT 1-

The same SR identified 1 RCT that evaluated the incidence of bacteriuria in adult women admitted to an obstetrics unit who needed the catheter to be inserted using the aseptic technique. It compared periurethral washing with tap water against washing with an antiseptic (chlorhexidine 0.1%) before inserting the catheter and found no difference between groups (OR 1.13, 95% CI 0.58-2.21).[359]

RCT 1+

These findings are taken into account by 2 CPGs, one of which is based on expert opinion and believes that washing the urethral meatus prior to insertion of the catheter with antiseptic preparations in a hospital environment is no better than washing the urethral meatus with normal sterile saline.[31] The other CPG believes there is insufficient evidence to support any recommendation regarding urethral meatus care before inserting the catheter.[33]

Expert opinion 4

Before inserting the catheter, 2 CPGs recommend using single use sterile lubricant or anaesthetic gel to minimise discomfort and urethral trauma.[31,34]

Expert opinion 4

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To care for patients with an indwelling catheter inserted, 2 CPGs[31,33] and 1 SR[355] collected evidence from the same studies and reached similar conclusions. The results of 8 RCTs and 3 observational studies[356] concluded that, once the catheter is inserted, the use of antimicrobial or antiseptic preparations for routine cleaning of the periurethral area does not reduce the risk of bacteriuria compared with washing with soap and water.[31,33,355]	RCT SR 1+/ Observational studies 2+
Additionally, 1 of these studies found increased bacteriuria in patient groups receiving special care in routine cleaning of the urethral meatus (twice daily cleaning with antiseptic solution and ointment or daily cleansing with non-antiseptic solution of soap and water) compared with those who received no special care (P<0.05).[355.356]	
A SR included a study which found that the absence of daily washing of the perineal area in adult patients hospitalised and catheterised for 3 or more days was associated with an increased risk of CAUTI (RR 2.49, 95% CI 1.32-4.69), especially in patients with faecal incontinence.[355]	Observational study 3
Two CPGs noted that urethral trauma, discomfort to the patient and the potential risk of CAUTI were minimised when the insertion and care of an indwelling urinary catheter was performed by trained and experienced health staff.[31,34]	Expert opinion 4

When making recommendations, the GDG considered the lack of studies and their methodological limitations; their heterogeneity in measuring outcome variables, with different studies evaluating the presence of ABU, bacteriuria or CAUTI; and the limited applicability of some results, especially those related to the tendency of catheter blockage in elderly patients catheterised for long periods of time. In addition, the identified studies focused mainly on the adult population, with only some mixing both adult and paediatric patients. Furthermore, many of them were performed on catheterised patients, regardless of the estimated catheterisation time, in strictly hospital environments, or in combination with catheterisation for outpatients or in the community.

Without more information on the efficiency or effectiveness of different catheter sizes, the GDG considered that it would be good practice to reduce the risk of damage to the urethral mucosa by using smaller diameter catheters; bearing in mind that no study of the efficacy and safety in paediatric patients was identified.

There was little evidence found to evaluate interventions required before inserting the urethral catheter. The only 2 RCTs included in a SR[359] were performed in a very specific context and in a population with very specific characteristics: adult patients catheterised before surgery and adult women admitted to the obstetrics department. Due to the limited evidence and applicability of the findings, the CPGs[31,33,34] consulted chose to provide recommendations based on expert opinion. The volume of evidence for care needed after the urethral catheter is inserted gave consistent results: antimicrobial or antiseptic preparations do not reduce the incidence of bacteriuria when compared with routine washing.

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Evidence summary

1-[343]/ 3[31]	No significant differences were found in the incidence of bacteriuria or ABU when comparing the use of different types of standard catheters in adult patients undergoing short-term indwelling catheterisation (≤14 days).[31,343]
1-	Silicone catheters reduce the risk of urethral side effects in adult males catheterised for short periods of time (≤14 days).[343]
3	Tests based on good practice suggest that the incidence of CAUTI in patients catheterised for up to one week is not influenced by the catheter material.[31]
3	Foley-type catheter balloons made of silicone are more likely to cause pain and damage to the patient than latex catheters when deflated and removed.[34]
1-	Some low quality testing suggests that, in adult patients catheterised for extended periods of time and prone to clogging, silicone catheters are better at preventing scale-type deposits, which make it difficult to evacuate the urine, than latex or Teflon-coated catheters. There were no differences between materials in elderly patients not considered prone to suffering such blockages.[33,356]
4	Choosing a smaller diameter catheter while still ensuring a free flow of urine causes less urethral trauma and urethral mucosa irritation.[31,34]
4	A health professional inserting the catheter in a hospital must use the aseptic technique and sterile equipment.[31,33]
4	Cleaning the meatus with antiseptic preparations prior to inserting the catheter does not offer advantages over cleaning with sterile saline solution.[31] The use of a single-use sterile lubricant or anaesthetic gel minimises urethral discomfort and trauma.[31,34]
1+/ 2+	After inserting the catheter, the use of antimicrobial or antiseptic preparations for routine care of the periurethral area does not reduce the risk of bacteriuria any more than washing/showering daily with soap and water.[31,33,355]
4	Inserting and taking care of the catheter should be carried out by trained and experienced health personnel.[31,34]

Recommendations

√	It is recommended to use silicone catheters.
D	It is recommended to take into account the clinical experience of the team, individual patient assessment and anticipated catheterisation duration when choosing the catheter.
D	It is recommended to choose the catheter diameter size based on an individual patient assessment and taking into account features such as age, urethral size, as well as the propensity for blocking the catheter.
D	When in hospitals, it is recommended to insert the catheter with sterile equipment using the aseptic technique.
D	It is recommended to clean the meatus with sterile saline or sterile water before inserting the urethral catheter.
D	It is recommended to use a single-use sterile lubricant to reduce the pain, urethral trauma and risk of infection.

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A	Daily personal hygiene with soap and water is all that is needed for the proper care and cleaning of the urethral meatus after inserting the catheter.
D	It is recommended that health professionals inserting the catheter have training and experience in the insertion and maintenance of urethral catheterisation.

18.2.2 Intermittent catheterisation

Key questions:

- What type of catheter (coated or uncoated) is more appropriate for reducing UTI associated with intermittent catheterisation?
- What is the most appropriate size catheter for reducing UTI associated with intermittent catheterisation?
- What is the most appropriate insertion technique for intermittent catheterisation?

Intermittent catheterisation (IC) consists of routine emptying of urine from the bladder, which can be done by the patients themselves or by others. There are numerous advantages which add to the quality of life of people who use it: it leaves no residual urine (which is prone to bacterial growth) and prevents bladder distension, which can irreversibly damage the different layers of the bladder and the detrusor muscle. The objectives of IC are to preserve the dynamics of micturition in its bladder filling and emptying stages, and decrease the frequency of complications that may arise via the urethra, such as stenosis, false channels, or kidney damage or complications arising from recurrent urinary tract infections associated with the use of a catheter.[360]

This technique must be performed in an aseptic or clean manner, and is not without potential complications, such as UTI. Given the number of different catheter materials and types on the market, it must be determined if any of them reduce or prevent the occurrence of UTI and which are better managed by these patients.[360]

Uncoated catheters were compared to the single-use variety. The uncoated catheters were generally made of PVC (polvinyl chloride), and were often re-used with a separate lubricant or without a lubricant (for excluding water); while the single-use coated catheters were designed to confer better lubrication to facilitate insertion. The most common coatings were hydrophilic (requiring added water) or pre-lubricated (water-soluble gel).

A SR[361] was identified whose aims included determining the type of catheter and insertion technique best suited for reducing the incidence of UTI, its complications and improving quality of life. The variety of the included studies meant the authors could not perform a meta-analysis of the results. All the studies were also of low quality, so their results are shown individually, along with those of the individual studies found from our search.[362,363]

Two studies included in the SR evaluated the incidence of ABU in adult patients, comparing coated and uncoated catheters. Both studies point to a non-significant reduction in the incidence of ABU with the use of coated catheters. Both studies had significant internal validity limitations.[361] RCTs 1-

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Another 4 studies included in this same SR compared coated and uncoated catheters, and evaluated the incidence of symptomatic UTI in adult patients (3 studies) and paediatric patients (1 study). Only 1 study, which was in adult patients, found a significant reduction in the incidence of symptomatic UTI using coated catheters: RR 0.78 (95% CI 0.62-0.97). The results of this study were limited by the high percentage of losses (54%) after randomisation. The 3 remaining studies found no significant differences between the groups.[361]

RCTs 1-

Patient satisfaction with the catheter was also reported in 3 of the previous studies, with comfort during insertion being assessed in 2 studies. In the first case, the 3 studies (including adult and paediatric patients) concluded that there was a greater preference for coated catheters from patients. Two studies (including adult and paediatric patients) reported about the comfort at the insertion of the catheter, with most patients scoring the coated catheters as more comfortable. One study also reported that patients preferred the coated catheters for their extraction and handling.[361]

RCTs 1-

One study by questionnaire in 35 paediatric patients who underwent IC (age range 5-20 years) compared the degree of satisfaction in using a new coated hydrophilic catheter and the normal patient catheter made of PVC. The study found that 86% of patients learnt the technique with the new catheter easily or very easily, with no differences between groups. With the normal catheter, there were 18 (51%) and 6 (17%) patients who reported discomfort when inserting and removing the catheter, respectively, compared to 5 (14%) and 1 (3%) patients, respectively, using the new coated catheter. The hydrophilic coated catheter was preferred by 70% of patients in the study, due to less discomfort and the increased convenience of not requiring lubrication. Although, 17% of patients reported that the coated catheter was more difficult to use, due to it slipping easily after being well lubricated. About 6% reported that it was more awkward to use because it required more time for preparation; and finally 1 patient reported that patients in wheelchairs with the new catheter required assistance from third parties, due to having to put it into water.[362]

Case series 3

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A Swedish study was identified which retrospectively evaluated the risk of urethral injury and epidimiditis in children with neurogenic bladder under IC. The study analysed the complication rate according to various factors, including the size of the catheter, the age of the patient (before or after puberty) and the ability of the patient to self-catheterise.

Observational study 3

The study grouped the results according to the size of catheter used: between 12Fr and 18Fr, or between 6Fr and 10Fr. All participants were catheterised for at least 10 years with all having at least 2 years of adolescence. The median age of patients when they began IC was 2 years (range 0-10 years) and the median follow-up was 16 years (range 10-21 years). The results were expressed as the sum of the exposure times that each participant contributed to the study. Under these conditions, they analysed the difficulties in inserting the catheter and/or existence of haematuria and major urethral injuries diagnosed by cystoscopy as a composite outcome. The study found that during the 250 years of exposure to IC with catheter gauges between 6Fr and 10Fr, there were 32 (13%) episodes where there was difficulty in inserting the catheter and/or haematuria, and 9 (4%) of major urethral lesions diagnosed by cystoscopy. However, in the 188 years of exposure to catheter gauges between 12Fr and 18Fr, there were 10 (5%) and 0 detected, respectively. The authors concluded that these favourable results for the larger catheter size, were due to two facts: the larger catheters had less pointed ends, and larger catheters were used by older patients, who were also the most likely to self-catheterise; none of the patients who self-catheterised suffered a major urethral injury.[363]

A SR included 3 studies in adults or elderly patients evaluating the incidence of symptomatic UTI and ABU in patients undergoing sterile IC vs the clean technique. There were no significant differences found between groups for any of the variables studied: ABU (RR 0.97, 95% CI 0.47-2.03) and UTI (RR 0.83, 95% CI 0.38-1.85), (RR 1.00, 95% CI 0.66-1.53) and (RR 1.67, 95% CI 0.45-6.17).[361]

RCTs 1-

When making recommendations, the GDG took into consideration the lack of statistical significance related to the main efficacy or effectiveness variable, which in our case was UTI. Only 1 of the studies included in the SR361 gave a significant reduction in the incidence of UTI using coated catheters; however, a recommendation to use one catheter type or another based on the results cannot be defended, given the methodological limitations of this study. Significant differences in the type of technique to be used in placing the catheter were also not found. For outpatients, clean catheterisation is recommended, due to the difficulty in using the sterile technique; given the frequency of catheterisation, the mobility of the patients and the resources under which these patients must be catheterised.

Because intermittent catheterisation is a process that in most cases will be maintained periodically, the preference of a single patient for one particular catheter type, be it coated or uncoated, must be considered; regardless of the statistical significance or not of results indicating a greater patient satisfaction with coated catheters.

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Evidence summary

1-	There were no significant differences in the incidence of ABU and/or symptomatic UTI related to the catheter type (coated vs. uncoated) in intermittently catheterised patients.[361]
1-	Adult and paediatric patients undergoing intermittent catheterisation prefer coated to uncoated catheters, due to their comfort and manageability during insertion and extraction.[361]
3	Paediatric patients reported discomfort while inserting and withdrawing the PVC catheter of 51% and 17%, respectively, compared with 14% and 3% using the coated hydrophilic catheter.[362]
3	70% of paediatric patients undergoing intermittent catheterisation preferred hydrophilic coated catheters to PVC ones. However, 17% and 6% reported disadvantages with their use, as they slip out easily and require more time of preparation, respectively. A patient in a wheelchair would need the help of third parties to perform catheterisation with a coated hydrophilic catheter.[362]
3	Paediatric patients with neurogenic bladder under intermittent catheterisation had less problems inserting the catheter and/or haematuria and less major urethral injuries, as diagnosed by cystoscopy, while subjected to 12Fr-18Fr gauge catheters, compared to 6Fr-10Fr gauge catheters.[363]
1-	No significant differences in the incidence of ABU or symptomatic UTI related to the insertion technique (sterile versus clean) were found in adults or elderly patients undergoing intermittent catheterisation.[361]

Recommendations

√	It is recommended that patients requiring intermittent catheterisation try different types of catheter, become familiar with their use and choose one or the other according to their perceived comfort and handling.
√	It is recommended to use the most appropriate catheter diameter according to the patient age taking into account the patient urethra size
√	Outpatients who have to perform intermittent catheterisation for bladder emptying should use a clean technique.
√	Patients requiring intermittent catheterisation should be instructed in how to do it themselves at the earliest possible age.
√	It is recommended to assess hospitalised or institutionalised patients individually before deciding on the intermittent catheterisation technique to use.

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18.2.3 Single sampling catheterisation

Key questions:

- Does the catheter material used in single sampling catheterisation affect the risk of CAUTI?
- Does the catheter size for single sampling catheterisation affect the risk of CAUTI?
- Does cleaning the urethral meatus prior to single sampling catheterisation reduce the incidence of CAUTI?

No specific studies with internal validity on single sampling urinary catheterisation were found to provide answers to the above questions.

As with short-term indwelling catheterisation, this type of catheterisation is performed in a health care setting, so it may be advisable to use sterile material and the aseptic technique.[31,34]

One study[364] was found comparing the incidence of UTI in children presenting to the emergency department with suspected UTI. They were catheterised to obtain a urine sample for culture analysis, and had their urethral meatus cleaned beforehand with sterile water vs. povidone iodine 10%. The study was not included in the volume of evidence due to selection bias limitations of the sample. The study sample consisted of patients attending emergency departments with suspected UTI, therefore the design was not appropriate for meeting the stated objective as it is not possible to establish whether the UTI detected was the result of catheterisation and cleaning via one process or the other.

More flexible catheters, such as nasogastric tubes, are often used for urinary catheterisation in low birth-weight newborns, due to their small urethra.[365] This type of catheter may form a knot inside the urinary bladder, due to inserting the catheter too far into the bladder. The knotting appears to occur when the catheter tube is too long and forms a loop on itself, helped by the decompression of the emptied bladder. When trying to remove the catheter, the loop tightens and forms a knot preventing its withdrawal.[366]

In especially younger children, sometimes a guide is used due to the difficulty of using a very small size catheter, mainly due to the ease with which it can kink at the slightest obstacle. The use of a guide requires special precautions to avoid creating false tracks.

From information about other types of catheters, it seems advisable to avoid latex catheters without any coating, as far as possible, or promote the use of catheters made from other materials.[31,33,34]

The urinary catheter is a procedure performed frequently and is usually safe, however, there are special risks in children, which are greater still in younger children. The use of suitable catheters, an understanding of the lower urinary tract anatomy and knowledge of how far to insert a urinary catheter are essential to reduce complications associated with their use.[366] By also using a catheter in situations where it is appropriate, a significant reduction in symptomatic UTI can be achieved.[367]

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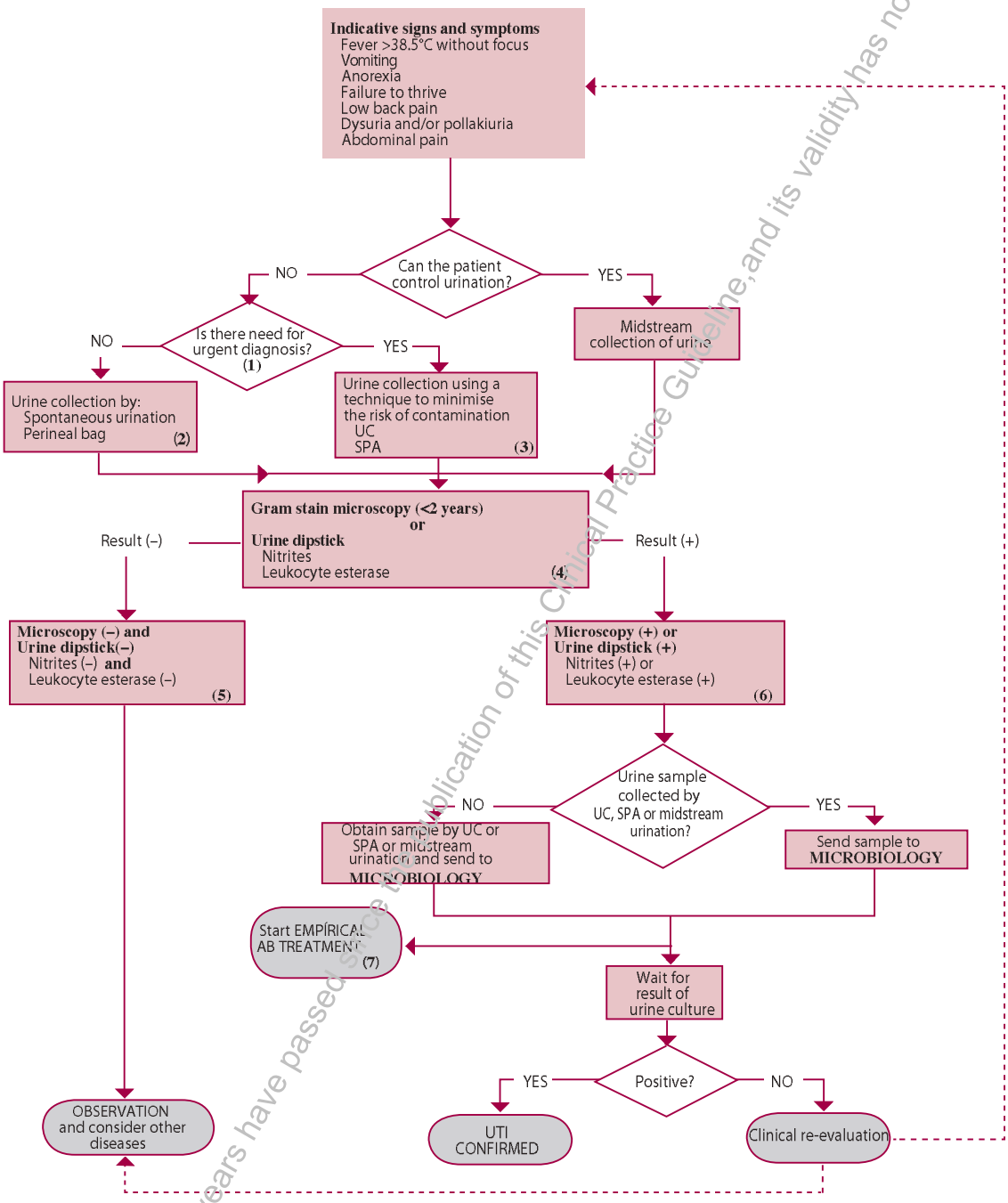
Recommendations

√	For single sampling catheterisation, use the catheter material with which the health professional is most familiar; avoiding to expose the health professional and the patient to latex.
√	For single sampling catheterisation, choose the catheter size according to the age of the patient. It is recommended to insert the catheter until urine flows freely and avoid inserting an excessive length of catheter tube into the bladder
√	It is recommended to use an aseptic technique with sterile media when performing single sampling catheterisation.

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19. Diagnostic and therapeutic strategies

Algorithm 1: ITU diagnosis



AB: Antibiotic; SPA: Suprapubic aspiration; UC: Urinary catheter; UTI: Urinary tract infection

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(1) A diagnostic or therapeutic emergency requiring immediate antibiotic treatment.

(2) The use of perineal bags for collecting urine has a high risk of bacterial contamination in comparison with samples obtained by catheterisation, suprapubic aspiration or midstream clean catch.

(3) Suprapubic aspiration (SPA) and urinary catheterisation (UC) decrease the risk of sample contamination. Use one or the other depending on the level of training and resources in the hospital setting. SPA should be performed with ultrasound guidance.

(4) Perform microscopy in children under 2 years old with a Gram stain if possible. Older children can be tested by dipstick for leukocytes (leukocyte esterase) and bacteria (nitrite test).

(5) A negative result virtually rules out UTI. However, the clinical symptoms and any prescription of antibiotics prior to collection of urine must always be assessed.

(6) A positive result for bacteria and/or leukocytes indicates a possible UTI. A urine culture analysis should be done for confirmation with urine collection by the technique that best minimises the risk of contamination (UC or SPA or midstream clean catch) in children who can control urination.

(7) For children with suspected UTI under 2 years of age or those who cannot control urination, start antibiotic treatment after collecting a urine culture sample if they have bacteriuria or positive nitrites from a reliable urine sample.

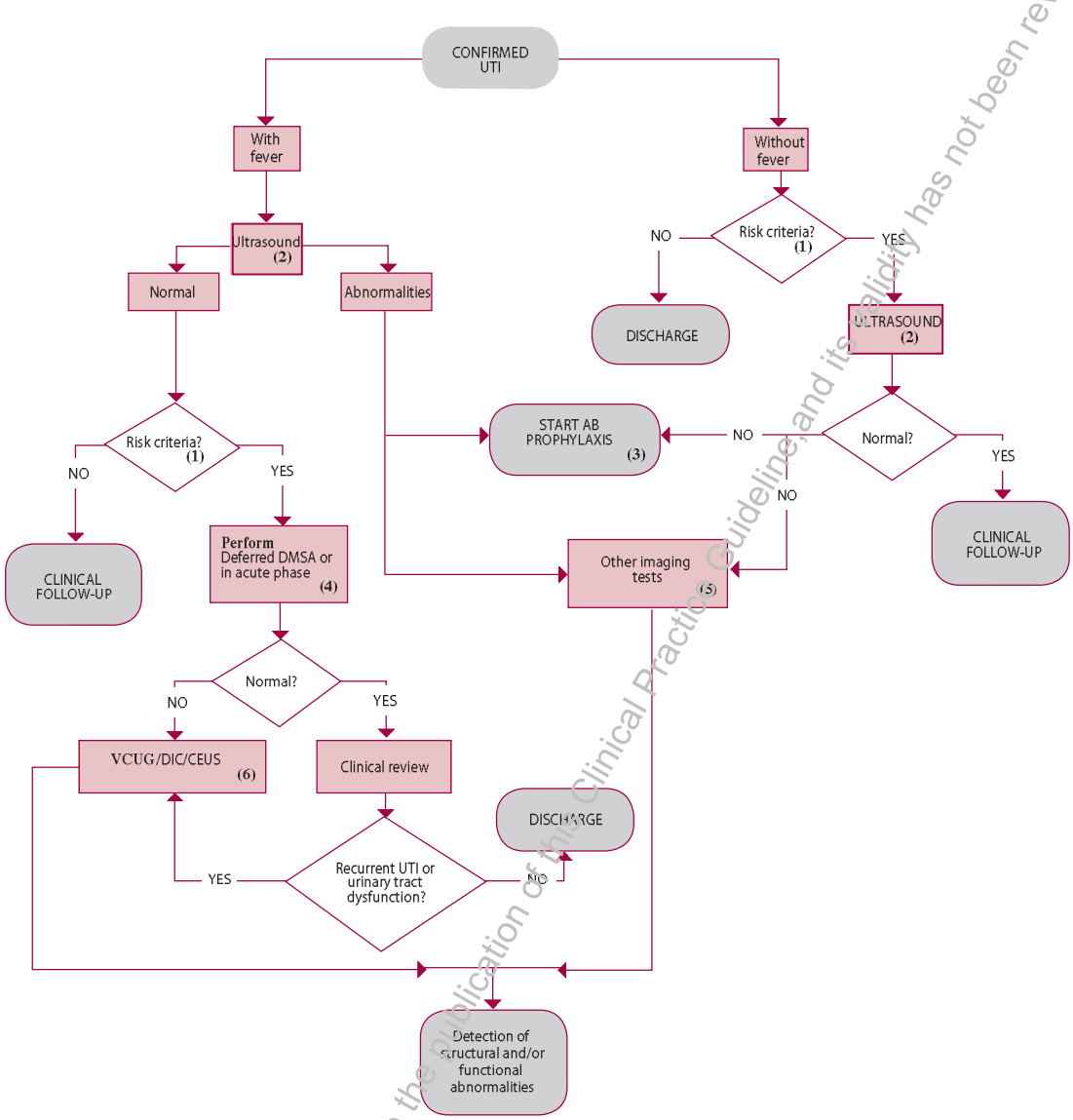
For children under 2 years of age or those who cannot control urination at risk of a severe disease (infants with fever of unknown origin), start antibiotic treatment after collecting urine, if bacteriuria or pyuria or nitrites are detected from a reliable urine sample.

For those over 2 years old, if there is a high clinical suspicion of UTI (specific symptoms with the presence of nitrites or bacteriuria, with or without leukocytes), start empirical antibiotic treatment after collecting a urine culture sample.

For those over 2 years old with leukocytes in urine only, perform a urine culture, and consider starting antibiotic treatment according to the likelihood of the symptoms and the clinical condition of the patient.

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Algorithm 2: Diagnosis by imaging tests of urinary tract abnormalities and follow-up after UTI



AB: Antibiotic; CEUS: Echocystography; DIC: Direct isotopic cystography; DMSA: Renal scintigraphy; UTI: urinary tract infection; VCUG: Voiding cystourethrogram

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(1) For each patient, assess if any of the following factors leading to suspicion of an atypical UTI are present. Helping us to establish an imaging study of the urinary tract:

- Atypical evolution (persistence of fever over 48 hours after starting treatment)
- Existence of vesicoureteral reflux (VUR) in the family
- Clinical signs of lower urinary tract dysfunction
- Palpation of renal masses or distended bladder
- Prenatal diagnosis of urinary tract dilatation
- Elevated creatinine levels
- Bacteraemia
- Recurrent UTI
- Bacteria other than *E. coli*

(2) Renal ultrasound after confirming diagnosis of UTI (in acute phase).

(3) Start antibiotic prophylaxis if there is severe dilatation or a suspected urinary tract obstruction and continue until diagnosis confirmation or problem resolution.

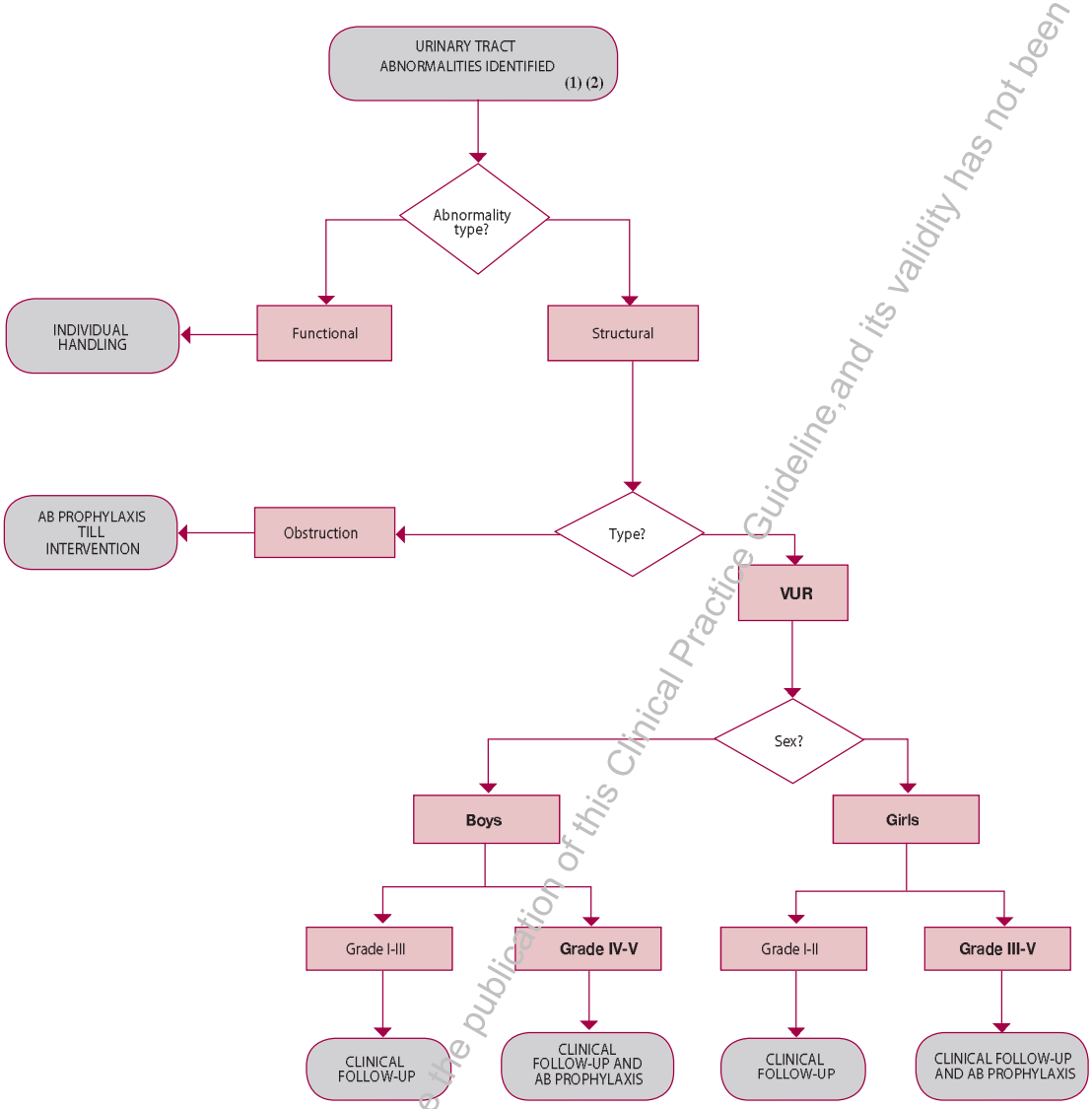
(4) Perform renal DMSA (the gold standard for kidney damage) 6 months after the initial episode. Selective use of DMSA in the acute phase can be considered according to availability if the result determines the subsequent diagnosis management for the patient (indication of treatment or additional tests).

(5) The imaging test chosen [voiding cystourethrogram (VCUG); renal scintigraphy with dimercaptosuccinic acid (DMSA); renal scan; intravenous urography (IVU); computed tomography (CT); nuclear magnetic resonance (NMR)] depends on the ultrasound findings - in the search for obstructive abnormalities, VUR or renal damage.

(6) Perform VCUG to look for VUR, its grade and the possibility of structural abnormalities in the lower urinary tract. The test is indicated if any of the following factors are present: existence of recurrent UTI or abnormality detected in any previous imaging tests performed (ultrasound, DMSA); association of UTI with clinical signs of lower urinary tract dysfunction or history of VUR with UTI in the family. Direct isotopic cystography (DIC) or CEUS are appropriate in case of requiring imaging study just to detect the presence of VUR.

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Algorithm 3: Antibiotic prophylaxis for urinary tract abnormalities after UTI



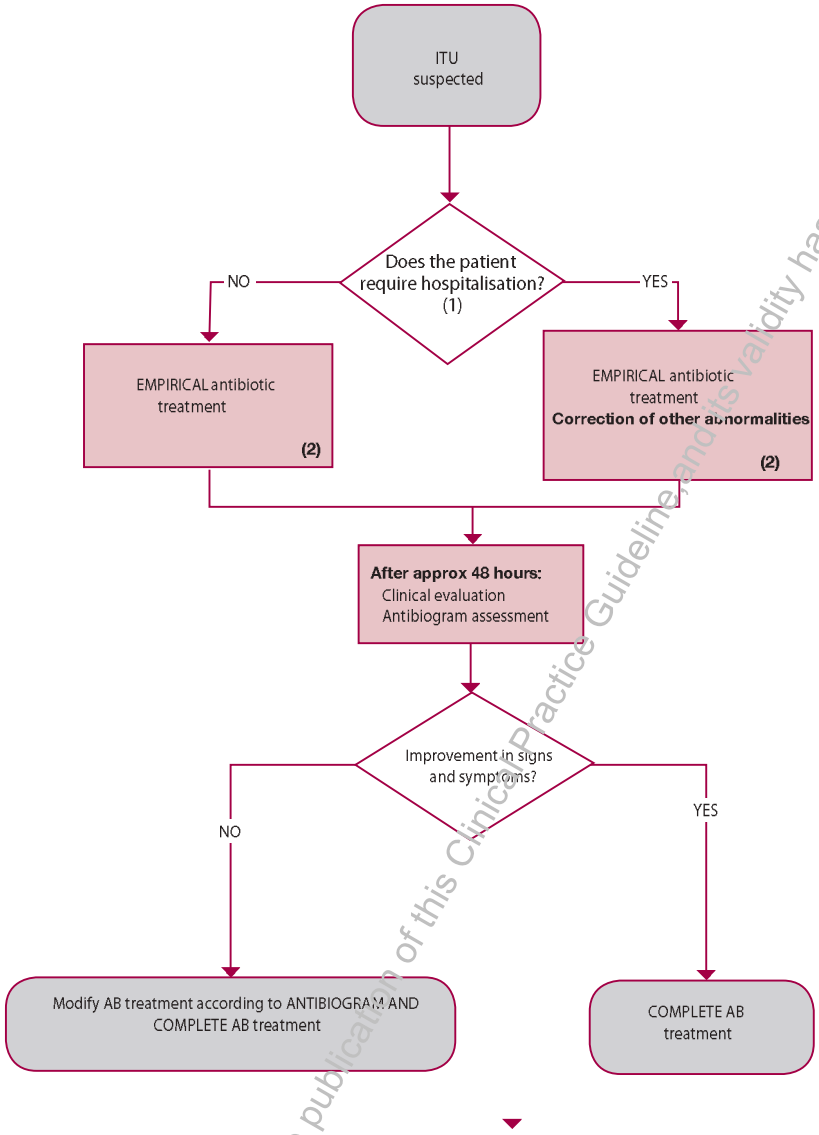
AB: Antibiotic; VUR: Vesicoureteral reflux.

(1) Abnormalities concerning the existence of VUR and confirmation of urinary tract obstructive abnormalities.

(2) This algorithm runs until prophylactic antibiotic treatment after diagnosis of the abnormalities described. The follow-up will be according to the protocols established at each centre.

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Algorithm 4: Empirical treatment of UTI



AB: Antibiotic; UTI: Urinary tract infection

(1) Hospitalisation is recommended for a child with febrile urinary tract infection meeting any of the following criteria:

- Age less than 3 months
- Deterioration in general health, poorly appearance
- Vomiting or intolerance to oral route
- Dehydration, poor peripheral perfusion
- Urinary system abnormalities: VUR, obstructive uropathy, renal dysplasia, single kidney
- Poor care or difficulty in monitoring
- Primary or secondary immunodeficiency
- Electrolyte or renal function disturbances

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Although hospitalisation may be considered, children with febrile urinary tract infection can also be treated on an outpatient basis under supervision if any of the following factors apply:

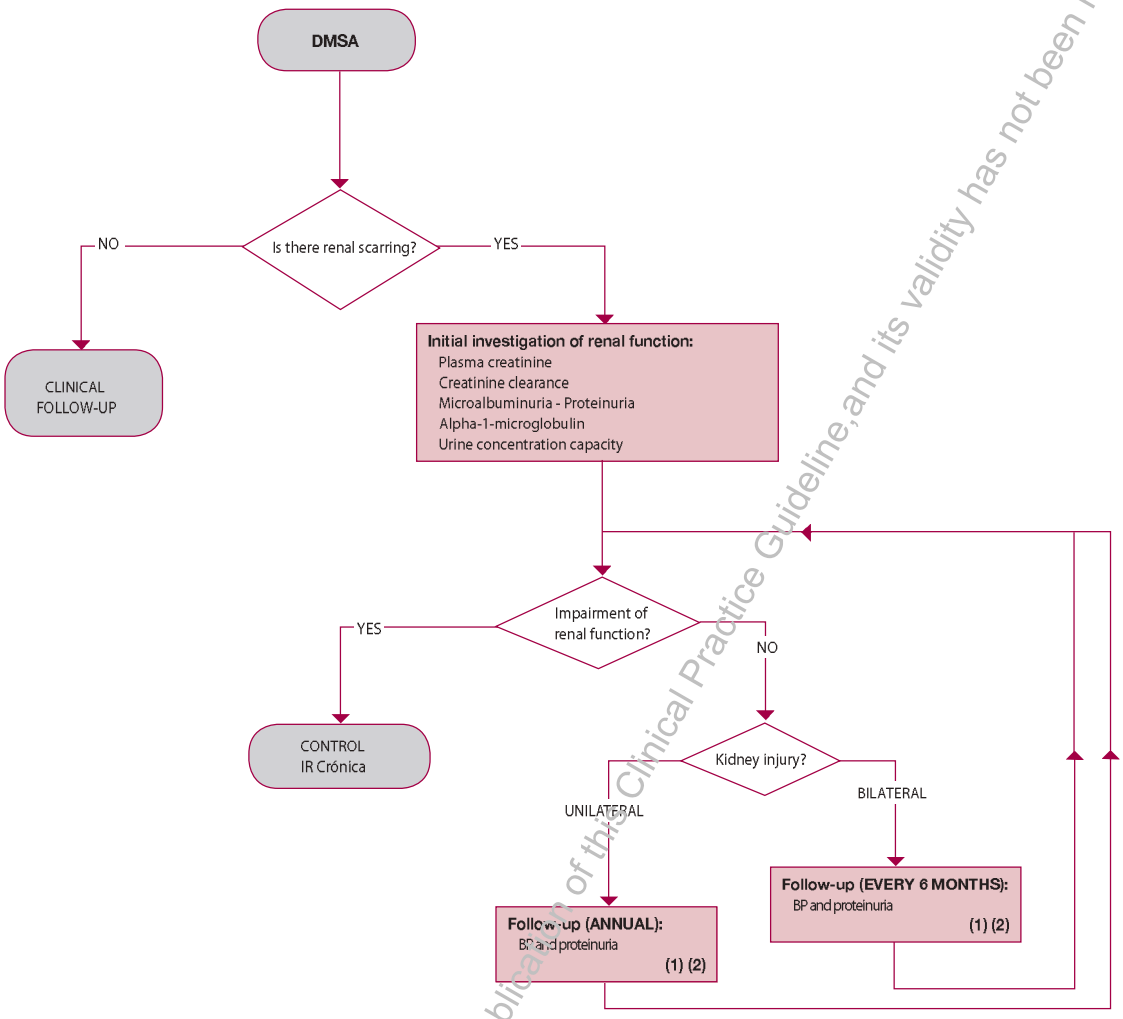
- High fever (≥38.5°C) in children of 3-6 months old
- Persistence of fever after 48 hours treatment
- Risk factors of an unusual bacteria (recent antibiotic therapy, recent hospitalisation, catheterisation)
- Family history of VUR or pre-natal ultrasound with congenital hydronephrosis
- Recurrent febrile urinary tract infections
- Significant increase in acute phase reactants

For all other cases, treat on an outpatient basis.

(2) Empirical antibiotic therapy according to local sensitivities and according to data from microbiology services.

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Algorithm 5: Follow-up after renal scarring



DMSA: Renal scintigraphy; BP: Blood pressure

(1) Follow-up by a paediatric nephrology specialist.

(2) Control of renal function, depending on the initial findings.

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20. Dissemination and implementation

The CPG is a tool to help professionals and users make decisions about the most appropriate health care. Therefore, the recommendations in this guide need to be introduced and implemented in those healthcare environment sectors relevant for their application, and to that end we recommend the following:

- Health authorities should present the CPG to the media.
- The CPG should be presented to the various national paediatric, paediatric nephrology and paediatric urology associations and societies.
- Presentation of the CPG to the relevant regional associations.
- Distribution of the abbreviated form to various institutions and organisations in the healthcare environment.
- Collaboration with the scientific societies who participated in the CPG review to promote its dissemination.
- Provision and distribution of the CPG to different CPG database compilers for its evaluation and inclusion in them.
- Free access to different versions of the CPG on the GuiaSalud website http:// www.guiasalud.es
- Dissemination and information about the CPG in scientific activities related to paediatrics, urology, nephrology and nursing.
- Translation of the complete version into English.

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21. Future research lines

7.1 The lack of hygiene as a risk factor for UTI: nappy use and presence of oxiurasis.

High quality methodological studies are recommended to assess the effects of the use and type of nappies for the incidence of UTI in children.

9.4.1 Diagnostic validity of clinical signs and symptoms.

Diagnostic studies are recommended on non-invasive procedures using biological samples from blood and urine to detect the presence of acute or chronic kidney damage.

10 Diagnosis of UTI by imaging

Studies are needed to evaluate the indications for and diagnostic performance of diagnostic imaging tests.

Follow-up studies are needed in those children with a confirmed first febrile UTI who have not been tested by DMSA

13.7 Symptomatic medication in the treatment of UTI

Well-designed RCTs in paediatric patients are needed to investigate the usefulness of NSAIDs and steroids in the treatment of UTI.

14.4 Other preventive measures: uropathogenic strain vaccines, ascorbic acid, cranberry juice and probiotics

Rigorous and well-designed studies in paediatric patients with UTI are recommended to establish the protective effect of prophylactic alternatives such as uropathogenic strain vaccines, ascorbic acid, cranberry juice and probiotics.

16.2 Prevalence of chronic kidney damage in paediatric patients with UTI

The prognostic significance of unilateral and small size renal scarring that does not affect renal function should be investigated.

18.2.2 Intermittent catheterisation

Coated and uncoated single-use catheters should be investigated in the community and compared for their cost effectiveness.

Uncoated single-use catheters should be compared with the multi-use variety for their therapeutic and cost effectiveness and to assess if the sterility or the single use of the catheter is of any importance.

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Annexes

Annex 1. Figures and tables

Table 13. AGREE scores for the different GPCs evaluated

AGREE instrument Area	NICE 2007[11]	CINCINATTI 2006[29]	RVU 2008[30]	EPIC 2[31]	EUROP ASIAN 2008[32]	HICPAC 2009[33]	NICE 2003[34]
1 Scope and Purpose	100%	86%	86%	92%	25%	92%	100%
2 Stakeholder Involvement	67%	44%	40%	67%	29%	54%	77%
3 Rigour of Development	87%	68%	85%	88%	39%	89%	89%
4 Clarity and Presentation	83%	79%	81%	88%	67%	90%	94%
5 Applicability	78%	0%	31%	72%	0%	67%	72%
6 Editorial Independence	96%	92%	96%	100%	96%	92%	92%

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Table 14. Symptoms and signs present in infants and children with UTI

Age group		Symptoms and signs	Most Common → Least common	
Infants under 3 months old		Fever Vomiting Lethargy Irritability	Refusing food Failure to thrive	Abdominal or suprapubic pain Jaundice Haematuria Foul-smelling and/or cloudy urine
Infants and children over 3 months old	Pre-verbal phase	Fever	Abdominal or suprapubic pain Lower back pain Vomiting Refusing food	Lethargy Irritability Haematuria Foul-smelling and/or cloudy urine Failure to thrive
	Verbal phase	Pollakiuria Dysuria	Changes in urinary continence Abdominal or suprapubic pain Lower back pain	Fever Feeling unwell Vomiting Haematuria Foul-smelling and/or cloudy urine

Adapted from the NICE CPG (2007).[11]

Table 15. Effective doses (ED) of radiation received by a 5-year old child during different imaging studies for nephrourologic pathology diagnosis, expressed in equivalent chest x-rays* and days of natural background radiation**

**1 chest x-ray causes an ED of radiation of 0.007 mSv (millisievert)*

*** 1 day of background radiation in Spain is 0.003 mSv*

Diagnostic study	Equivalent number of chest x-rays	Equivalent number of days of background radiation
Retrograde cystography (VCUG)	32	73
Isotopic cystography	20	47
DMSA renal scintigraphy	16	37
Diuretic renogram	16	37
Intravenous urography	44	103
Abdominal CT	300	700

Table adapted from the Rodriguez et al. 2005[368] and Roson et al. 2008 studies.[369]

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Table 16. Kappa coefficient[370]

Kappa	Degree of agreement
<0.00	None
0.00-0.20	Slight
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Substantial
0.81-1.00	Almost perfect

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Annex 2. General considerations on information for families and patients

As with any medical intervention, when starting the study, treatment or care of children with UTI, the rights of both the patient (depending on their age) and their relatives or carers to be fully informed must be taken into account. Only after receiving accurate information can relevant decisions be made and consent given to receive timely care proposals. While consent is granted by relatives or carers, the opinions of patients between 12-16 years of age must also be considered.[371]

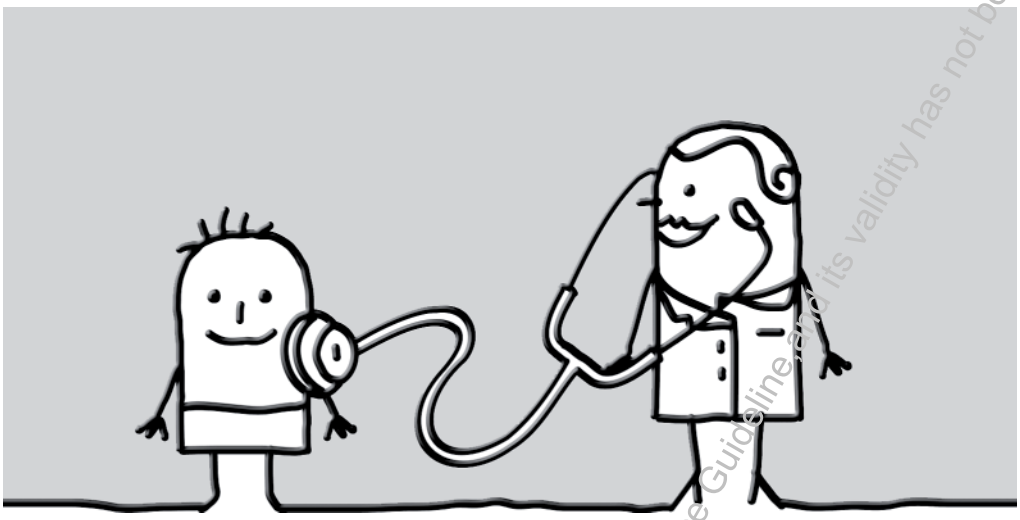
Medical professionals should be respectful, sensitive and understanding, and seek to provide simple, clear information about UTI. The information should include details of the potential risks and benefits of treatment and tests to be scheduled.

Families and patients should be encouraged to ask questions on any aspect of UTI. Moreover, the religious, ethnic and cultural family environment and difficulties related to the language should be taken into account.

SUMMARY
An effort must be made to give the best information about this process.
The information should include aspects related to diagnosis, treatment, preventive measures and prognosis.
When making special tests, information should be given about their nature, risks and benefits, when they should be done, whether hospitalisation is needed, as well as appropriate information on the results.
Information should be tailored to the personal, family, social and cultural rights of patients.

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Annex 3. Patient information.
Urinary Tract Infection in Children



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Contents

- Introduction
- **What** is urinary tract infection (UTI) and how common is it?
- What are the **signs and symptoms** for suspecting UTI?
- How is UTI **diagnosed**?
- How **is** UTI treated?
- What is UTI **recurrence**?
- How can we **prevent** UTI recurrence?
- What kinds of tests are performed with UTI?
- What is the **prognosis** after UTI?

Introduction

This annex is intended for families and carers of children. It may also be useful for patients over 12 years of age, who are able to understand the situation. The aim of this chapter is to help understand the care and treatment options available for a child with urinary tract infection.

What is urinary tract infection (UTI) and how common is it?

The urinary system consists of the kidneys, the bladder, the tube connecting these, the ureter, and the urethra, which is the tube where urine exits the body (Fig. 1). The kidneys filter blood and produce urine which passes through the ureters to the bladder, where it is stored for a time before being ejected to the exterior, either automatically in young children or voluntarily in those older. This whole urinary tract area is sterile, i.e. free of bacteria or germs.

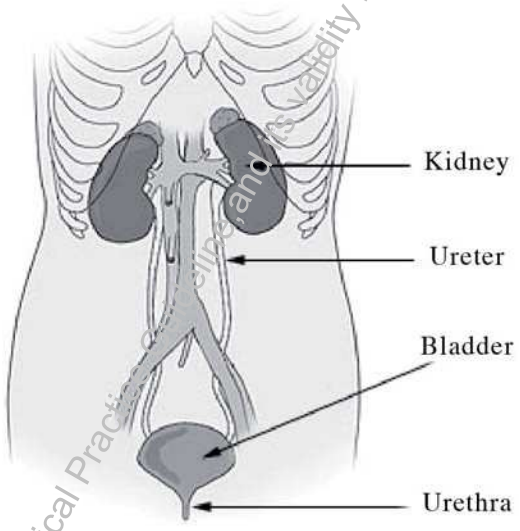


Figure 1. Urinary system components

When bacteria appear and grow in this urinary space, they can cause tissue abnormalities and lead to a number of symptoms, either of a general type, such as high fever or feeling unwell, or a local type, such as pain or itching or abnormal urination; this is what is known as "urinary tract infection (UTI)".

The infection can affect any part of the urinary tract. When it affects only the lower part (the bladder and urethra), there are usually local symptoms (pain or burning during urination) with little fever. This type of UTI does not cause kidney damage and can also be called "cystitis", "urethritis", "afebrile UTI" or "lower UTI". When the infection spreads to the upper urinary tract, reaching the kidneys, it usually causes fever and is called "febrile UTI," "acute pyelonephritis (APN)" or "upper UTI".

Sometimes, even when the patient is completely well without any symptoms, there are bacteria in the urine. This situation is called "asymptomatic bacteriuria". It is best not to treat asymptomatic bacteriuria, as it poses no risk or harm to the patient. However, treatment with antibiotics does pose risks to the patient, such as allergic reactions to medications and increased bacterial resistance. When this happens, antibiotics may not be effective in removing other infections that can be more severe.

Bacteria coming mostly from the intestinal tract can enter the urinary tract via the skin around the anus. This is especially so for girls, who are thus advised to clean themselves from front to back (instead of back to front) after going to the toilet. There are situations that promote the occurrence of UTI, such as urine going back into the ureters or kidneys, a situation known as vesicoureteral reflux; urinary tract malformations or impaired bladder function, which prevent urine from draining properly; or poor hygiene of the area surrounding the urethra.

Urinary tract infections are not contagious.

UTI appears in about 9% of girls and 2% of boys below seven years of age. Although during the first months of life, UTI is more common in boys than in girls, from twelve months of age this proportion is reversed, and there are more girls with UTI than boys.

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REMEMBER

- √ The diagnosis of UTI is based on finding **bacteria in the urinary tract, associated with clinical symptoms** of a general type (fever or feeling unwell) or local type (pain or burning when urinating).
- √ When fever is the main or only symptom, this is called **febrile UTI, upper UTI or acute pyelonephritis**. This can temporarily affect one or both kidneys. Sometimes it can leave permanent damage, but almost always of a small extent.
- √ When local symptoms predominate (pain or burning during urination) without fever, this is called **afebrile UTI, cystitis, urethritis or lower UTI**; it does not lead to kidney damage.
- √ UTI is not contagious.

What are the signs and symptoms for suspecting UTI?

It can be very difficult for both physicians and families or carers to know if a child has UTI, especially younger children, when the symptoms for UTI are common to other types of infections:

- √ Seemingly inexplicable fever
- √ Vomiting
- √ Fatigue
- √ Irritability
- √ Lack of appetite and no weight gain



Conversely, there may be more specific signs and symptoms that, when observed by those close to the patient, may help in diagnosing UTI:

- √ Pain and a burning sensation when urinating
- √ Feeling of urgency and increased number of voids
- √ Leakage of urine during the day or night from a child usually capable of controlling urination.
- √ Pain in the abdomen, lower abdomen or side
- √ Cloudy urine with an unpleasant odour
- √ Urine with blood at the beginning or end of urination

The smaller the child, the less specific the symptoms are, and in most cases the only symptom will be high fever, usually above 38.5°C, without observing any other symptoms that may indicate another type of infection, such as coughing, diarrhoea, runny nose, etc. This is fever "without focus".

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REMEMBER

- √ **Febrile UTI** produces more general symptoms such as malaise, flank pain and chills.
- √ **Afebrile UTI or cystitis** is not often accompanied by fever and produces specific symptoms localised to the bladder or urethra.
- √ The smaller the child, the **less specific are the symptoms**; most of the time the only symptom is fever "without focus" which is above 38.5°C.

How is UTI diagnosed?

UTI may be suspected after reviewing the clinical history and examination by the physician. The diagnosis is guided by analysis with dipsticks (urine test strips impregnated with substances which change colour when detecting bacteria or leukocytes in the urine, see Figure 2), or by microscopic examination (direct viewing of bacteria or leukocytes in the urine, see Figure 3). If microscopic examination or dipstick analysis detects no bacteria or leukocytes, UTI is rarely present. When bacteria and/or leukocytes are detected by any of the previous procedures, the possibilities of UTI are high. If this is the case, a urine sample is sent to the lab for a urine culture analysis to identify the bacteria type and study its sensitivity to antibiotics. This will confirm the diagnosis of UTI.



Figure 2. Dipsticks

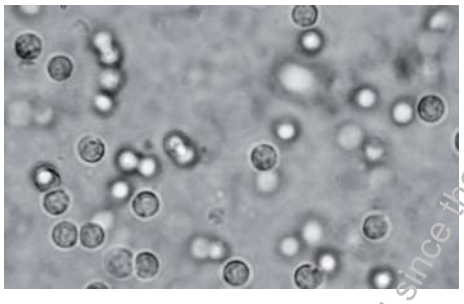


Figure 3. Leukocytes viewed under a microscope in a sample of urine with UTI

Proper urine collection is important, without the sample being contaminated by commonly occurring bacteria in the skin or faeces. It is therefore essential to follow the instructions for collecting urine to avoid contaminating the sample.

When the child is older and capable of controlling urination, the sample is collected directly from the urine stream after a little has been released; this is the mid-stream clean catch method of collection.

For children who cannot control urination, a sterile bag is stuck to the skin around the labia or penis, depending on whether it is a girl or boy. This method may lead to contamination of the urine by the bacteria present in the skin, so the result is trustworthy only if the result is normal or the culture is negative. Sometimes the doctor will require a urine sample collected at home, in which case families or carers should request all information necessary for the adequate collection and proper preservation of the urine until delivery to the doctor.

Sometimes, more invasive urine collection techniques must be used to prevent diagnostic errors arising from contamination of the urine collection bag. This involves the use or the introduction of a small sterile catheter through the urethra, which is a very simple procedure in girls, or suprapubic aspiration. The latter technique involves puncturing the bladder above the pubis,

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like an intramuscular injection, and aspirating a small amount of urine into a sterile syringe. This technique is usually done with ultrasound guidance to see the bladder, and usually more in boys to avoid having to catheterise.

As an aid to diagnosis of UTI, the health professional will probably ask for the following information to compile a medical history:

- √ History of renal disease in close family members.
- √ History of relatives who have had abnormalities or malformations of the urinary tract.
- √ Report on the results of the scans made at the time of pregnancy.
- √ Other early episodes of fever without a cause which the child had, and any diagnosis of them.

In addition, the doctor may ask about certain urination habits, for example, if the patient now has urine leakage when before they did not; if the patient cannot wait to go to the bathroom; or if instead urination occurs only a few times a day; or if the child adopts strange postures before going to the bathroom: e.g., sitting on his heels, crossing his legs, dancing or squatting.

Bowel habits may also be asked about, e.g., if the child is constipated or there is a leakage of faeces or underwear is stained.

REMEMBER

- √ **Diagnosis of UTI** is confirmed by a positive urine culture, which detects the bacteria causing the problem and leads to the choice of the most effective antibiotic.
- √ **Proper collection of urine is essential** for diagnosis. Instructions for sterile (without contamination) sample collection must be followed to preserve it until it reaches the laboratory.
- √ Remember or observe the **child's voiding habits** and communicate them to the doctor.

How is UTI treated?



UTI is generally treated with antibiotics, although urinary antiseptics may be used for cystitis or afebrile UTI. Sometimes treatment will begin before the culture analysis result is known, by considering the most effective antibiotics in the patient's environment. Depending on the results of the urine culture, this treatment may be modified, when the most effective antibiotic against the bacteria is known.

Treatment may be in hospital, on an outpatient basis at home, depending on several factors:

- √ Age: Children with febrile UTI under three months old are generally hospitalised, as they may have or develop more serious complications
- √ Severity of the illness, based on appearance and the opinion of the attending physician.
- √ Inability of the patient to drink fluids or medication, or constant vomiting.
- √ Inability to control the process.

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Medication can be administered intravenously, according to general status or oral tolerance. Once the patient's situation has improved, treatment can be completed orally.

In most cases, fever and symptoms disappear within 48-72 hours of starting the treatment. If the symptoms and fever within that period persist, the health professional will review the situation and will likely decide on further urine analysis and other tests to rule out urinary tract malformations or kidney damage. The duration of antibiotic therapy in febrile UTI is usually 10 days. If there are major malformations of the urinary tract or renal abscesses, this period may be extended up to 2-3 weeks, although this is very rare.

If the UTI is afebrile, the treatment period is usually 3-5 days. As mentioned above, a urinary antiseptic can be used; this is excreted in the urine and kills the bacteria.

As a general rule, it is very important to complete the recommended treatment.

In addition to treatment, any poor urinary or bowel habits the children have must be corrected, i.e., urination should be performed with a given frequency, it should be performed calmly by taking time to try and evacuate all the urine in the bladder; and constipation must be resolved.

There is no objection to administering medication to relieve pain or fever, such as paracetamol.

REMEMBER

- √ **UTI is treated with antibiotics** that are effective in the environment where the patient lives against the common micro-organisms found in the urine cultures.
- √ **Oral treatment** is as effective as intravenous treatment, but sometimes treatment is started this way because of difficulties in oral intake.
- √ In general, it is **not necessary to go into hospital**, unless the patient is younger than 3 months, is in a poor state or cannot tolerate oral medication and intravenous medication must be administered.
- √ **48-72 hours** after initiation of treatment, clinical symptoms and fever may return to normal, and no bacteria will be detected in the urine.
- √ **Bladder and bowel habits must be corrected or educated** upon as part of the treatment and to prevent recurrent UTI.
- √ It is important to **complete the antibiotic treatment** according to the medical prescription.

What is UTI recurrence?

Children who have suffered UTI may suffer it again. This is called a "relapse" or "recurrence" of UTI.

Children who have had a first UTI may experience a recurrence, especially within 3-6 months after the first episode. It is estimated that approximately 18% of boys and 26% of girls may suffer a recurrence within the first 12 months.

After the first year of life, recurrent UTI in boys is rare, while in girls it can reach 40-50%.

Possible causes of recurrence, such as the following, must be investigated:

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- √ Urinary tract abnormalities (e.g., birth defects, vesicoureteral reflux, kidney stones).
- √ Abnormalities in bladder and/or urethra functioning that hinder their coordination (lower urinary tract dysfunction). It is sometimes accompanied by problems in the complete elimination of faeces.
- √ Hygiene-related conditions in young children, or phimosis in boys.
- √ There are times when no reason to explain the recurrence of UTI can be found. This may be due to personal predisposing factors which may be related to genetic factors.

How can we prevent UTI recurrence?

Prevention of UTI recurrence is based on the following factors:

- √ Correction of structural and functional urinary tract abnormalities, assessed by urologists.
- √ Correction and education of bladder and bowel habits: urinating frequently, proper posture during urination and relaxation. Also adequate fluid intake; combating constipation via a proper diet; use of laxatives or cleansing enemas, as prescribed.
- √ Encouraging breastfeeding in the first months of life.
- √ Evaluating correction of phimosis by a healthcare professional.
- √ Teaching girls to wipe from front to back after using the bathroom, so that bacteria from the rectum does not reach the vagina.
- √ Frequent change of nappies.
- √ Wearing cotton underwear instead of synthetic fibre underwear.

REMEMBER

- √ **Preventing further recurrences of UTI** depends on correcting predisposing factors detected in the patient.
- √ Sometimes a **urologist must be consulted** to resolve structural or functional problems.

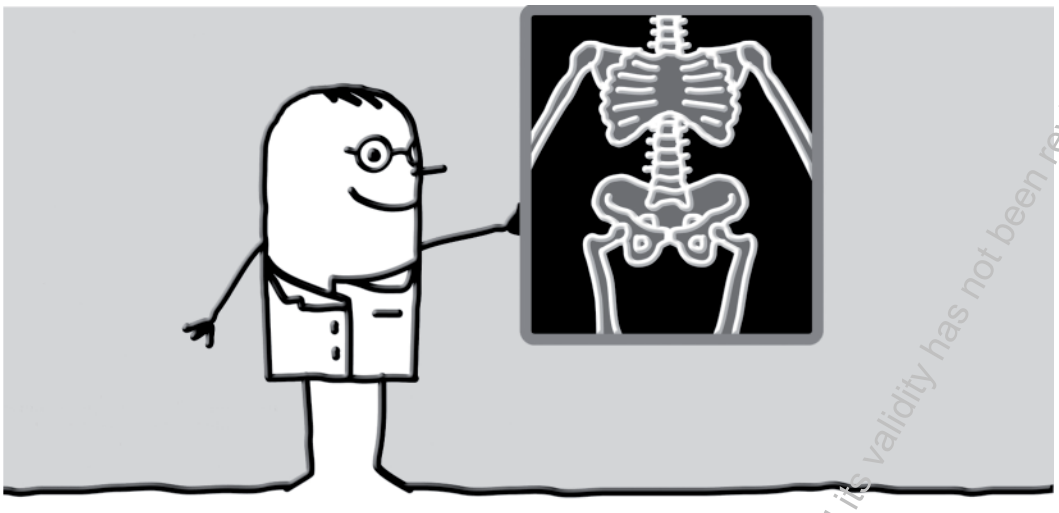
What kinds of tests are performed for UTI?

There is a relationship between UTI and anomalies or malformations of the urinary tract. Therefore, some further tests may be needed after the diagnosis of a UTI.

Firstly, it is important to know the results from ultrasound scans performed during pregnancy, to see the development of the urinary tract during pregnancy.

The type of scans to be performed may vary from one health facility to another, as the protocols for each centre are different. The tests required will depend on the family history of urinary tract disorders, the patient's age when diagnosed, the severity of the UTI, if there have been recurrences or not, if there are other malformations in other areas and according to the patient's response to treatment.

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However, the tests more frequently performed are as follows:

√ **Ultrasound of kidney and urinary tract, including the bladder.** This is a safe, non-invasive exploration, requiring no injection of any contrast and no side effects. It is useful for detecting malformations or kidney or urinary tract defects.

√ **Renal scintigraphy.** This test involves administering a radioactive contrast intravenously. It shows any acute (temporary) or chronic (permanent) kidney damage. It can be done in the acute phase, i.e., a few days after the UTI is diagnosed or 6-12 months later. The substance administrated does not cause any allergic type reaction, and in a child of about 5 years of age it produces radiation similar to that of 16 chest radiographs (Annex 1, Table 15).

√ **Cystographic studies** are used to look for vesicoureteral reflux or abnormalities of the bladder or urethra. The technique involves inserting a catheter into the bladder and injecting a substance that acts as a contrast. The risks of the test are associated with the catheter, its inconvenience and the radiation involved if done by radiology or isotope. This test may be indicated in the acute phase (a few days after the UTI) or 1-2 months after treatment for the UTI. This test produces radiation equivalent to 20-32 chest radiographs in a child of 5 years old, depending on the type of test (Annex 1, Table 15).

√ In very specific cases, another type of examination, such as **intravenous urography**, may be necessary. This test involves injecting a contrast containing iodine through a vein to obtain a photographic image and anatomical details of the kidney and urinary tract. There are radiation hazards and the possibility of an allergic reaction to the injected contrast dye. This test produces radiation equivalent to about 44 chest radiographs in a 5-year old child (Annex 1, Table 15).

√ Some cases may also need **blood and urine tests** to study the function of the kidney.

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REMEMBER

- √ Given the importance of **birth defects or other structural and functional alterations of the urinary tract** as a factor favouring UTI, other tests may need to be done to find the cause.
- √ These tests may include **blood and urine tests** to assess kidney function.
- √ As a general rule, **hospitalisation is not needed** to conduct these tests.

What is the prognosis after UTI?

Most cases of UTI are cured with antibiotic treatment without any complications, even if there is recurring infection.

A small number of patients will develop permanent kidney damage, and this occurs in approximately 5-15% of cases of febrile UTI. If the kidney damage affects only one kidney and is of little extension, there are usually no complications. However, the patient must attend the follow-up visits and controls established by the physician.

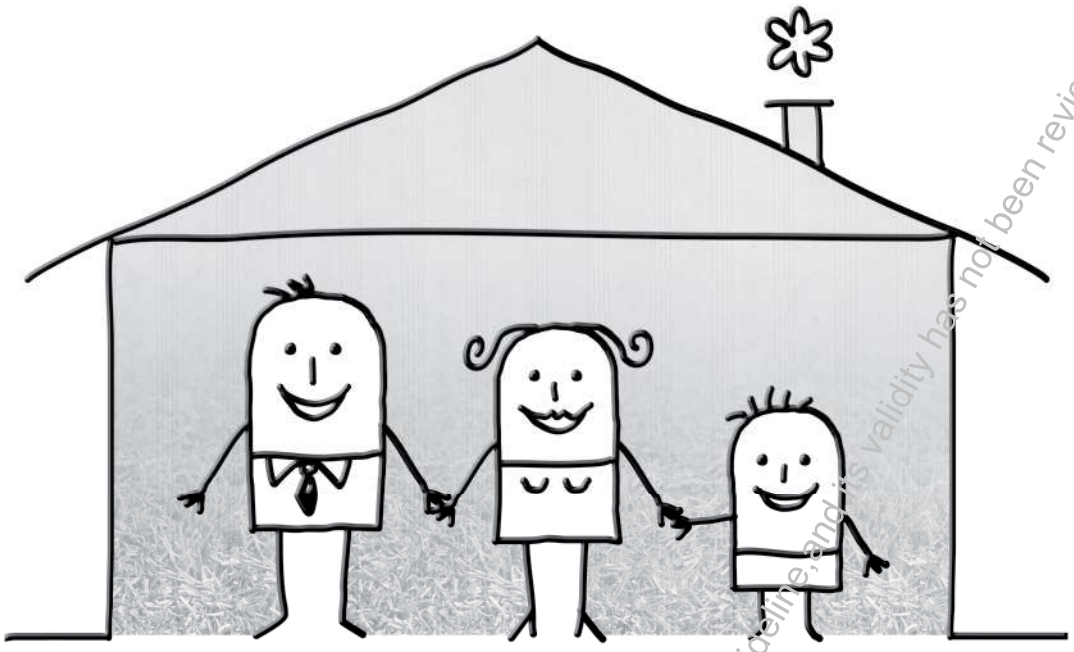
A poor prognosis or evolution will depend on any urinary tract malformations or severe vesicoureteral reflux affecting both ureters or those which are very dilated. In these cases, kidney damage may have been caused by a developmental abnormality in the kidneys of the foetus while growing in the womb, so-called "renal dysplasia". The association of renal dysplasia with UTI, especially if not treated properly, may result in a greater progression of kidney damage.

The consequences therefore result from impaired kidney function and may lead to serious complications such as hypertension, loss of protein in the urine and chronic kidney damage. In these cases, the patient should be monitored in a paediatric nephrology unit.

REMEMBER

- √ The **antibiotic treatment prescribed** resolves the urinary tract infection in the vast majority of cases**.**
- √ The long-term prognosis depends not so much on the UTI itself, but those **factors which contributed to its occurrence**, such as malformations, vesicoureteral reflux and severe lower urinary tract dysfunction, especially with coexisting renal dysplasia.

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Annex 4. Abbreviations

ABPM	Ambulatory blood pressure monitoring
ABU	Asymptomatic bacteriuria
AFBN	Acute focal bacterial nephritis
AGREE	Appraisal of Guidelines for Research & Evaluation
ALN	Acute lobar nephronia
Amoxicillin-clavulanate	Amoxicillin and clavulanic acid
APN	Acute pyelonephritis
ARI	Absolute risk increase
ARR	Absolute risk reduction
BD	Bladder or urinary dysfunction
BP	Blood pressure
CAT	Computed tomography
CAUTI	Catheter-Associated Urinary Tract Infection
CEUS	Echocystography with contrast
CI	Confidence interval
CKD	Chronic kidney disease
CPG	Clinical Practice Guidelines
Cr	Creatinine
CrCl	Creatinine clearance
CRP	C-reactive protein
DES	Dysfunctional Elimination Syndrome
DIC	Direct isotopic cystography
DMSA	Renal scintigraphy with technetium-labelled dimercaptosuccinic acid (99mTc-m)
EPINE	Prevalence study of nosocomial infections in Spain
ESR	Erythrocyte sedimentation rate
ESRD	End-stage renal disease
Fr	French catheter scale
GDG	Guideline developmentgroup
GF	Glomerular filtration rate
HR	Hazard ratio
HT	Hypertension
IC	Intermittent catheterisation
IL	Interleukin
IM	Intramuscular
IQR	Interquartile range
IVU	Intravenous urography
LE	Leucocyte esterase
LR-	Negative likelihood ratio

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LR+	Positive likelihood ratio
MAG3	Mercaptoacetyltriglycine
MAP	Mean arterial pressure
MA_u	Microalbumin in urine
MIF	Macrophage migration inhibitory factor
NAG_u	N-acetylglucosaminidase in urine
NICE	National Institute for Health and Clinical Excellence
NMR	Nuclear magnetic resonance
NNH	Number needed to harm
NNT	Number needed to treat
NPV	Negative predictive value
OR	Odds ratio
Osm_u	Urine osmolality
PC	Primary care
PCr	Plasma creatinine
PCT	Procalcitonin
PMN	Polymorphonuclear
PPV	Positive predictive value
RA	Renal abscess
RCT	Randomised clinical trial
RN	Reflux nephropathy
RR	Relative risk
RRF	Relative renal function
RS	Renal scarring
SIGN	Scottish Intercollegiate Guidelines Network
SMX	Sulfamethoxazole
sns	Sensitivity
SNS	Spanish National Health System
SPA	Suprapubic aspiration
spc	Specificity
SR	Systematic review
TLR	Toll-like receptor
TMP	Trimethoprim
TMP-SMX	Trimethoprim and sulfamethoxazole
UTI	Urinary Tract Infection
VCUG	Voiding cystourethrogram
VUR	Vesicoureteral reflux

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Annex 5. Glossary

Acquired renal scarring: Non-dysplastic segmental renal injury, characterised by interstitial fibrosis and tubular atrophy, which is secondary to UTI. Although VUR may accompany this type of injury, it does not cause it. The term chronic pyelonephritis is sometimes used.

Acquired vesicoureteral reflux: A not very well-defined process that includes any reflux appearing after birth which is closely related to UTI and a malfunctioning bladder (bladder or sphincter dysfunction).

Acute focal bacterial nephritis: See "acute lobar nephronia".

Acute lobar nephronia: Nephritis confined to a kidney lobule, which may progress to a renal abscess. Also called "acute focal bacterial nephritis".

Acute pyelonephritis: Bacterial infection of the upper urinary tract, usually with fever, which causes kidney damage; the term upper UTI is sometimes used. The kidney damage has to be checked with an imaging study such as renal scintigraphy. See "febrile urinary tract infection".

Afebrile urinary tract infection: UTI with temperature below 38.5°C. See "cystitis".

Asymptomatic bacteriuria: Presence of bacteria in the urine without specific symptoms associated.

Bacteriuria: Presence of bacteria in the urine with or without associated symptoms.

Catheter-associated urinary tract infection: Presence of symptoms or signs of urinary tract infection in patients who are catheterised or who recently underwent catheterisation.

Charriere: Measure used to express the different diameters of medical devices including catheters and catheter tubes. Each Charriere unit is equivalent to 0.33 mm.

Chronic Kidney Disease: Progressive loss of renal function determined by glomerular filtration, classified into the following stages:

Stage I: Kidney damage with a GFR >90 ml/min/1.73m^2.

Stage II: Decrease in GFR: 60-89 ml/min/1.73m^2.

Stage III: Decrease in GFR: 30-59 ml/min/1.73m^2.

Stage IV: Decrease in GFR: 15-29 ml/min/1.73m^2.

Stage V: Decrease in GFR: <15 ml/min/1.73m^2

Chronic pyelonephritis: See "renal scarring".

Clean catheterisation: The use of clean gloves (or without gloves if performed by the patient), a cleaning but non-sterile solution and a clean receptacle for the urine. It can be performed using a sterile or a clean (multi-use) catheter tube.

Coated catheter: One with a hydrophilic or other lubricant as coating. Coated catheters are not intended to be re-used, and so are considered sterile catheters.[361]

Congenital renal scarring: Malformation with dysplastic features accompanying congenital primary VUR, which reflects abnormal metanephric development in utero.

Constipation: Delay or difficulty in defecation lasting for 2 or more weeks and sufficient to cause discomfort in the patient.[372]

Continuous antibiotic prophylaxis: Long-term treatment with low doses of urinary antibiotics or antiseptics, taken once at night only, to prevent recurrent episodes of UTI and renal damage.

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Cystitis: Inflammation of the bladder that produces clinical signs in the lower tract; generally associated with afebrile UTI or lower urinary tract UTI. See "Afebrile urinary tract infection".

Daytime wetting or dysfunctional voiding: Abnormal pattern of bladder emptying of unknown etiology characterised by both urinary and faecal leakage and retention.

Dimercaptosuccinic acid renal scintigraphy with Tc99m: This is the "gold standard" for identifying acute or chronic renal parenchymal defects (renal scarring). The DMSA uptake in each kidney can be compared, giving an estimate of the relative function of each.

Direct isotope cystography: Cystographic study with a small dose of a radioactive isotope (Tc-99m-pertechnetate) diluted in water. This test is very sensitive to the lower degrees of reflux. It is insufficient to assess anatomical detail and degree of VUR.

Dysuria: Difficulty with or without pain in starting urination.

Echocystography: (Cystosonography or cystouretrosonography) Ultrasound method of diagnosing VUR with a liquid contrast (microparticles in suspension) introduced by catheter into the bladder. VUR is identified by the appearance of echoes of these particles in the ureter and collecting system. It has the advantage of not using ionising radiation and can explore the anatomy of the urinary tract at the same time.

Encopresis: Voluntary or involuntary passage of stools in a child of 4 years or more (or mental age equivalent) after excluding organic causes. It must occur at least once a month for 6 months.[372]

Enuresis: Intermittent urinary incontinence during sleep, also called bedwetting. The term is used regardless of whether or not incontinence occurs during the day or night or there are other lower urinary tract symptoms. The qualifier 'nocturnal' can be added for clarity.[372]

Febrile urinary tract infection: UTI with temperature above 38.5°C. See "acute pyelonephritis".

Goldraich classification of renal scarring by DMSA[30]

- Type 1: No more than 2 areas of scarring.
- Type 2: More than 2 scarring areas with areas of normal parenchyma between them.
- Type 3: Widespread damage throughout the entire kidney, similar to obstructive nephropathy. For example, global contraction of the kidney with or without scars on the outline.
- Type 4: Final stage, kidneys very small, with little or no uptake of the radiopharmaceutical.

Haematuria: Blood in the urine.

Hydronephrosis: Dilatation of the renal pelvis or calyces.

Indwelling catheterisation: Urinary catheter inserted under sterile conditions and maintained for an indefinite period of time (usually 6-10 days in children).

Intermittent catheterisation: Urinary catheter inserted in non-sterile (clean) conditions at fixed intervals to empty the bladder.

Intravenous urography: Intravenous injection of iodinated contrast medium which is eliminated by the kidney. It provides details of the urinary tract anatomy.

Kappa coefficient: An index that determines the degree of agreement, above that expected by chance, of several methods or evaluators classifying the patient into mutually exclusive categories.

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Kidney damage: See "Renal scarring".

Phimosis: Condition in which the foreskin cannot be fully retracted over the glans penis.

Power Doppler ultrasound: Ultrasound technique based on the changes in amplitude of the Doppler signal, capable of displaying low speed flows such as renal perfusion.

Primary vesicoureteral reflux: A heterogeneous process defined as the retrograde non-physiological passage of urine from the bladder to the ureter with no anatomical or neurological reason to explain it.

Probiotic dietary supplements: Contain live microorganisms that stay alive in the gut after ingestion and contribute to the balance of bacterial flora.

Pyonephrosis: Distention of the kidney with pus and suppurative renal parenchymal destruction. It is often associated with renal obstruction and can lead to complete, or almost complete, loss of kidney function.

Pyuria: Discovery of more than 5 leukocytes per field in a centrifuged urine specimen viewed under a microscope with 400X power.

Pyuria: Presence of pus in the urine.

Recurrent urinary tract infection: 2 or more episodes of febrile UTI or APN; 1 episode of APN or febrile UTI with 1 of afebrile UTI; or more than 3 episodes of afebrile UTI.

Reflux nephropathy: See "renal scarring".

Renal dysplasia: Abnormal metanephric development in utero.

Renal scarring: A broader term and more modern term than the so-called "reflux nephropathy", referring to kidney damage, which may be focused or diffuse, with irreversible renal parenchyma. Its etiology is multifactorial. In some cases it is present at birth, thus suggesting a congenital origin. This term applies to both acquired (or post-natal) abnormalities and pre-natal anomalies, also called primary or congenital; both types may or may not be associated with VUR. The reference imaging technique is dimercaptosuccinic acid renal scintigraphy with Tc99m.

Renal ultrasound: Use of high frequency sound waves reflecting from internal structures which are reconstructed into images, giving excellent anatomical information without irradiating the patient. This technique cannot determine kidney function and is insensitive to assessing renal scarring. There are no known risks with this technique.

Single sampling catheterisation: Urinary catheter inserted under sterile conditions at a given time for a single purpose, most often for diagnostic procedures (sampling for urine culture, cystography, urodynamics, urinary retention and interventions that require control of urine or urination).

Sterile catheterisation: The implementation of this technique involves the use of sterile gloves, sterile single-use catheter, sterile drain pan and an aseptic technique to insert the catheter.

Uncoated catheter: Catheter which requires a lubricant to be applied before insertion. When used once, it is considered as sterile; if reused, it is considered as clean and for multiple use.[361]

Urinary or bladder dysfunction: Any abnormality in the activity of the detrusor or sphincters, either alone or in combination, in the absence of underlying neurological damage. As a result, it can lead to increased intravesical pressure or post-voiding residue that may induce deterioration in the upper urinary tract.

Urinary tract infection: Presence of bacteria in the urine combined with clinical symptoms (fever, urinary symptoms, general symptoms).

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Urine dipstick: Semi-quantitative diagnostic test consisting of a strip impregnated with chemical reagents to detect leukocytes, glucose, protein, blood, nitrites and other compounds in a urine sample.

Vesicoureteral reflux: A heterogeneous process defined as the retrograde non-physiological passage of urine from the bladder into the upper urinary tract.

Voiding cystourethrography (VCUG): The "gold standard" for demonstrating VUR. The study is performed with a contrast media inserted into the bladder via a catheter and shows fluoroscopic images of the urinary tract. It offers good anatomical detail of the bladder and urethra and allows the degree of VUR to be established by the International Reflux Grading System.

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Annex 6. Conflicts of interest

The following members of the development group declare absence of interests: Ramón Carlos Areses Trapote, José Antonio Castillo Laita, Gloria María Fraga Rodríguez, Susana García Rodríguez, César Joaquín García Vera, Andrés Gómez Fraile, Jesús Gracia Romero, César Loris Pablo, Juan Ignacio Martín Sánchez, Carlos Ochoa Sangrador, Lidia Rocha Gancedo, Teresa Serrano Frago and Blanca Valenciano Fuente.

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The following expert collaborators declare they have absence of interests: Antonia Andréu Domingo, M.ª del Mar Bruna Martín, Luisa Ceres Ruiz, Laura Espinosa Román and Víctor Manuel García Nieto.

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The following external reviewers declare they have absence of interests: Mar Espino Hernández, Elena García Martínez, Serafín Málaga Guerrero and Ángel Villanueva Mateo.

Javier González De Dios has received fees from Mead Johnson for presenting papers.

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