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GUIDELINES

Evidence-based clinical practice guideline for management of urinary tract infection and primary vesicoureteric reflux

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Abstract

We present updated, evidence-based clinical practice guidelines from the Indian Society of Pediatric Nephrology (ISPN) for the management of urinary tract infection (UTI) and primary vesicoureteric reflux (VUR) in children. These guidelines conform to international standards; Institute of Medicine and AGREE checklists were used to ensure transparency, rigor, and thoroughness in the guideline development. In view of the robust methodology, these guidelines are applicable globally for the management of UTI and VUR. Seventeen recommendations and 18 clinical practice points have been formulated. Some of the key recommendations and practice points are as follows. Urine culture with $> 10^4$ colony forming units/mL is considered significant for the diagnosis of UTI in an infant if the clinical suspicion is strong. Urine leukocyte esterase and nitrite can be used as an alternative screening test to urine microscopy in a child with suspected UTI. Acute pyelonephritis can be treated with oral antibiotics in a non-toxic infant for 7–10 days. An acute-phase DMSA scan is not recommended in the evaluation of UTI. Micturating cystourethrography (MCU) is indicated in children with recurrent UTI, abnormal kidney ultrasound, and in patients below 2 years of age with non-*E. coli* UTI. Dimercaptosuccinic acid scan (DMSA scan) is indicated only in children with recurrent UTI and high-grade (3–5) VUR. Antibiotic prophylaxis is not indicated in children with a normal urinary tract after UTI. Prophylaxis is recommended to prevent UTI in children with bladder bowel dysfunction (BBD) and those with high-grade VUR. In children with VUR, prophylaxis should be stopped if the child is toilet trained, free of BBD, and has not had a UTI in the last 1 year. Surgical intervention in high-grade VUR can be considered for parental preference over antibiotic prophylaxis or in children developing recurrent breakthrough febrile UTIs on antibiotic prophylaxis.

Keywords Children · Pediatrics · Recommendation · Urinary tract infection · Vesicoureteral reflux

Introduction

We present the revised Indian Society of Pediatric Nephrology (ISPN) guidelines for the management of urinary tract infection (UTI) and primary vesicoureteric reflux (VUR) in children aged less than 18 years (for health care providers of patients with UTI and VUR). The first guideline on the management of UTI in children was formulated by the ISPN in 2001, which was revised in 2011 [1]. The first guideline was chiefly a consensus statement while the revised guideline was quasi-evidence-based. Since the publication of the last guideline, several studies with robust methodology have been published. The guideline is aimed at providing updated, evidence-based, clinical practice recommendations for the management of UTI and VUR in children and can be used internationally. However, this guideline does not address

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fungal UTI and UTI in complex congenital anomalies such as posterior urethral valve and neurogenic bladder.

Methods

These guidelines adhere to international standards; Institute of Medicine and AGREE checklists were used to ensure transparency, rigor, and thoroughness in the guideline development [2, 3]. The process for guideline development began in October 2020 with formation of six core work groups and an evidence review group (ERG) with expertise in systematic literature search and evidence synthesis. A series of recommendations and clinical practice points were drafted. The guideline has recommendations that are evidence-based and actionable. The evidence for recommendation is chiefly supported by good quality systematic reviews and meta-analyses. In instances where systematic review was not feasible due to dearth of data, clinical practice points were drafted based on limited evidence or expert opinion (Supplementary material Appendix F). The final recommendations were voted to obtain > 80% consensus of the entire guideline development group. The guidelines were also sent to parents of patients with primary VUR for input. Subsequently, the guidelines were externally reviewed by eight national and international experts who were not involved in guideline development. The external review panel consisted of pediatricians, pediatric nephrologists, and urologists from within and outside the country.

Detailed methodology (Supplementary Table S1 to S8) and the evidence used to draft the guideline (Summary of Finding Tables S9 to S30) are available in the supplementary material. Briefly, individual work groups prepared an initial draft of relevant questions that were refined by the guideline panel. The selected questions included population, intervention, comparator, outcome and methods (PICOM format) relevant to the guideline. Systematic reviews when available were updated; if none was available, a systematic review was conducted. We performed nine new and used seven existing systematic reviews for these guidelines. Cochrane group methodology was followed during conduct of all systematic reviews for intervention and diagnostic test accuracy studies [4]. The ERG provided methodological inputs for performing literature search, selection of relevant studies, data extraction, and critical appraisal of included studies and subsequent meta-analyses. The work groups and ERG quantitatively synthesized the evidence wherever feasible, assessed quality of evidence, and drafted final recommendations. Evidence to recommendation framework of GRADE approach was used to develop recommendations [5]. A Summary of Finding Table, which included study population, intervention, comparator, relative and absolute effect estimates, and grading of quality of the evidence, was generated using the *GRADEPro* guideline development tool [6].

Formulation of final recommendation

Final recommendations were drafted based on the balance of desired and undesired consequences, certainty of evidence, value and preferences, cost and resource use, and consideration for implementation. The formulation of recommendation from evidence was done using *GRADEPro* software. The strength of recommendation is reported as described in Table 1. Each recommendation is followed by paragraphs on balance of benefits and harm, certainty of evidence, values and preferences, resource use and cost, and considerations for implementation. Seventeen recommendations (14 for UTI and 3 for primary VUR) have been formulated, and all

Table 1 Grading the quality of evidence and assigning strength of recommendations

	Description
Quality of evidence (depiction)	
High (⨁⨁⨁⨁)	We are confident that the true effect lies close to the final pooled effect estimate and it is unlikely to be change with new trials
Moderate (⨁⨁⨁◯)	True effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different, and it may change with further studies
Low (⨁⨁◯◯)	True effect may be substantially different from final pooled effect estimates, and it is likely to be change with new studies
Very low (⨁◯◯◯)	We are very uncertain about the final pooled effect estimate and very likely it was far from truth
Strength of recommendation (depiction)	
Strong recommendation (1)	Guideline panel was confident that desirable effects of intervention outweigh its undesirable effects or vice-versa
Weak (conditional) recommendation (2)	Guideline panel judged that the desirable effects probably outweigh undesirable effect or vice-versa but with some uncertainty

are reported with the strength of recommendation (strong and weak) and certainty of evidence (high, moderate, low, and very low). Eighteen practice points (12 for UTI and 6 for primary VUR) have been formulated and are mentioned as statements, algorithms, and tables with the rationale described in text.

Clinical features

UTI is a common infection in childhood, with 2% of boys and 7% of girls experiencing at least one episode of UTI before 6 years of age [7, 8]. Infection of the urinary tract is diagnosed based on the growth of a single uropathogen with a significant colony count in the presence of symptoms. The symptoms of UTI can be non-specific and vary with age, making the diagnosis difficult in infants (Table 2). Constipation, neurogenic bladder, labial adhesions in girls, and obstruction of the urinary tract are important risk factors. Evaluation of a child should include physical examination to identify predisposing disorders. The bladder may be palpable in children with underlying obstructive uropathy, a palpable kidney suggests hydronephrosis, and palpable fecoliths indicate constipation. The lower back is examined for signs of occult meningomyelocele. A neurological examination of lower limbs and perineal sensations is performed to identify neurologic deficits that might indicate the presence of a neurogenic bladder [9]. External genitalia are examined for anatomic abnormalities including phimosis, hypospadias, labial adhesions, and cloacal malformations (Table 2) [9–11].

Diagnosis

Clinical practice point

We suggest using the clean-catch method for urine collection in toilet-trained children.

For non-toiled trained stable children, clean-catch should be attempted initially; if unsuccessful, the urine sample may be collected by catheterization or suprapubic aspiration.

For sick infants, catheterization and suprapubic aspiration are the preferred methods for urine collection.

Rationale

Choice of urine collection method is chiefly determined by contamination rate, feasibility, and sickness level in children with suspected UTI. While non-invasive methods (clean-catch, adhesive bags, and nappy pads) are easy to use, the urine collection time is longer than invasive methods (suprapubic aspiration and catheterization). Collection time in clean catch can be shortened by using strategies for voiding stimulation such as *Quick-Wee* among others in infants [12, 13]. While suprapubic aspiration is a painful procedure, when performed under ultrasound guidance the success rate of obtaining a urine specimen is high (~90%), and complications are rare [14, 15]. Catheterization has the highest success rate in obtaining urine samples, but complications such as microscopic hematuria are slightly higher than suprapubic aspiration [16].

Adhesive bags and nappy pads are associated with 30–80% and 64% contamination rates, respectively, and cannot be used for sample collection for urine culture [17,

Table 2 Clinical symptoms and signs in a child with UTI

History	
Age group	*Symptoms*
< 2 months	Fever, vomiting, irritability, lethargy, poor feeding, failure to thrive, jaundice, hypothermia, hematuria
2–24 months	Fever, vomiting, lethargy, abdominal pain, frequency, hematuria, malodorous urine, cloudy urine
> 2 years	Fever, frequency, vomiting, lethargy, abdominal pain, dysuria, incontinence, hematuria, suprapubic pain, loin pain and tenderness, cloudy urine
Physical examination	
Clinical finding	*Likely diagnosis*
Palpable kidney Poor urinary stream	Obstructive uropathy, neurogenic bladder
Costovertebral angle tenderness	Pyelonephritis
Palpable bladder/suprapubic tenderness	Obstructive uropathy/neurogenic bladder
Palpable fecolith	Constipation
Sacral dimple/tuft of hair/lipoma, abnormal neurological evaluation of the lower limbs and/or abnormal perineal sensations	Occult meningomyelocele

18]. Contamination rate of clean-catch (5%) is acceptable when directly compared with specimens obtained from catheterization (8%) in young infants aged < 3 months [19]. Contamination rates in clean-catch vary based on gender and age group [19, 20]; perineal cleaning by soap has been shown to reduce contamination rates in a clinical trial [21]. Since contamination rate is higher in first-stream urine (5–7%) as compared to late-stream (0–2%), it is better to collect urine late-stream during catheterization. Considering acceptable contamination rate compared to other non-invasive methods and ease of use, clean-catch is the most preferred method for toilet-trained children. While it is challenging to secure urine specimens by clean-catch in non-toilet trained children, it should be attempted wherever feasible. Clean-catch was also found to be the most cost-effective, non-invasive method [22]. Suprapubic aspiration and catheterization are reserved for sick infants and in patients where clean-catch has failed to obtain urine for culture.

Recommendation

We suggest using a urine dipstick (leukocyte esterase and nitrite combination) as a first-line screening test for UTI (2⊕⊕◯◯).

When feasible, urine microscopy (for bacteriuria and leukocyturia) in a freshly voided sample can be used as an alternative to the dipstick for screening of UTI (2⊕⊕◯◯).

The guideline panel places a relatively moderate value on this recommendation, based on low to very-low quality evidence suggesting that urine dipstick (leukocyte esterase or nitrite) has good sensitivity and specificity compared to urine culture for diagnosis of UTI. Urine microscopy for bacteriuria has good sensitivity and excellent specificity for diagnosing UTI. However, clinicians may find it difficult to perform microscopy for bacteriuria on the freshly voided urine sample.

Balance of benefits and harms

Non-specificity of signs and symptoms of UTI in infants and young children and delay in availability of urine culture report makes it essential to have a good screening test to enable the presumptive diagnosis of UTI. This would help in timely initiation of antimicrobial therapy. Urinalysis should be performed in a freshly voided sample (within 1–2 h at room temperature or 4 h with refrigeration) to ensure good diagnostic accuracy [23, 24]. A urine dipstick is an easy-to-perform bedside test for screening of UTI. The leukocyte esterase alone has good specificity (90%), but only moderate sensitivity (79%) (Table S9), and nitrite has excellent specificity (99%) but poor sensitivity (47%) (Table S10). Analysis of pooled data from 32 studies (2953 participants) showed that combination, i.e., presence of either a positive leukocyte esterase or nitrite, has good sensitivity (84%) and specificity (88%) (Table S11). The presence of both positive leukocyte esterase and nitrite has excellent specificity (98%) but low sensitivity (64%) for the diagnosis (Table S12).

Urine microscopy for leukocyturia (≥ 10 leukocytes per mm^3 in a fresh uncentrifuged sample or > 5 leukocytes per high power field in a centrifuged sample) [23, 25, 26] showed moderate sensitivity (76%) and good specificity (90%) for screening for UTI (Table S13). Analysis of data from 21 studies (21,545 participants showed that presence of bacteriuria in the freshly voided sample has excellent specificity (94%) and good sensitivity (86%) (Table S14). The addition of leukocyturia to bacteriuria does not improve sensitivity (89%) or specificity (83%) (Table S15). While performing dipstick and microscopy is not associated with any side effects, choosing a screening test with poor sensitivity may result in some children not receiving antibiotic therapy for UTI.

Certainty of evidence

The quality of evidence for the pooled sensitivity and specificity estimates was low for all these tests. Quality of evidence was downgraded for serious methodological limitations in studies, high heterogeneity across studies, and indirectness of outcomes (Table S9 and S10).

Values and preferences

The guideline panel judged that making a presumptive diagnosis of UTI based on urine dipstick or microscopy would be important for parents. However, the availability of microscopic examination of freshly voided urine for rapid diagnosis would remain a concern for clinicians in busy resource-constrained settings. Considering that urine dipstick performs fairly well for presumptive diagnosis of UTI and the ease of performing this test in the outpatient setting, most clinicians and parents would prefer dipstick for screening for UTI.

Resource use and costs

The guideline panel judged that using urine dipstick as an alternate to microscopic urine examination would require less infrastructure and trained personnel and may reduce the overall cost.

Considerations for implementation

The guideline panel felt that there would be no major barriers to implementing this recommendation.

Rationale

Timely initiation of antimicrobial therapy is essential to reduce the risk of kidney scarring [27]; hence, easy to perform bedside screening tools are crucial for making a rapid presumptive diagnosis of UTI. Microscopic examination for bacteriuria, while it shows good sensitivity and excellent specificity for the diagnosis of UTI, needs to be performed in the freshly voided urine sample [23, 24], and requires infrastructure and trained personnel. On the contrary, urine dipstick is easy to perform, readily available, and shows good diagnostic performance for screening of UTI. Considering that the final diagnosis of UTI is based on urine culture, the marginally lower specificity of dipstick is acceptable for presumptive diagnosis. Based on these considerations, the guideline panel suggests using a urine dipstick (combination of leukocyte esterase and nitrite) for presumptive diagnosis of UTI, while awaiting the results of urine culture.

The diagnostic utility of dipstick in infants is limited (Fig. 1) as they tend to void frequently and the incubation period for bacteria in the bladder is short. Other factors which may contribute to lower diagnostic utility of urine dipstick nitrite are lower urine pH (< 6) and insufficient concentration of urinary nitrate [28]. Pooled synthesis of the data on urine dipstick nitrite in children aged less than 2 years showed significantly lower sensitivity compared to older children; however, specificity is similar in both age groups [28]. Based on this data, we suggest that clinicians need to be cautious while interpreting the urine dipstick in young infants. They can consider starting empirical antibiotics in setting of negative urine nitrite test in the presence of risk factors or high suspicion of UTI in infants less than 6 months old (Fig. 1).

Clinical practice point

We suggest that diagnosis of UTI should be confirmed based on significant growth of a single bacterial species on urine culture in the presence of symptoms suggestive of UTI.

The growth of single uropathogenic bacteria $\geq 10^3$, $\geq 10^4$, and $\geq 10^{4-5}$ (CFU/mL) in urine obtained by suprapubic aspiration, catheterization, and clean-catch, respectively, are highly suggestive of UTI.

Rationale

The confirmatory diagnosis of UTI should be based on clinical symptoms and significant growth of single pathogenic bacteria in urine culture. In the absence of significant bacterial growth, leukocyturia alone is insufficient to diagnose UTI since this may be seen with febrile illness, glomerulonephritis, kidney stone, and foreign body in the urinary tract [29]. Similarly, a proportion (10–15%) of children may have UTI in the absence of leukocyturia, especially with uropathogens other than *E. coli* [30, 31].

For urine culture, the sample should be processed as promptly as possible; if not feasible, the urine specimen should be refrigerated at 4 °C to prevent bacterial overgrowth [23, 24]. Urine cultures are reported positive or negative based on the number of colony forming units (CFU) on culture media. The concept of significant bacterial growth is to differentiate true infection from contamination, considering that the periurethral area and distal urethra are colonized by the same organisms which may cause UTI. Hence, in the urine collected by suprapubic aspiration, any bacterial growth (corresponds to 10^3 CFU/mL) is considered as evidence of true infection.

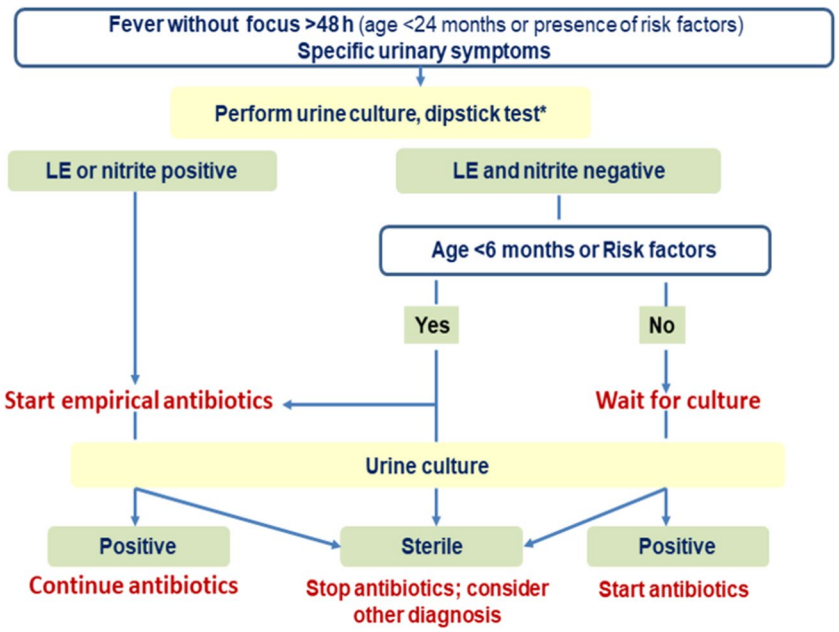

Fig. 1 Approach to diagnosis of urinary tract infection in children. Risk factors: bladder bowel dysfunction, primary vesicoureteric reflux, and previous history of UTI. *Combination of leukocyturia and bacteriuria on microscopy may be used as an alternative to dipstick; leukocyturia alone has moderate sensitivity. Due to the lower diagnostic accuracy of urine dipstick, we suggest initiating antibiotic therapy in patients aged < 24 months in the presence of risk factors or in young infants (age < 6 months)

There is a debate on significant CFU in urine collected by catheterization and clean-catch. The most commonly used cut-off of $\geq 10^5$ CFU/mL was proposed almost six decades ago [32]. The CFU were determined by multiple factors such as incubation time of bacteria in the urinary bladder, transportation of sample, and type of culture media used [33, 34]. This conventional cut-off of $\geq 10^5$ CFU/mL has been challenged by studies in young children aged < 2 years [35–41]. We reviewed studies evaluating young children (< 2 years) with paired urine sampling by suprapubic aspiration and clean-catch [35–41]. These studies showed that a considerable proportion (10–25%) of children with CFU $\geq 10^3$/mL on suprapubic aspiration had CFU $< 10^5$/mL CFU on simultaneous clean-catch specimen. This finding suggests that use of a strict conventional cut-off ($\geq 10^5$ CFU/mL) might miss the diagnosis of UTI in some children. Hence, the guideline panel suggests using a range of bacterial count of 10^{4-5} CFU/mL for urine collected by clean-catch, especially in infants. Since the risk of contamination from periurethral bacteria is lower with the catheterized sample, we suggest using a lower cut-off $\geq 10^4$ CFU/mL for this method. While these cut-offs are the guiding principles, clinicians should always interpret culture reports in the clinical context considering that infants and non-*E. coli* uropathogens may show lower colony counts. Figure 1 depicts the diagnostic algorithm for a child with suspected urinary tract infection.

Asymptomatic bacteriuria

Asymptomatic bacteriuria (ABU) is defined by the presence of positive urine culture ($> 10^{4-5}$ CFU/mL of a single uropathogen in clean-catch urine specimen, $> 10^4$ CFU/mL in catheterized and any growth ($> 10^3$ CFU/mL) in a suprapubic specimen in the absence of symptoms. A recent meta-analysis reported prevalence of ABU 0.37% (95% CI, 0.09–0.82) in boys and 0.47% (95% CI, 0.36–0.59) in girls up to 19 years of age [42]. The prevalence of ABU was higher in boys below 2 years of age compared to older boys, while it was higher in older girls than the younger ones. Almost half of these children had ABU with leukocyturia [42]. While *E. coli* is the commonest organism in ABU, the strains in ABU express fewer virulence factors than the uropathogenic species that cause UTI. Further, the host response in ABU is also altered, indicating some form of commensalism [43].

Treatment

Treatment of UTI is guided by the age at presentation, the severity of the illness, site of infection (pyelonephritis versus cystitis), presence of structural abnormalities in the urinary tract, and local antimicrobial susceptibility pattern. Antibiotics form the cornerstone of treatment apart from general measures such as adequate hydration and antipyretics. Antibiotic therapy aims to eradicate the causative uropathogens and prevent the progression of infection and kidney damage and related complications.

Clinical practice point

We suggest that antibiotic therapy should be initiated as early as possible, preferably within 48–72 h of the onset of fever.

Rationale

Early initiation of antibiotics in children with febrile UTI has been shown to reduce morbidity and kidney damage. Two initial studies evaluating the timing of initiation of antibiotic treatment did not observe a significant difference in kidney scarring [44, 45]. Subsequent studies with a larger sample size showed significantly higher risk of kidney scarring with delay in initiation of antibiotic therapy 48–72 h after the onset of fever [27, 46].

Recommendation

We suggest using 3rd-generation cephalosporins or co-amoxiclav as initial empirical antibiotic therapy in children with suspected febrile UTI (2⊕◯◯◯).

We suggest first-generation cephalosporin (cephalexin, cefadroxil) or co-amoxiclav as initial empirical therapy in adolescents with cystitis (2⊕◯◯◯).

The guideline panel put moderate value on low-certainty evidence showing no difference between persistent bacteriuria and recurrence of UTI after completion of therapy with 3rd-generation cephalosporin and other antibiotics. Evidence does favor treatment with 3rd-generation cephalosporin when compared to cotrimoxazole for persistence of clinical symptoms at the end of therapy.

Balance of benefits and harms

Pooled analysis did not find any significant difference in persistent bacteriuria (3 studies, 439 participants, risk ratio (RR) 2.41; 95% CI 0.98–5.93), persistent fever for > 48 h (RR 5.0; 95% CI 0.27–92.6), and recurrent UTI (RR 1.23; 95% CI 0.32–4.74), after end of therapy between 3rd-generation cephalosporins and co-amoxiclav or cotrimoxazole (Table S16) [47]. A meta-analysis of three studies (471 participants) showed that a significantly greater number of children receiving cotrimoxazole had persistence of clinical symptoms in comparison to those receiving cephalosporins (RR 0.28; 95% CI 0.13–0.62) [48–50]. However, one large study reported a higher incidence of symptomatic recurrent UTI after treatment with ceftibuten than with cotrimoxazole [48]. Adverse effects reported in all studies were mainly gastrointestinal and not significantly different between two antibiotics [47].

Certainty of evidence

The certainty of evidence for all reported outcomes was low as it was downgraded for serious risk of bias and imprecision.

Values and preferences

Resolution of fever and recurrence of UTI following treatment would be important outcomes for parents and clinicians. Considering the overall low certainty evidence of no difference between cephalosporin and other antibiotics for these outcomes, but higher antimicrobial resistance to cotrimoxazole, would result in most parents choosing 3rd-generation cephalosporins as the initial antibiotic for treatment.

Resource use and costs

While cost-effectiveness analysis was not performed, the guideline panel judged that cost of therapy is similar between 3rd-generation cephalosporins and co-amoxiclav.

Considerations for implementation

The guideline panel judged that there would not be any major barriers in implementing this recommendation.

Rationale

The latest Cochrane review found no significant difference in bacteriological and clinical outcomes between children receiving 3rd-generation cephalosporin and other antibiotics [47]. However, considering overall antibiotic sensitivity pattern and rising antibiotic resistance and common bacteria causing UTI in children, the guideline panel recommended using either 3rd-generation cephalosporin or co-amoxiclav as first line initial antibiotic therapy. However, physicians should also consider local antibiotic sensitivity patterns for selecting the appropriate antimicrobial agent.

Recommendation

We suggest preference of oral over intravenous antibiotic therapy for treatment of acute febrile UTI in all children except: (i) infants less than 2 months of age, (ii) severely ill patients, and (iii) patients who are unable to ingest oral antibiotics (2⊕◯◯◯).

When intravenous antibiotic therapy is initiated, it may be switched over to oral therapy after 3–4 days (1⊕⊕◯◯).

The guideline panel placed high value on evidence showing no difference in persistent kidney scarring at 6–12 months (moderate quality) and recurrent UTI (low quality) between oral and intravenous followed by oral administration of antibiotics.

Balance of benefits and harms

No significant difference was observed in time to resolution of fever (2 studies, 808 participants, mean difference 2.05 days; 95% CI 0.84–4.94), persistence of fever at day 3 (RR 0.79; 95% CI 0.30–2.06), recurrence of UTI within 6 months (RR 0.65; 95% CI 0.28–1.51), and kidney damage at 6–12 months (RR 0.82; 95% CI 0.59–1.12) between oral therapy and initial intravenous therapy followed by oral therapy (Table S17). One study showed that kidney scar at 6 months was higher in the oral therapy group compared to intravenous, followed by oral therapy in high-grade VUR (RR; 7.33, 95% CI 1.0–54) [51].

Short duration intravenous therapy reduces the cost of treatment, time of hospital stay, and risk of nosocomial infections. Pooled evidence from studies comparing short duration intravenous therapy (3–4 days) followed by oral therapy with prolonged intravenous therapy (7–14 days) found no significant difference in the risk of persistent bacteriuria after treatment (3 studies, 265 participants, RR 0.78; 95% CI 0.24–2.55), recurrent UTI within 6 months (4 studies, 328 participants, RR 0.97; 95% CI 0.58–1.62), and persistent kidney damage at 3–6 months (4 studies, 726 participants, RR 1.01; 95% CI 0.8–1.29). There was no significant difference in gastrointestinal side effects in patients receiving short and prolonged intravenous therapy (RR 1.29; 95% CI 0.55–3.05) (Table S18, S19).

Certainty of evidence

The quality of evidence for the kidney scarring and recurrent UTI was moderate to low because of serious study limitations and imprecision.

Values and preferences

Recurrence of UTI and kidney damage would be a critical outcome for parents and clinicians. Similarly, the resolution of fever would also be an important outcome. Considering no difference in efficacy between the oral route and short intravenous followed by oral therapy, but more discomfort, cost, and longer hospital stay with the latter regimen, most parents would prefer to use oral antibiotic to treat UTI.

Resource use and costs

A cost-effectiveness analysis showed that the per patient cost of oral antibiotic therapy was one-half compared to intravenous followed by oral treatment [51]. Cost of a short course of intravenous antibiotic therapy followed by oral therapy

was significantly less than a long course of intravenous antibiotic therapy.

Considerations for implementation

The guideline panel judged that there would be no major barriers in implementing this recommendation.

Rationale

Oral antibiotic therapy facilitates outpatient management and causes less family discomfort, reduces the cost of treatment and inconvenience associated with intravenous therapy. No significant difference in clinical, bacteriological, and radiological outcomes was observed between oral antibiotic therapy and initial intravenous therapy followed by oral therapy in a Cochrane review, though data were insufficient to extrapolate findings in neonates [47]. These data support a shorter duration of parenteral therapy for 3–4 days, followed by oral treatment [52]. Similarly, there was no difference between the short duration of intravenous (3–4 days) therapy followed by oral therapy and the long duration of IV therapy (7–14 days) for persistent bacteriuria after treatment, recurrent UTI within 6 months, and persistent kidney damage at 3–6 months [47]. Hence, the guideline panel recommended using oral antibiotics as initial route in all children except in infants less than 2 months, those with inability to ingest oral medication, and those with septicemia (Fig. 2). Even in patients requiring parenteral antibiotics, duration can be shortened to 3–4 days and then switched to the oral route.

Similar data on the successful reduction of intravenous antibiotic therapy duration to 3–4 days has been reported in infants [53–55]. Data on intramuscular (IM) route administration of antibiotic therapy for treatment of UTI is limited. Hence, IM route may only be used if IV route is not feasible.

Clinical practice point

We suggest changing initial antibiotic therapy only in patients with clinical treatment failure regardless of antibiotic sensitivity patterns.

Rationale

Almost ~ 90% children with febrile UTI showed resolution of fever within 48–72 h of initiating therapy with antibiotics [56]. Persistence of fever beyond 48–72 h should raise suspicion of complications and should be re-evaluated with ultrasound scan of kidney, ureter, and bladder. A considerable discordance between in vitro susceptibility and in vivo clinical response has been reported in the literature [57, 58]. The guideline panel suggests that clinical response is crucial while assessing the effectiveness of antibiotic therapy and initial therapy need not be changed based on sensitivity pattern if a patient is improving clinically. However, these patients should be monitored carefully for recurrence of symptoms.

Clinical practice point

We suggest 7–10 days of therapy with the antibiotic in children with acute symptomatic UTI.

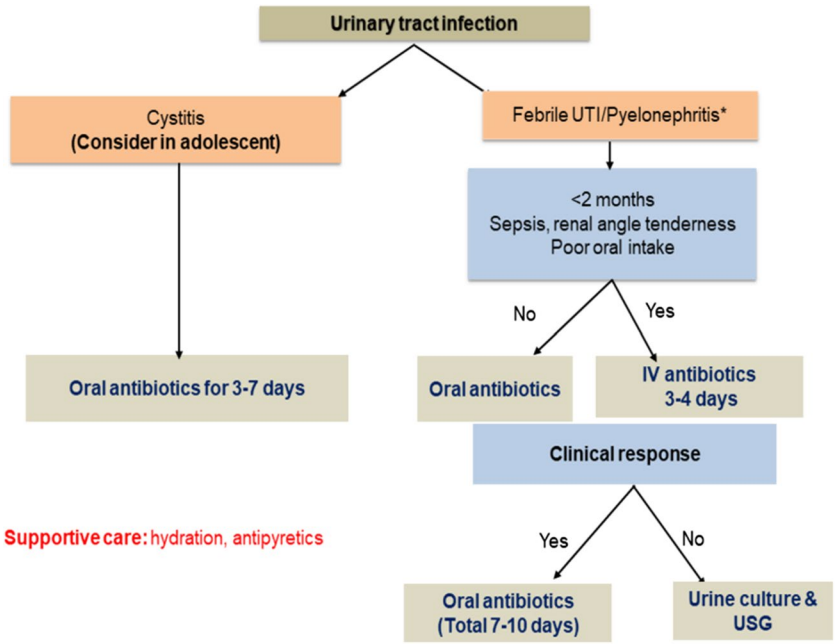

Fig. 2 Treatment of urinary tract infection in children. *Febrile UTI in young children is considered as acute pyelonephritis unless proven otherwise. Failure to respond to therapy within 2–3 days suggests the presence of risk factors and the non-sensitivity of the uropathogens; hence, repeat urine specimens should be cultured, and ultrasonography performed to exclude complications such as pyonephrosis and congenital anomaly of the urinary tract. Urine culture should not be repeated after completion of therapy if the patients show clinical response. IV, intravenous; UTI, urinary tract infection

Rationale

The ISPN 2011 guideline on UTI had suggested 10–14 days of antibiotic therapy in infants and children with complicated UTI and 7–10 days for uncomplicated UTI [1]. A meta-analysis in adults with pyelonephritis and septic UTI showed that the clinical and bacteriological failure rate with 7 days of antibiotic therapy is similar to longer duration treatment [59]. A recent study showed no significant difference in treatment failure rates between the recipients of short course (6–9 days, median 8 days) and long course (≥ 10 days, median 11 days) antibiotic therapy (odds ratio (OR) 1.22; 95% CI 0.75–1.98). Similarly, treatment failure rates between short- versus long-duration therapy groups in children with or without urological abnormalities were not significantly different (OR 1.49; 95% CI 0.69–3.24 and OR 1.07, 95% CI 0.56–2.04 respectively) [60]. A recent study compared 5 days versus 10 days antibiotic therapy and observed that 5 days therapy is not non-inferior to 7 days [61]. Hence, the guideline panel suggests that children with febrile UTI should receive 7–10 days of antibiotic therapy.

Recommendation

We suggest 3–7 days of oral antibiotic therapy in children with cystitis (1⊕⊕◯◯).

For this recommendation, the guideline panel puts moderate value on low certainty evidence showing no difference in persistence of bacteriuria at the end of therapy, recurrence, or reinfection between short and standard duration antibiotic therapy in cystitis.

Balance of benefits and harms

The recent Cochrane review on antibiotics for cystitis in children found no significant difference in persistence of bacteriuria at the end of therapy (3 studies; 265 participants, RR 1.09; 95% CI 0.67–1.76), recurrence of bacteriuria (4 studies; 328 participants, RR 1.25; 95% CI 0.74–2.13), or re-infection (2 studies; 211 participants, RR 0.88; 95% CI 0.44–1.74) between short course (3–7 days) and long course (10–14 days) antibiotic treatment (Table S20) [62]. Short course of antibiotic therapy is expected to reduce cost of therapy, improve compliance, reduce emergence of resistant uropathogens, and may result in fewer side effects.

Certainty of evidence

Certainty of evidence was downgraded to low in view of very serious methodological limitations and imprecision. Also, use of different antibiotics in two treatment arms could have a confounded the results of meta-analysis.

Values and preferences

In view of similar efficacy of short course as compared to prolonged antibiotic therapy, and lower cost of therapy and fewer side effects, parents would prefer a short course of therapy in children with lower UTI.

Resource use and costs

Cost analysis for varying duration of antibiotic therapy has not been evaluated systematically. Based on their clinical experience, the guideline panel judged that there would be lower cost with shorter duration of antibiotic therapy for children with lower UTI.

Considerations for implementation

The panel judged that there would not be any major barriers in implementing this recommendation.

Rationale

The optimal duration of antibiotic therapy has both cost and practical implications. No significant difference in the important outcomes was observed between short course (3–7 days) and long course (7–10 days) of antibiotic treatment for lower UTI in children (Table S20) [62, 63]. Hence, the guideline panel recommended treating for 3–7 days in children with lower UTI. Figure 2 describes the approach to treatment of UTI in children.

Clinical practice point

We do not suggest the use of antibiotics for the treatment of asymptomatic bacteriuria. We suggest that routine urine cultures should not be performed in asymptomatic children.

Rationale

In most cases, ABU resolves spontaneously with time; the median time of persistence has been variably reported from 1.5 months to 2.5 years [64, 65]. Follow-up studies have revealed no significant difference in the development of UTI or permanent kidney damage among those treated with antibiotics versus placebo [66–69]. Long-term follow-up studies in children with ABU and scarred kidney or VUR have also shown no difference in glomerular filtration rate and kidney growth in treated and untreated children [70–72]. There is some evidence to suggest that antibiotic treatment for unrelated infection in children with ABU may result in symptomatic UTI [65]. Treatment of ABU may be considered in children undergoing instrumentation of the urinary tract [73–75]. Existing data does not support treating ABU

in kidney allograft recipients beyond 2 months of transplantation [75, 76]. Similarly there is no data to support that antibiotic therapy is beneficial for ABU in settings of immune deficiency and diabetes; however, treatment of ABU in pregnancy can be beneficial [75, 77].

Role of other interventions

Role of adjunctive corticosteroid therapy and vitamin A for the prevention of kidney scarring has been studied in children with febrile UTI [78, 79]. Meta-analysis of three randomized controlled trials (RCTs) (529 children) on the role of corticosteroid therapy in the prevention of kidney scarring in children with acute pyelonephritis showed that adjunctive corticosteroids in addition to oral antibiotic therapy significantly reduced the risk of kidney scarring in comparison to those who received placebo (RR 0.57; 95% CI 0.36–0.90), without concomitant increase in the risk of bacteremia (RR 1.38; 95% CI 0.23–8.23) and hospitalization (RR 0.87; 95% CI 0.3–2.55). Only one study reported corticosteroid-related adverse effects, such as fussiness and gastrointestinal disturbances [80]. Quality of evidence was downgraded to low because of small number of studies, inconsistency in reporting adverse effects with the use of corticosteroids, and serious methodological limitations. Two further clinical trials on efficacy of corticosteroids failed to show any efficacy in reducing kidney scarring in children with febrile UTI [80, 81]. Similarly, pooled estimates from 4 studies (286 participants) on the role of vitamin A in prevention of kidney scarring showed that vitamin A supplementation in addition to antibiotics significantly decreased the risk of kidney scarring in children with febrile UTI (RR 0.56; 95% CI 0.45–0.68) [79]. Based on the current evidence, the guideline panel concluded that it is difficult to decide for or against the additional use of corticosteroids or vitamin A in children with febrile UTI. More studies are necessary to demonstrate their efficacy and safety.

Imaging following UTI

Imaging after treatment for UTI has traditionally been performed to detect conditions predisposing a child for UTI [82, 83], VUR being the most common [84]. The gold standard for diagnosing VUR is MCU. It provides anatomical details of the genitourinary tract and also allows grading of VUR. Recently, the rationale behind imaging aggressively to detect VUR has been questioned for several reasons. First, all modalities for diagnosing VUR involve either the discomfort of urethral catheterization, exposure to ionizing radiation, or both [85, 86]. Second, VUR is present only in approximately one-third of children with UTI [87]. Finally, no intervention, antibiotic prophylaxis, surgical reimplantation, or endoscopic correction has been proven beneficial in reducing the most critical outcome, i.e., kidney damage associated with VUR [88]. However, if VUR is detected, antibiotic prophylaxis or anatomical correction may be of benefit in preventing the recurrence of UTI. Considering the balance of evidence, a less aggressive imaging approach to detect VUR seems appropriate, as summarized in Fig. 3.

Clinical practice point

Ultrasound scan of the urinary tract should be performed after first episode of UTI in all children.

Rationale

Ultrasonography scan (USG) is a modality of imaging that is readily available and does not involve exposure to ionizing radiation. USG is helpful in the assessment of the kidneys and urinary bladder but not the urethra [89]. USG can be performed any time after the episode of UTI [86]. However, it should be performed during treatment of UTI if there is no clinical improvement within the first 48 h of antibiotic therapy to diagnose pyonephrosis, renal or perirenal abscesses, and with features suggestive of obstruction [24]. Many congenital anomalies of the kidney that are associated with UTI are detected on USG [83]. Some experts suggest that USG scan can be avoided in patients with cystitis as they are less likely to have abnormalities of urinary tract.

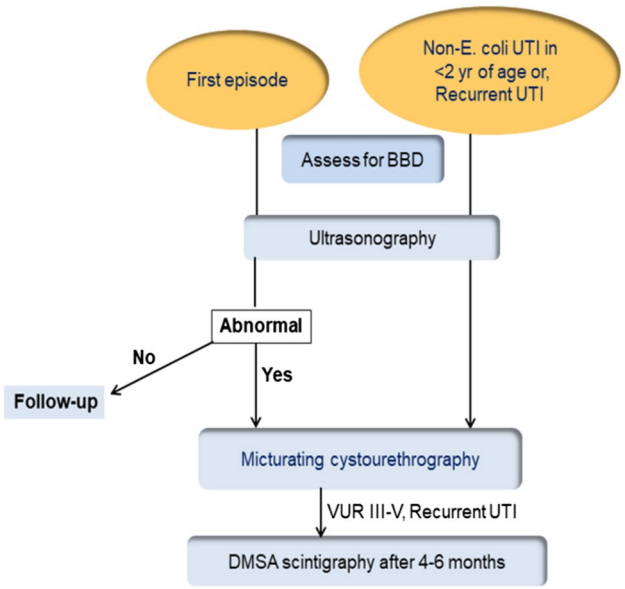

Fig. 3 Approach to imaging after an episode of urinary tract infection. Recurrent UTI is defined as two episodes of febrile UTI during childhood. Abnormal ultrasound is indicated by the presence of small kidneys, abnormal renal echogenicity, pelvi-caliceal dilatation, ureteral dilatation, uro-epithelial thickening of the renal pelvis, bladder wall thickness, and bladder diverticulum. BBD, bladder bowel dysfunction; DMSA, dimercaptosuccinic acid; VUR, vesicoureteric reflux

Clinical practice point

We suggest performing micturating cystourethrography in children with one of the following: (a) UTI caused by non-*E. coli* uropathogens in children less than 2 years, (b) abnormal ultrasound scan, or (c) history of recurrent UTI.

Rationale

MCU is the gold standard for the diagnosis and grading of VUR, although it involves discomfort to the child and exposure to radiation [90]. Other imaging modalities to detect primary VUR include contrast-enhanced USG (CE-USG), direct radionuclide cystography (DRCG), indirect radionuclide cystography (IRCG), and magnetic resonance urography (MRU). VUR is present in approximately one-third of children with UTI [87]. This implies that if imaging for VUR is performed in all children with UTI, two-thirds will undergo the inconvenience and hazards of imaging with negative results. Hence, the MCU study should be reserved for children with high suspicion of VUR. Low-quality evidence suggests that the yield of MCU will increase without much loss of sensitivity if it is restricted to children with UTI caused by *non-E. coli* organisms, abnormal USG findings, and recurrent UTI [91–94].

MCU can be performed any time after completion of therapy with antibiotics. The procedure should be performed using a protocol involving fluoroscopy and minimal radiation exposure, keeping the principles of ALARA (as low as reasonably achievable). The procedure should be performed under aseptic precautions to avoid the risk of developing a UTI following urinary catheterization. An RCT from India demonstrated that prophylactic antibiotics reduce the risk of UTI following the MCU study [95]. The protocol recommended by the American Academy of Pediatrics can be used [96]. VUR is conventionally graded on MCU using the International Reflux Study classification [97].

Recommendation

We do not recommend performing an acute-phase DMSA scan in children with febrile UTI (2⊕◯◯◯).

This recommendation places relatively moderate value on very low-quality evidence suggesting that acute phase (within 2 weeks of the onset of UTI) DMSA scan does not increase the yield of MCU for detecting high-grade VUR. While acute-phase DMSA scan is highly specific for diagnosing acute pyelonephritis, its findings neither alter the management of febrile UTI in clinical practice nor predict high-grade VUR [98].

Balance of benefit and harms

Pooled data from 21 studies (4047 participants) showed that acute-phase DMSA scan showed good sensitivity (0.94; 95% CI 0.85–0.97) but poor specificity (0.45; 95% CI 0.34–0.56) in predicting the high-grade VUR, considering MCU as the reference test (Table S21). DMSA scan is associated with radiation exposure.

Certainty of evidence

The certainty of the evidence for acute-phase DMSA scan in predicting high-grade VUR is low to very-low quality. Overall certainty was downgraded due to serious concerns about the quality of studies and significant heterogeneity between studies.

Values and preferences

The guideline panel judged that while detecting *high-grade* VUR is important, the diagnostic utility of acute-phase DMSA scan is limited; hence, most parents and physicians would opt against performing this imaging.

Resource use and costs

The guideline panel judged that this imaging strategy would not significantly alter the number of MCU procedures or reduce resource use and costs. DMSA scan may not be readily available in resource-limited settings and result in inequities.

Considerations for implementation

There are no barriers in implementing this recommendation.

Rationale

Considering its poor specificity for predicting high-grade VUR, inability to identify permanent kidney scarring, cost, limited availability, and variability in interpretation, acute-phase DMSA scan is not recommended as a screening tool for predicting high-grade VUR.

Clinical practice point

We suggest performing a late-phase DMSA scan to assess kidney scarring in children with recurrent UTI or high-grade VUR.

Rationale

Kidney parenchymal damage following an episode of UTI is a critical outcome. Risk factors for kidney scarring include delay in instituting antibiotic therapy, duration of fever, number of febrile UTI, high-grade VUR, high neutrophil/lymphocyte ratio, and abnormal findings on acute-phase DMSA scan [99–107]. Renal cortical scintigraphy, using DMSA,

is considered the gold standard to assess kidney scarring either consequent to UTI or in association with VUR. To detect permanent kidney scarring consequent to acute pyelonephritis, the scan should be performed 4–6 months after an episode of UTI [108]. Kidney scars are seen as focal or diffuse areas of diminished tracer uptake associated with loss of renal contour and cortical thinning. SPECT and pinhole images are more sensitive in detecting defects than planar images [109]. There is interest in alternate imaging modalities to detect kidney damage because of the exposure to ionizing radiation associated with the DMSA scan. Non-contrast MRI is sensitive for detecting scarring but is expensive and often requires sedation [110, 111]. An algorithm for imaging following an episode of UTI in children is reported in Fig. 3.

Prevention of UTI

Following febrile UTI ~ 10–30% children may experience recurrence of UTI [112, 113]. Primary VUR and bladder bowel dysfunction (BBD) are important risk factors for recurrence [112, 114]. Since 10–15% of patients with acute pyelonephritis may develop kidney scarring, it is important to prevent febrile UTI [105].

Recommendation

We suggest against using antibiotic prophylaxis for prevention of UTI in patients with a normal urinary tract and absence of BBD (2⊕◯◯◯).

This recommendation places a relatively moderate value on very low-quality evidence suggesting that antibiotic prophylaxis has little or no efficacy in preventing symptomatic UTI in patients with normal urinary tract and a relatively higher value on moderate quality evidence of prophylaxis resulting in an increased risk of antimicrobial resistance.

Balance of benefit and harms

A considerable proportion (17.3%) of children with normal urinary tract experience recurrence of UTI over 24 months [112]. Recurrence of UTI causes fever, pain, irritability, and discomfort to the child and anxiety, stress and inconvenience to the family, and increases the risk of kidney damage [115]. Antibiotic prophylaxis had been used in the past with the assumption that it would prevent UTI in children at risk of recurrence; hence, older guidelines [116] recommended it for every child following a febrile UTI, but evidence for the same was limited [117]. Pooled evidence from 5 trials (664 participants) suggests that antibiotic prophylaxis, as compared to placebo or no therapy, has little or no effect on the recurrence of symptomatic UTI (RR 0.53; 95% CI 0.12–2.40) (Table S22). Furthermore, long-term antibiotic prophylaxis increases the risk (2.4 times) of UTI due to organisms resistant to these antibiotics (Table S22).

Certainty of evidence

The quality of evidence for the critical outcome of preventing symptomatic UTI by antibiotic prophylaxis was very low, while it was moderate quality for the important outcome of antimicrobial resistance. Quality of evidence was downgraded for serious methodological limitations in studies, high heterogeneity across studies, and imprecision (Table S22). Critical outcomes of kidney scarring and kidney failure were not reported in any of the included trials.

Values and preferences

Considering that antibiotic prophylaxis has little or no efficacy in preventing the recurrence of symptomatic UTI at the expense of significant risk of antimicrobial resistance, the guideline panel judged that most well-informed parents would choose against antibiotic prophylaxis in patients with a normal urinary tract.

Resource use and costs

The guideline panel judged that not using antibiotic prophylaxis for children with normal urinary tract would not lead to significant increased risk of recurrence and might reduce the incidence of antimicrobial resistance. Hence, this strategy may reduce overall costs by decreasing UTI caused by resistant uropathogens.

Considerations for implementation

The panel judged that there would be no major barriers in implementing this recommendation and would require dissemination of the guidelines and education of the parents and pediatricians.

Rationale

Based on pooled estimates for desirable and undesirable outcomes for antibiotic prophylaxis. The guideline panel provided a weak recommendation against antibiotic prophylaxis in children with a normal urinary tract.

Recommendation

We suggest using antibiotic prophylaxis for the prevention of recurrent febrile UTI in patients with high-grade (grades 3–5) primary VUR (2⊕⊕◯◯).

Clinical practice points

Antibiotic prophylaxis may be considered in preference to surveillance in patients presenting with recurrent febrile UTI and BBD, irrespective of presence or absence of primary VUR.

In infants with recurrent febrile UTI and low-grade primary VUR, clinicians may consider using antibiotic prophylaxis.

This recommendation places relatively high value on the moderate quality data demonstrating that antibiotic prophylaxis may be effective in reducing recurrence of febrile UTI in children with high-grade (grades 3–5) primary VUR and moderate value on low certainty evidence that antibiotic prophylaxis increases the risk of antimicrobial resistance. This recommendation places relatively low value on the very low-quality evidence suggesting that antibiotic prophylaxis does not prevent kidney scarring.

Balance of benefit and harm

The risk of febrile UTI recurrence in children with high-grade primary VUR is 2.7 times higher than in low-grade VUR (Table S23). While antibiotic prophylaxis may be beneficial for the critically important outcome of preventing recurrent febrile UTI in high-grade VUR (9 studies, 845 participants, RR 0.75; 95% CI 0.53–1.06), the same cannot be concluded for low-grade VUR (7 studies, 817 participants, RR 0.65; 95% CI 0.34–1.24) (Table S23). Efficacy of antibiotic prophylaxis was not observed for another critically important outcome of kidney scarring. Risk of recurrent UTI with resistant uropathogens was threefold higher in patients receiving antibiotic prophylaxis. The efficacy of antibiotic prophylaxis in preventing febrile UTI did not differ according to sex and age of patients (Table S23) [24].

Certainty of evidence

For the prevention of febrile UTI, the quality of evidence was moderate in children with high-grade VUR as it was downgraded due to serious methodological limitations in included trials. In patients with low-grade VUR, and for kidney scarring, certainty of the evidence was rated low due to serious study limitations and imprecision (Table S23). For kidney scarring, evidence was downgraded to low due to serious study limitations and imprecision. For the undesirable outcome of antibiotic resistance, the quality of evidence was low as it was downgraded for serious study limitations, serious inconsistency, and serious imprecision despite being upgraded for a large effect estimate. For other adverse events, evidence was rated as moderate quality (serious study limitations). The overall quality of evidence on antibiotic prophylaxis was moderate for high-grade VUR and low for low-grade VUR.

Values and preferences

Prevention of febrile UTI reduced morbidity and kidney damage by antibiotic prophylaxis was judged by the guideline panel to be critically important. The panel also judged that an increased risk of resistance to prophylactic antibiotics would be important for many parents. The panel judged that given the incremental risk of recurrent febrile UTI, most well-informed parents would choose antibiotic prophylaxis in their children with high-grade VUR.

Resource use and costs

A recent study from the USA suggests that antibiotic prophylaxis for grade 4 primary VUR is cost-effective but not when it was used in patients for all grades of primary VUR [118]. Considering these factors, the panel judged that antibiotic prophylaxis would be cost-effective for patients with high-grade VUR.

Considerations for implementation

There would not be any significant barriers in implementing this recommendation.

Rationale

The previous guideline by ISPN on the management of UTI in 2011 [119] recommended antibiotic prophylaxis in all children with primary VUR irrespective of severity. Moderate quality of evidence suggests that the benefits of the antibiotic prophylaxis probably outweigh the harm in patients with high-grade VUR. However, evidence does not support this strategy for the prevention of UTI in patients with low-grade VUR. Considering the cost-effectiveness, the guideline panel provided a weak recommendation in favour of antibiotic prophylaxis in children with high-grade primary VUR. Since this is a weak recommendation, an alternative approach of active surveillance with prompt therapy in children with suspected UTI can be considered for management of these children.

Since we did not observe any difference in efficacy in preventing febrile UTI among boys and girls, we recommend using the same approach for children of different sex. Low-quality evidence from one trial suggests that antibiotics may be effective in children with BBD and primary VUR irrespective of severity. Hence, we provide guidance for clinical practice that physicians may consider using antibiotic prophylaxis in children with BBD and any grade VUR [112, 114]. In view of the lack of separate data in infants, the guideline panel suggests that clinicians may consider using antibiotic prophylaxis in infants presenting with recurrent febrile UTI and low-grade VUR.

Recommendation

We suggest not using antibiotic prophylaxis for the prevention of symptomatic UTI in children with antenatally detected hydronephrosis while awaiting evaluation (2⊕◯◯◯).

The guideline panel places a relatively moderate value, for this recommendation, on very-low quality evidence suggesting that antibiotic prophylaxis has little or no efficacy in preventing symptomatic UTI in infants with antenatally diagnosed hydronephrosis. Similarly, a relatively higher value was placed on the moderate quality evidence of antibiotic prophylaxis resulting in an increased risk of antimicrobial resistance.

Balance of benefit and harm

Infants with antenatally detected hydronephrosis are considered to be at higher risk of UTI (6–8%) [120, 121] as compared to febrile infants without any risk factors (5.3%) [122]. While primary VUR is considered an important risk factor for UTI in infants, it constitutes only 10–20% of all children diagnosed to have antenatal hydronephrosis. Antibiotic prophylaxis had been used in the past with the assumption that it would prevent UTI, but evidence to support this recommendation is limited and of low quality [123, 124]. Two recent studies suggest that antibiotic prophylaxis may not be effective in preventing UTI in this cohort [125, 126]. Pooled evidence from 19 studies (4924 infants) suggests that antibiotic prophylaxis is not effective in preventing symptomatic UTI (RR 1.16; 95% CI 0.75–1.8) (Table S24). One RCT also reported that long-term prophylaxis increases the risk of UTI caused by resistant uropathogens (RR 4.0; 95% CI 1.2–13.5) (Table S24) [125].

Certainty of evidence

The quality of evidence for the critical outcome of prevention of symptomatic UTI by antibiotic prophylaxis was very low, while it was moderate quality for the important outcome of antimicrobial resistance. Quality of evidence was downgraded for serious methodological limitations in studies, high heterogeneity across studies, and wide 95% CI (Table S24).

Values and preferences

The guideline panel judged that preventing recurrence of symptomatic UTI and associated morbidity would be critically important for parents. However, side effects associated with long-term antibiotic prophylaxis would be important to pediatricians and parents. Considering that antibiotic prophylaxis has little or no efficacy in preventing symptomatic UTI and that too at the expense of antimicrobial resistance, the panel judged that most well-informed parents would choose against using antibiotic prophylaxis in their infants with antenatal hydronephrosis.

Resource use and costs

The guideline panel judged that not using antibiotic prophylaxis for infants with antenatal hydronephrosis while awaiting imaging would not lead to significantly increased risk of recurrent UTI and may reduce the incidence of antimicrobial resistance in uropathogens.

Considerations for implementation

The panel judged that there would be no major barriers in implementing this recommendation, as it would require dissemination of the guidelines and education of the parents and clinicians.

Rationale

Since the publication of the last guideline, new scientific literature has emerged, and the role of antibiotic prophylaxis is even more limited in children with primary VUR. Based on pooled estimates for desirable and undesirable outcomes for antibiotic prophylaxis for infants with antenatal hydronephrosis and due consideration to other factors, the guideline panel suggested against antibiotic prophylaxis in antenatal hydronephrosis.

Recommendation

We suggest using cotrimoxazole or nitrofurantoin as the first-line antibiotic for prophylaxis in children older than 3 months (2⊕⊕◯◯).

This recommendation places relatively moderate value on low-quality evidence suggesting that nitrofurantoin is more effective than co-trimoxazole in preventing recurrent UTI. High value was placed on low-quality evidence showing higher gastrointestinal side effects resulting in poor compliance to nitrofurantoin.

Balance of benefit and harm

Cotrimoxazole is less effective than nitrofurantoin in preventing the recurrence of symptomatic UTI (2 studies, 145 participants, RR 1.76; 95% CI 1.08–2.87). Bacterial resistance to prophylactic medications was higher with cotrimoxazole than nitrofurantoin (2 studies, 96 participants, RR 1.86; 95% CI 1.09–3.20). Adverse event rate (1 study, 120 participants, RR 0.46; 95% CI 0.29–0.72) and discontinuation of therapy (1 study, 120 participants, RR 0.32; 95%

CI 0.14–0.74) were lower with cotrimoxazole as compared to nitrofurantoin (Table S25). While prevention of UTI is better with nitrofurantoin, poor compliance and side effects are significant concerns. Cotrimoxazole has a better safety profile, which is supported by its use in major clinical trials for antibiotic prophylaxis [127–131].

Certainty of evidence

Evidence was downgraded for serious study limitation and serious imprecision; hence, it was rated as low quality for the prevention of UTI and bacterial resistance to the prophylactic agent. The certainty of evidence for adverse event rate and discontinuation of therapy was moderate due to downgrading for serious study limitation and serious imprecision and upgrading for large effect estimate (Table S25).

Values and preferences

The guideline panel judged that deciding on an antibiotic for prophylaxis in children, the efficacy for preventing UTI would be critically important for parents and clinicians. Bacterial resistance to the prophylactic antibiotic, side effects, and compliance with therapy would also be important for many parents. While many parents would prefer nitrofurantoin based on better efficacy in preventing UTI, others may prefer cotrimoxazole for its better safety and compliance.

Resource use and costs

We did not perform any cost-effectiveness analysis for cotrimoxazole versus nitrofurantoin. Based on their clinical experience, the guideline panel judged that there is no difference in resource use and costs of antibiotic prophylaxis with co-trimoxazole and nitrofurantoin.

Considerations for implementation

The panel judged that there would not be any major barriers in implementing this recommendation.

Rationale

Nitrofurantoin and cotrimoxazole are the most extensively used antibiotics for prophylaxis against UTI in children (Table 3). They are inexpensive, have a narrow spectrum, are less toxic, and do not significantly alter the normal microbiota of the gut. Based on the trade-off between desirable and undesirable outcomes, the panel provided a weak recommendation to use either of these antibiotics for prophylaxis in children > 3 months old. For young infants, an alternative antibiotic such as cephalexin can be used to avoid the risk of hemolysis associated with cotrimoxazole or nitrofurantoin in patients with glucose-6-phosphate dehydrogenase deficiency. No specific dose of these antibiotics can be recommended, although the traditionally suggested dose is one-quarter to one-third of the therapeutic dose.

Recommendation

We suggest discontinuing antibiotic prophylaxis in children older than 2 years of age if they satisfy all three criteria: (i) toilet training, (ii) absence of BBD, and (iii) no febrile UTI in the preceding 1 year (2⊕◯◯◯).

This recommendation places relatively high value on very low-quality evidence suggesting that UTI recurrence before and after cessation of antibiotic prophylaxis did not depend on patient age at antibiotic discontinuation.

Balance of benefit and harm

UTI recurrence rate (2 studies, 284 participants, RR 0.60; 95% CI 0.27–1.3) was similar before and after antibiotic cessation if the patient age at discontinuation ranged from 2–4 years. When antibiotic was discontinued in older children (aged > 4–6 years), the recurrence rate of UTI (3 studies, 654 participants, RR 1.24; 95% CI 0.80–1.92) did not differ before and after the cessation of antibiotic prophylaxis (Table S26). Considering this evidence, the guideline panel judged that the minimum age for considering cessation of antibiotic prophylaxis should not be less than 2 years. Early discontinuation of antibiotic prophylaxis has potential benefits in reducing antibiotic resistance and may improve compliance with antibiotic prophylaxis.

Certainty of evidence

The quality of evidence for this recommendation is very low as evidence was based on observational studies.

Values and preferences

The panel judged that recurrence of UTI following cessation of antibiotic prophylaxis would be critically important for most parents. Considering these factors and their clinical experience, the guideline panel judged that most parents would prefer to discontinue antibiotic prophylaxis as early as feasible.

Resource use and costs

There is a lack of scientific literature, and based on the experience, the panel judged that early cessation of prophylaxis would neither increase cost nor require extra resource.

Table 3 Antibiotic commonly used for treatment and long-term prophylaxis

Antibiotics	Route	Dose (mg/kg/day)
Treatment		
Amoxicillin-clavulanic acid	Oral	30–40 of amoxicillin, in 3 divided doses
	Intravenous	60–100 of amoxicillin, in 3 divided doses
Cefixime	Oral	8–10, in 2 divided doses
Cefuroxime axetil	Oral	20–30, in 2 divided doses
Cephalexin	Oral	40–60, in 2–3 divided doses
Cefpodoxime	Oral	10, in 2 divided doses
Ceftriaxone	Intravenous	75–100, in 1–2 divided doses
Cefotaxime	Intravenous	100–150, in 2–3 divided doses
Ciprofloxacin	Oral	10–20, in 2 divided doses
Ofloxacin	Oral	15–20, in 2 divided doses
Amikacin	Intravenous or intramuscular	10–15, single dose
Gentamicin	Intravenous or intramuscular	5–6, single dose
Prophylaxis		
Co-trimoxazole[1]	Oral	2 of trimethoprim single dose
Nitrofurantoin[2]	Oral	1–2, single dose
Cephalexin[3]	Oral	10–12.5, single dose
Cefadroxil	Oral	5, single dose
Amoxicillin[4]	Oral	15, single dose

[1]Avoid in infants < 3 months, G-6PD deficiency; [2]may cause significant nausea, vomiting, avoid in infants < 3 months, G-6PD deficiency, eGFR < 45 mL/min; [3]preferred in infants less than 6 months, better avoid in older children as it is a broad-spectrum antibiotic; higher risk of resistance; [4]advised only if organism resistance to all other agents recommended for prophylaxis

Considerations for implementation

The guideline panel judged that there would not be any major barriers in implementing this recommendation.

Rationale

Common determinants for discontinuation of antibiotic prophylaxis across all observation studies have been the absence of BBD, toilet training, and lack of recurrence of UTI in the last 12 months [132–137]. Pooled estimates from these observational studies suggest that recurrence of UTI is not significantly high if antibiotic prophylaxis was stopped, taking due consideration of these factors. Hence, the guideline panel provided a weak recommendation for early cessation of prophylaxis after due consideration for toilet training, absence of BBD, and absence of febrile UTI in the last 1 year.

Recommendation

We suggest that circumcision can be considered as one of the interventions for the prevention of UTI in children at-risk (high-grade VUR or recurrent UTI) of recurrence (2⊕⊕⊕◯).

This recommendation places a relatively high value on moderate-quality evidence demonstrating a lower rate of UTI in circumcised children as compared to their uncircumcised counterparts. Similarly, high value was also placed on complications related to circumcision.

Balance of benefit and harms

Moderate quality evidence chiefly from 24 observational studies (419,964 children) showed that the relative risk of UTI (RR 0.18; 95% CI 0.13–0.25) is significantly lower in children who are circumcised (Table S27). Complications related to circumcision are relatively low but depend on the personnel performing the procedure and the age of the child. A previous systematic review reported the median frequency of any adverse events to be 1.5% following circumcision [138]. However, three large studies from the developed world where circumcision is chiefly performed by trained medical personnel, reported a very low (0.3–0.5%) complication rate [139–141]. The rate of complications is 10–20 times higher when it is performed beyond infancy [139].

Certainty of evidence

The quality of evidence for the critically important outcome of UTI was downgraded due to serious methodological limitations and very serious inconsistency but was upgraded for very large effect estimate. The overall quality was graded as moderate (Table S28).

Values and preferences

The guideline panel judged that while prevention of UTI would be critically important for parents, a significant proportion would prefer to avoid circumcision due to social and religious issues and the risk of complications. The panel judged that many parents if informed about the benefits and harms of circumcision would want it, but a considerable proportion may choose against it.

Resource use and costs

While we did not perform a cost-effectiveness analysis, based on scientific literature and clinical experience, the guideline panel judged that considering many life-time benefits and relatively low costs and complications, this would be a cost-effective intervention in infants [142, 143].

Considerations for implementation

Since there may be concerns in implementing this recommendation in our country, benefits and harms of circumcision need to be explained in detail to parents and physicians.

Rationale

Pooled estimates showed that circumcision reduces the risk of UTI by 82% in children (Table S28). In normal, healthy, uncircumcised boys, the risk of UTI is almost 1–2%, and complications following circumcision are low (0.3–0.5%) in trained hands [139, 140], but can be as high as 1.5–2% [138]. Since risk of UTI is significantly higher (10–30%) in at-risk children (high-grade VUR and children with previous history of UTI) [112, 113], the benefit from circumcision outweighs the harm associated with it. The recommendation is weak as the guideline panel judged that many well-informed parents would choose circumcision, but some may decide against it.

Recommendation

We suggest cranberry products can be used for the prevention of UTI in children with recurrent UTI and normal urinary tract (2⊕⊕◯◯).

This recommendation places relatively moderate value on low-quality evidence showing the effectiveness of cranberry products in preventing UTI. This recommendation places equally moderate value on concerns about the acceptability and feasibility of the desired amount of cranberry administration. A clinical trial showed that 300 mL of cranberry juice (~36 mg of proanthocyanidins) is needed for its anti-adhesive effect on uropathogens; however, a larger dose of 72 mg proanthocyanidins may offer better protection [144].

Balance of benefit and harms

Pooled estimates from 4 studies (416 participants) showed that UTI recurrence rate (RR 0.39; 95% CI 0.25–0.61) was lower in children receiving cranberry products as compared to placebo in children with normal urinary tract. When cranberry products were compared with antibiotic prophylaxis, UTI recurrence was not significantly different between these two groups (RR 0.79; 95% CI 0.43–1.43) (Table S28). None of the included studies reported adverse effects and the rate of antibiotic resistance in both groups. However, there are concerns of poor compliance with cranberry products due to the taste and large volumes that need to be ingested by children.

Certainty of evidence

The quality of evidence for the critical outcome of UTI recurrence rate was moderate as it was downgraded for serious study limitations and serious inconsistency across studies and upgraded for a large effect estimate. In comparing cranberry products versus antibiotic prophylaxis, evidence for UTI recurrence rate was downgraded to low due to serious inconsistency and serious imprecision.

Values and preferences

UTI recurrence would be a critically important outcome for parents when deciding on cranberry products. The panel judged that concern related to the availability of cranberry products and poor compliance of children would also be important for parents. However, considering the efficacy and potentially avoiding the risk of antimicrobial resistance to UTI, most parents would choose this intervention, if feasible and available.

Resource use and costs

While we did not perform any cost-effectiveness analysis, one small RCT evaluated the cost-effectiveness of cranberry extract versus cotrimoxazole in premenopausal women. While cranberry products are expensive, it would potentially save costs by decreasing the risk of UTI recurrence; hence, the panel judged that cost-effectiveness may not be against this intervention.

Considerations for implementation

A minimum amount of cranberry product must be ingested to achieve a targeted concentration of proanthocyanidins (36–72 mg) in the urinary tract to inhibit the adhesion of uropathogens. Achieving the desired concentration through cranberry juice may not be acceptable to most children as they need to ingest large volumes. The availability of cranberry extract with the desired concentration of proanthocyanidins is perhaps necessary.

Rationale

This recommendation places a high value on a lower UTI recurrence rate with cranberry products compared to placebo and a similar recurrence rate to antibiotic prophylaxis. The recommendation for cranberry product use is weak due to overall low quality evidence and concerns in implementation due to its availability and feasibility.

Bladder bowel dysfunction

Clinical practice point

We suggest that all toilet-trained children with UTI should be evaluated for bladder bowel dysfunction.

Rationale

Bladder bowel dysfunction (BBD) is commonly observed in children with UTI and encompasses a spectrum of lower urinary tract symptoms accompanied by constipation and/or encopresis [145]. A recent meta-analysis (9 studies; 920 patients) reported pooled prevalence of BBD in patients with UTI to be 41% (95% CI 26–55%). The prevalence of BBD in patients with primary VUR (30 studies, 5060 patients) was 49% (95% CI 43–56%) [114]. The meta-analysis also showed that the presence of BBD in patients with primary VUR increased the risk of recurrent UTI by 2.1 (95% CI 1.7–2.5) times [114]. Similarly, the RIVUR trial also reported that BBD was an important risk factor for recurrence of UTI [112]. Assessment of children for BBD includes history of incontinence, voiding postponement, frequency, urgency, postures of voiding postponement (Vincent's curtsy, crossing one's legs and bending down from the waist, pinching the glans of the penis between fingers, squatting with a heel at the perineum); history of constipation (stool firmness, frequency, pain with defecation); and/or encopresis and examination for a palpable fecal mass in the left iliac fossa. Clinical evaluation is supplemented with at least a 2-day voiding diary (< 4 and > 7 voids in a day is abnormal) and details of bowel movements over 2 weeks, which provides useful information about the voiding and bowel habits [145]. Clinicians may use a validated questionnaire such as dysfunctional voiding symptom score (DVSS) [146] recommended by the International Children's Continence Society [145] to diagnose BBD. Similarly, Rome IV criteria [147] and the Bristol Stool Form Scale [148] may aid in the diagnosis of constipation. Transverse rectal diameter can be used as a simple but reliable tool for documenting fecal loading in children [149]. The presence of a post-void residual volume of > 20 mL or 10% of bladder capacity in age group of 4–6 years, post-void residual volume of > 10 mL or 6% of bladder capacity in age group of 7–12 years, and thickened bladder wall (> 3 mm for an empty bladder and > 5 mm for a full) are suggestive of BBD on an ultrasound scan [145, 150]. Uroflowmetry should be advised for toilet-trained children who do not respond to 3–6 months of initial urotherapy. Invasive urodynamics is reserved for patients with suspected neurological defects or non-neurogenic bladder and bowel dysfunction that does not improve with initial therapy. In non-toilet trained children, it is difficult to assess bladder function. Hence, a 4-h observation of voiding is suggested to assess the bladder function. When combined with ultrasound scan to assess the post-void residue, it may help in identifying infants who need treatment [151].

Recommendation

We recommend that all children with BBD should be managed with urotherapy for prevention of UTI recurrence (1⊕◯◯◯).

This recommendation places relatively high value on low-quality evidence showing the significant reduction in rate of recurrent UTIs following the institution of urotherapy. The guideline panel places relatively moderate value on the fact that urotherapy is easy to administer and is not associated with any side effects.

Balance of benefits and harms

BBD is common in children with UTI and is considered an important risk factor for recurrence of UTI [114, 152]. The International Children's Continence Society recommends urotherapy as the first line of management for all children with BBD (Table 4). Pooled estimates from seven cohort studies (393 participants) showed that no UTI recurrence was observed in 68% (95% CI 54–81) children following administration of urotherapy over 6–36 months of the follow-up period (Table S29). None of the included studies reported adverse effects.

Certainty of evidence

The quality of evidence for the critical outcome of UTI recurrence rate was low as it was downgraded for serious study limitations and serious inconsistency across studies.

Values and preferences

UTI recurrence would be a critically important outcome for parents when deciding on the institution of urotherapy. The guideline panel judged that while it may be time-consuming for clinicians to explain to parents about urotherapy, however, it would be easy for parents to administer it. Thus, considering the efficacy and lack of any associated risk, most parents would choose this intervention for their children.

Resource use and costs

We did not perform any cost-effectiveness analysis. Management of children with BBD requires frequent monitoring of voiding volume, fluid intake, and bowel habits. Behavioural education for caregivers and children about urinary tract and bowel physiology may require help from a psychiatrist or psychologist. The guideline panel judged that cost-effectiveness may not be against this intervention.

Considerations for implementation

The guideline panel judged that implementation of this intervention would be easy with proper training, counselling, and education of children and caregivers.

Rationale

The presence of BBD increases the risk of UTI recurrence, delays the resolution of VUR, and increases failure rates of surgical interventions. Quantitatively synthesized evidence from 7 cohort studies suggests that urotherapy reduces the risk of UTI recurrence in children. The recommendation is strong because the guideline panel judged that all or nearly all well-informed parents and patients would choose urotherapy for the management of BBD in all children.

Management of primary vesicoureteric reflux

VUR is the retrograde passage of urine into the upper urinary tract during detrusor contraction. Primary VUR is considered an important risk factor for recurrence of febrile UTI along with BBD. Primary VUR also increases risk of post-infection kidney scarring [153]. Almost 7–17% kidney failure is reported to be associated with primary VUR, which is chiefly caused by congenital hypodysplasia rather than acquired post-UTI kidney scarring [154–156]. In most patients, even high grades of VUR resolves spontaneously over a period of time. Hence, the primary focus during management of patients with primary VUR is to prevent recurrence of UTI.

Table 4 Treatment of bladder-bowel dysfunction

	Therapy	Description	Remarks
First line	Urotherapy	Voiding diary Increase fluid intake (6–8 cup/day) Reduce intake of caffeine, chocolate Frequent (2–4 hourly); double voiding Adequate posture; support both feet on stool/flat surface	Ensure compliance to urotherapy Should be continued for at least 6 months
	Bowel regimen	Hydration, increase intake of fibre, bowel training Polyethylene glycol: 1–1.5 g/kg/d for 3 days followed by 0.25–0.5 g/kg/d	
Second line	Overactive bladder	Oxybutynin: 0.2 mg/kg/dose 2–3 times daily Tolterodine: 2–4 mg/day Mirabegron: 12.5–25 mg/day or Neuromodulation	Side effects of oxybutynin includes constipation, dry mouth blurred vision, headache, drowsiness
	Dysfunctional voiding	Tamsulosin: 0.2–0.4 mg/day Doxazosin: 1 mg/day Biofeedback therapy	Hypotension, CHF
	Underactive bladder	Clean intermittent catheterization Biofeedback therapy	No specific pharmacotherapy for underactive bladder
Third line	Botulinum toxin	50–100 IU injected For overactive bladder: intra-detrusor injection of botulinum toxin For refractory dysfunctional voiding: injection into the bladder neck	Used as last option in refractory patients

Recommendation

We suggest that antibiotic prophylaxis should be the first-line of management in patients with high-grade VUR (2⊕⊕⊕◯).

We suggest that surgical reimplantation be considered in patients with high-grade VUR with recurrent breakthrough febrile UTI on antibiotic prophylaxis (2⊕⊕⊕◯).

These recommendations place relatively higher value on moderate quality evidence demonstrating little or no difference in kidney parenchymal abnormality (scars and parenchymal thinning) between patients receiving antibiotic prophylaxis alone and those treated with the combination of surgery and antibiotic prophylaxis. Similarly, this recommendation places a relatively high value on avoiding moderate resource expenditures to achieve little or no reductions in kidney scarring and long-term adverse outcomes. Conversely, the recommendation places relatively lower value on moderate-quality evidence that surgical correction compared with antibiotic prophylaxis reduces the risk of febrile UTI.

Balance of benefit and harm

Surgery plus antibiotic prophylaxis compared with antibiotic prophylaxis made little or no difference to the number of children developing a new kidney parenchymal abnormality, either at 2 years (2 studies, 171 participants, RR 1.06; 95% CI 0.33–3.42) or at 4–5 years (4 studies, 572 participants, RR 1.09; 95% CI 0.79–1.49). The risk of progression of an existing abnormality was also similar at 4–5 years (3 studies, 468 participants, RR 0.99; 95% CI 0.69–1.42). Analysis showed that at 5-year follow-up, the risk of repeat febrile UTI was lower in the surgery plus antibiotic group (2 studies, 429 participants, RR 0.43; 95% CI: 0.27–0.70) (Table S30) [88].

Adverse events in either group were not well reported in the included studies. Complications reported for surgical intervention were postoperative obstruction, transient ureteral and renal pelvic dilatation, urine retention, aspiration during anesthesia, abdominal pain with pelvic dilatation and decreasing kidney split function, and fibrous narrowing of the bulbar urethra. No study reported on whether bacterial resistance developed to the prophylactic drug in subsequent symptomatic UTIs [88].

Certainty of evidence

The guideline panel judged kidney scarring as the most critical outcome. Evidence was downgraded for serious risk of bias in three of the four studies included in the meta-analysis (Table S30). Therefore, the overall certainty of the evidence was moderate.

Values and preferences

The panel judged that most parents will place a higher value on avoiding the pain, cost, and inconvenience of surgery and possibly would be willing to accept the long-term follow-up associated with oral antibiotic prophylaxis. However, the panel also felt that if informed well about the benefits and harms of surgery, many parents would not deny it if absolutely indicated.

Resource use and costs

We did not perform a cost-effectiveness analysis but the guideline panel placed a relatively high value on avoiding moderate resource expenditures associated with surgery to achieve little or no reductions in kidney scarring.

Considerations for implementation

The panel judged that benefit and harm of surgery need to be explained in detail to parents and physicians. There will not be any major concern in implementing this recommendation.

Rationale

In the absence of data on critically important outcomes of kidney failure or hypertension, the kidney scarring was taken as a surrogate. While the guideline panel judged the overall risk of surgical complications to be small, the overall balance of benefit versus harm was thought to favor antibiotic prophylaxis as the first-line agent and surgery be reserved for patients with recurrent febrile UTI (two episodes of febrile UTI) on antibiotic prophylaxis. The panel places a high value on avoidance of moderate resource expenditure associated with surgery and the small risk of complications associated with it. Thus, the panel provides weak recommendations for antibiotic prophylaxis as the first-line management option for children with high-grade VUR.

Clinical practice point

In children with high-grade VUR, surgical intervention may be an alternative for parental hesitancy to use antibiotics.

Rationale

When surgery is indicated, open ureteric reimplantation is preferred to endoscopic correction as it has a higher success rate

of resolution of VUR and a lower complication rate [157–159]. It is the preferred modality for those with BBD [160] and following failure of endoscopic correction [161]. However, prolonged hospital stay, the need for postoperative analgesia, and the risk of postoperative complications should be expected.

There is no consensus on the type of surgical intervention. While open re-implantation (extra- or intra-vesical approach) is the gold standard, laparoscopic or robotic-assisted laparoscopic reimplantation has a lower average length of hospital stay [161, 162]. The disadvantages include a longer learning curve, longer operating time, and higher cost. These techniques can be considered only as alternate options based on the availability of surgical expertise and parental preference.

Clinical practice point

When surgical intervention is indicated, patients may be given the option of endoscopic injection of bulking agent as initial therapy with guidance from a physician about its minimally invasive nature but lower success rate as compared to ureteric reimplantation.

Rationale

When surgical intervention is indicated, open ureteric reimplantation is preferred to endoscopic correction as the former has a higher success rate of resolution of VUR and lower complication rate. It is the preferred modality for those with BBD and following failure of endoscopic correction [160, 161]. However, longer hospital stays, need for post-operative analgesia, and risk of post-operative complications need to be explained to the parents. For those with grade 3 VUR and in case of parental preference, endoscopic correction may be offered. Success rates with different bulking agents for endoscopic correction are still under evaluation [163]. Figure 4 depicts the approach to management of primary VUR.

Follow-up of patients with primary vesicoureteric reflux

Clinical practice point

Children with high-grade VUR and reflux nephropathy need periodic follow-up to detect long-term complications: their growth, blood pressure, proteinuria, and kidney function checked during each hospital visit.

Rationale

Reflux nephropathy is defined as the presence of photopenic areas and contour changes detected on a DMSA scan

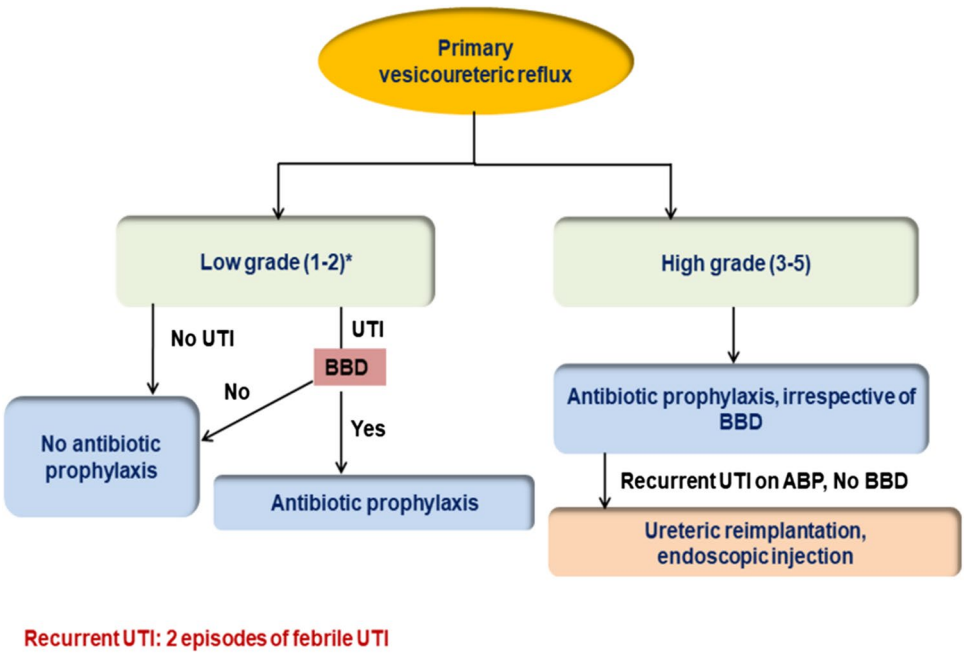

Fig. 4 Treatment of primary vesicoureteric reflux in children. *Antibiotic prophylaxis can be considered in infants with low-grade vesicoureteric reflux. Antibiotic prophylaxis can be stopped in children who fulfill the following three criteria: toilet-trained, free of BBD, and no UTI in the last 1 year. Surgical intervention is considered in children with recurrent UTIs despite antibiotic prophylaxis and appropriate management of BBD. Surgical intervention may also be considered based on parental preference. ABP, antibiotic prophylaxis; BBD, bladder-bowel dysfunction; UTI, urinary tract infection

in patients with primary VUR [105]. Children with VUR, especially high-grade, are more likely to develop kidney scarring. Older children with VUR, recurrent symptomatic UTI and VUR with concomitant BBD, are risk factors for the development of reflux nephropathy [27, 112, 115, 164, 165]. Delay in initiation of antimicrobial therapy for febrile UTIs and high-grade VUR are also associated with progressive kidney damage [27, 164]. Long-term follow-up studies in children with reflux nephropathy have shown the progressive nature of the disease leading to various complications like hypertension, proteinuria, and chronic kidney disease, including kidney failure [166, 167]. Risk of these long-term complications is higher in children with congenital dysplasia than those with acquired kidney scarring. Renal dysplasia with reflux was the leading cause of pediatric kidney failure in the UK Renal Registry, accounting for 32.6% of prevalent cases [168]. The collated data from five international registries, from Europe, Australia, New Zealand, the USA, and the UK, suggest that kidney scarring associated with VUR accounts for 6–17% of kidney failure [169]. Hence, children with primary VUR, especially those with reflux nephropathy, need periodic follow-up for early recognition and management of complications.

Clinical practice point

Ultrasound is suggested to be performed periodically to monitor the kidney growth in children with persistent high-grade VUR.

Rationale

Although studies doubt the utility of follow-up ultrasonography [170, 171], it is suggested to be performed annually to monitor the kidney growth in young children with persistent high-grade VUR; less frequently in an asymptomatic and older child.

Clinical practice point

We suggest that DMSA should be repeated during follow-up only in children with recurrence of UTI.

Rationale

Kidney scarring in children with primary VUR does not worsen due to reflux of sterile urine [172]. However, new kidney scars can form after a febrile UTI in children with VUR. Hence, DMSA should be repeated during follow-up only in children having a recurrence of febrile UTI to assess for worsening or appearance of new kidney damage. This follow-up DMSA should be performed 4–6 months after the last episode of UTI.

Clinical practice point

We suggest that repeat cystography for documenting resolution of reflux is not required; however, it may be performed after 4–8 years following the initial diagnosis if deemed necessary by treating physicians in children with high-grade VUR.

Rationale

Limited studies and guidelines are available on follow-up MCU in children with VUR [173]. A good correlation was seen between direct radionuclide cystography (DRCG) and MCU in diagnosing VUR [174–176]. The advantage of DRCG is lower radiation hazard compared to MCU; however, its major limitation is that the grading of VUR and urethral anatomy on MCU cannot be replicated on DRCG [176]. The guideline panel suggested repeating MCU in children where surgical intervention is planned. For the resolution of reflux, DRCG or MCU can be performed. The overall resolution rates of primary VUR vary from 40 to 70%, depending on the time of imaging following diagnosis [177–180]. The resolution rate was 72% in grade 1, 61% in grade 2, 49% in grade 3, and 32% in grades 4 and 5, according to a nomogram constructed by Estrada et al. [177]. The probability of resolution of VUR is affected by several factors, including the grade of reflux, laterality, sex, mode of presentation (UTI vs. prenatal hydronephrosis or sibling screening), presence of kidney scarring, and associated BBD [166, 177–179]. VUR presenting in infancy and during the evaluation of antenatal hydronephrosis has a higher chance of resolution [177, 181]. The presence of kidney scarring and BBD decreases the chances of spontaneous resolution of VUR [178, 182]. The resolution time is shorter for low-grade than high-grade reflux [166, 178, 183]. Since low-grade reflux resolves spontaneously in most children and is less likely to result in the recurrence of febrile UTI, the focus for long-term evaluation is on the patients with high-grade VUR. For patients with reflux nephropathy and progressive kidney failure, a repeat cystography may be required before kidney transplantation. The median time to resolution in high-grade reflux may vary from 4 to 8 years [166, 178]; hence, the guideline panel suggests that the earliest time a clinician can assess for resolution is 4–5 years following initial diagnosis.

Clinical practice point

We suggest screening siblings (aged less than 3 years) of children with primary VUR with an ultrasound scan.

Rationale

Evidence indicates that the prevalence of VUR in screened siblings of children with primary VUR is higher than that of the age-matched general population [184–188]. We performed a systematic review of studies that evaluated VUR in siblings of index patients and found that 31% (95% CI 24–38) had VUR [184, 185, 188–201]. However, the studies of sibling VUR are limited by varying primary outcomes and the extent of radiological investigations. The prevalence of high-grade VUR (grades 3–5) in siblings of index VUR varied based on screening methodology and the age at which screening was performed. High-grade VUR was present in 20–60% of siblings younger than 3 years [185, 188, 193, 202, 203]. We found that ~ 20% of siblings of index cases of VUR also had kidney scars [187, 199, 201, 203–211]. Kidney scars in siblings were associated with a history of UTI [185, 212]. The prevalence of chronic kidney disease associated with sibling VUR is reported to be low [184, 186]. There is no evidence-based consensus on the indications to perform imaging studies in siblings of VUR patients. Based on existing studies, the guideline panel suggests that all siblings of children with primary VUR should be screened for a history of UTI. If there is a history of UTI, further imaging (ultrasound, MCU and DMSA) should be performed according to the guidelines for children with UTI. We suggest screening young siblings (< 3 years) with ultrasound of the kidneys. Those with abnormalities on ultrasound may undergo MCU to confirm VUR. Siblings diagnosed with VUR should be managed as per guidelines for index patients.

Syndromic VUR and VUR associated with CAKUT

There is no evidence to suggest that the management of syndromic VUR is different from primary non-syndromic VUR. However, patients with VUR should be investigated carefully for other lower urinary tract abnormalities. Anomalies like ureterocoele and associated vesicoureteric junction obstruction or secondary VUR may require surgical correction [213], whereas VUR associated with duplex kidneys can be managed without surgery [214, 215].

Transfer of care

Patients with reflux nephropathy should be transferred to adult nephrology care as they achieve adulthood. The transition process to the adult unit needs coordination between pediatric and adult nephrologists. A consensus statement on the transition of care to adult units has been provided, endorsed by the International Society of Nephrology and the International Pediatric Nephrology Association [216]. A survey found that the transition process to the adult unit would be better if the process were initiated earlier during adolescence [217].

Glossary of terms

Acute pyelonephritis	Bacterial infection involving the upper urinary tract (kidney parenchyma)
Bacteriuria	Presence of one or more bacteria per oil immersion field in a freshly voided uncentrifuged sample
Cystitis or lower UTI	Bacterial infection localizing to the bladder
Febrile urinary tract infection	Fever (temperature ≥ 38 °C) with a positive urine culture defined by presence of significant colony count of a single uropathogen
High-grade vesicoureteric reflux	Grade 3 to 5 vesicoureteric reflux on micturating cystourethrography
Kidney scarring	Acquired kidney damage due to acute pyelonephritis
Leukocyturia	Presence of ≥ 10 leukocytes per mm^3 in a fresh uncentrifuged sample, or > 5 leukocytes per high power field in a centrifuged sample
Low-grade vesicoureteric reflux	Grade 1 and 2 vesicoureteric reflux on micturating cystourethrography
Primary vesicoureteric reflux	The passage of urine from the bladder back into a ureter and kidney in the absence of obstructive uropathy and neurogenic bladder dysfunction
Recurrent urinary tract infection	Two episodes of urinary tract infection during any time period in childhood
Reflux nephropathy	Abnormalities in the renal cortex associated with primary VUR

	(congenital dysplasia or acquired scarring)
Renal dysplasia	Congenital abnormalities in the renal cortex due to abnormal metanephric differentiation

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Declarations

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