DIAGNOSIS AND TREATMENT OF URINARY TRACT INFECTION IN CHILDREN: LONG TERM MANAGEMENT – RECURRENT URINARY TRACT INFECTION AND VESICOURETIC REFUX

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Scope of Guidelines

Specialist assessment and management is required for children who are considered at high risk of serious illness (underlying structural urinary tract abnormalities or neurogenic bladder or kidney transplant recipients). These children are beyond the scope of these guidelines and it is important that they are excluded from the recommendations detailed below.

GUIDELINES

Antibiotic prophylaxis

a. We do not recommend the routine use of prophylactic antibiotics for children after a first urinary tract infection (UTI). (1A)

b. We suggest that antibiotic prophylaxis be considered in young infants with a severe index UTI and for children with recurrent UTI and/or Grades III-V vesicoureteric reflux (VUR). (2B)

Surgical interventions for recurrent UTI

c. We do not recommend routine circumcision for boys after a first UTI. (1B)

d. We suggest that circumcision be considered for boys with recurrent UTI or high grade VUR. (2C)

e. We do not recommend surgical interventions to correct vesicoureteric reflux as a means of preventing UTI. (1C)

Alternative therapies

f. We suggest that Cranberry concentrate not be used for the prevention of UTI. (2C)

UNGRADED SUGGESTIONS FOR CLINICAL CARE

Antibiotic Prophylaxis

a. Some children at high risk of morbidity relating to further UTI may benefit from the use of prophylactic antibiotics. (ungraded)

b. There is no data that determines the appropriate duration of antibiotic prophylaxis. Most studies have administered prophylaxis for 6 months to 2 years. (ungraded).
c. For those children offered prophylaxis, based on results of the PRIVENT and RIVUR trials [1, 2], the following dose and duration is considered appropriate (ungraded)
   - 6 months of cotrimoxazole at a dose of 2mg of trimethoprim plus 10 mg of sulphamethoxazole per kilogram of body weight per day; or
   - 0.25mL of suspension [containing 40 mg of trimethoprim and 200 mg of sulphamethoxazole per 5mL] per kilogram to the nearest 0.5mL.

**Surgical interventions for recurrent UTI**

   d. Surgical interventions to correct vesicoureteric reflux can correct the anatomical abnormality but there are too few robust data to support this intervention as a preventative for repeat UTI (ungraded).

**Alternative therapies**

   e. Probiotics, Vitamin A, nasturtium and horseradish, methenamine hippurate and UroVaxom have no well demonstrated efficacy in prevention of recurrent UTI (ungraded).

   f. Avoidance of constipation, increasing fluid intake, avoiding bubble baths and improving cleaning methods after bowel motions are harmless and possibly beneficial for preventing UTI (ungraded).

**IMPLEMENTATION AND AUDIT**

Units should consider an audit of current practices of assessment and treatment of children with symptoms of UTI that includes a review of patient outcomes and alignment of current procedures with the guideline recommendations. Following audit and review, key areas for focus of an implementation strategy should be identified and a site specific plan developed.

**BACKGROUND**

Urinary tract infection in children is common, about 6% of girls and 2% of boys will experience an episode before their 7th birthday [3]. Having had one infection the child is at a 13 - 21% risk of having another UTI [4-6]. UTI causes pain, discomfort and irritability to the child, and anxiety, stress and inconvenience to the family. Preventing further infections would be considered beneficial from a family’s perspective and may also protect the child’s kidneys from damage.

For many years long term, low dose antibiotics were given to children at risk of recurrent infection under the assumption this treatment would prevent further UTI. Little evidence existed to support the practice and systematic reviews published in 2000 and 2001 [7, 8] highlighted the poor quality and insufficient evidence to justify this practice. A number of larger, better designed trials were commenced and the most recent systematic reviews [9, 10] that included these show a small benefit of low dose antibiotics. The small benefit (6-13 % absolute risk reduction [1, 2]) and considerably increased rate of antibiotic resistance (risk ratio 2.42) to the prophylactic drug suggests this treatment might best be reserved for those children at most risk of recurrent UTI.

Studies of children with UTI [4, 6] have shown that those with vesicoureteric reflux are at increased risk of repeat infection. Interventions that focus on this abnormality include open and laparoscopic surgery to reimplant the ureter in an attempt to prevent the backward flow of urine toward the kidney. Later techniques include injecting a bulking agent to prevent backward flow of urine. To date, evidence that stopping reflux by correction of the anatomical abnormality prevents morbidity from UTI and prevents kidney damage or hypertension is unconvincing. Such invasive treatment should be considered only for those with recurring symptomatic infections unimproved by other preventative treatment.

Complementary therapies such as cranberry products, probiotics, methenamine hippurate, nasturtium and horseradish along with immune-active bacterial fractions have been trialled for the purpose of preventing recurrent UTI to some extent. These have been conducted primarily in adults and generally demonstrate a benefit however rigour and power in study design are usually lacking.
Practitioners working with children with UTI, often recommend treating constipation, increasing fluid intake, avoiding bubble baths, hygiene issues and addressing dysfunctional voiding patterns to prevent further UTI. Trials to explore the efficacy of these interventions are absent, but given the harmless nature and possible benefits of these options, parents may appreciate awareness of them [11, 12].

**SEARCH STRATEGY**

**Databases searched** MeSH terms and text words for UTI, bacteriuria, bacterial infection, pyuria, or pyelonephritis with MeSH terms and text words for recurrent infection, anti-bacterial-agents, antibiotic prophylaxis, complementary therapies, cranberry, vitamin A, hippurates, nasturtium, horseradish or probiotics combined with MeSH terms and text words for paediatric populations. The search was carried out in Medline. The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

**Date of search/es:** 1950 to 15 August 2014.

**WHAT IS THE EVIDENCE?**

Thirteen systematic reviews of trials of interventions to prevent recurrent UTI have been published, most of the reviews group the trials based on a specific intervention, while several group together trials based on presence of vesicoureteric reflux [8-10, 13-21]. Table 1 details the individual reviews and primary studies of trials where reviews are absent. The two updated Cochrane reviews contain the largest number and most recent trials. A large and well-designed study, RIVUR [2] was published after completion of the searches for this guideline, with findings very similar to PRIVENT and is not yet included in a systematic review. Six reviews include trials that compare antibiotic prophylaxis with placebo or no treatment. Early reviews conclude an absence of evidence to support use of antibiotics, however inclusion of larger, better designed trials demonstrate a consistent, small benefit in antibiotic prophylaxis. Adding RIVUR data to the complete data set gives a risk ratio 0.72 (95%CI: 0.52 to 0.99) and limiting to the high quality trials; risk ratio 0.61 (95%CI: 0.48 to 0.78). The benefit is similar when data are limited to children with vesicoureteric reflux, risk ratio; 0.62 (95%CI: 0.42 to 0.91). The pooled data for antibiotic resistance on repeat infection gives a risk ratio of 2.42 (95%CI: 1.43 to 4.07).

One systematic review [9] summarises the evidence for surgical intervention for VUR. Three trials compared antibiotics alone with antibiotics plus surgical correction for the outcome of repeat symptomatic UTI. Two trials reported this outcome at 1-2 years, with opposite results and a non-significant summary point estimate. The International reflux trial, with European and American arms, reported repeat symptomatic UTI at 5 and 10 years with point estimates favouring surgery plus antibiotics but this was significant only for febrile UTIs. At 5 years the relative risk of febrile UTI was 0.43 (95%CI: 0.27 to 0.70) and 10 years 0.54 (95%CI: 0.32 to 0.92). This translates to eight children undergoing combined surgical and antibiotic treatment to prevent one additional child developing febrile UTI by five years with no benefit in prevention of renal parenchymal abnormality. Numerous case series also exist, most of which demonstrate that the intervention generally resolves the physical abnormality but little more can be concluded from this type of study design [15, 22-32].

A Cochrane review of RCTs of medical circumcision performed at time of birth or first 4 weeks versus no circumcision, failed to identify any trials [33]. A systematic review of randomised trials and observational studies of circumcision shows that circumcision reduces the risk of UTI but 111 boys would need to undergo surgery to prevent a single UTI [20]. Authors conclude that boys with a high risk of UTI, that is those with high grade vesicoureteric reflux or a past history of recurrent UTI, could be considered for circumcision with the benefit likely to outweigh the harm.

A systematic review of trials of cranberry products showed some evidence that cranberry juice decreases the number of symptomatic UTIs in women with recurrent UTI but it's effectiveness in other groups is less certain [16]. Two paediatric trials have been published; one small trial in girls with normal renal tracts demonstrated a reduced rate of UTI in those taking cranberry and the second in children with vesicoureteric reflux grades I – IV showed no difference in numbers of UTIs between those taking cranberry compared to antibiotics cefaclor. Both paediatric trials were small and sub-optimally designed and results should be interpreted with caution.
A systematic review of methenamine hippurate showed some benefit in preventing UTI in adults without renal tract abnormalities but no trials in children were included [17].

A trial of Nasturtium and Horseradish in adults with recurrent UTI showed no difference between treated and placebo groups [34].

A meta-analysis of 5 trials of immune-active E.coli fractions (Uro-vaxom) demonstrated effectiveness but no children were included, studies were small and study designs caused bias [13].

A trial of probiotic treatment (Lactobacillus acidophilus) in children with vesicoureteric reflux who had taken antibiotic prophylaxis for 1 year showed no difference in recurrence of UTI in children taking Lactobacillus compared to those taking cotrimoxazole [35]. Similarly a trial of probiotic treatment (Lactobacillus acidophilus) versus placebo in new born infants with gestational age <33 weeks or birth weight less <1500g admitted to neonatal intensive care units showed no difference in the incidence of UTI [36].

Refer to Table 1 for a summary of key studies described above.

**SUMMARY OF THE EVIDENCE**

There is a small benefit in low dose antibiotics for preventing further urinary tract infection in children, but the benefit should be weighed by harms such as increased bacterial resistance to the prophylactic drug. Cranberry product may be helpful if tolerated. Circumcision may be warranted in boys with high grade vesicoureteric reflux or recurrent UTI.

**WHAT DO THE OTHER GUIDELINES SAY?**

**European Association of Urology. Guidelines on urological infections** (April 2010) [37].
If there is an increased risk of pyelonephritis, e.g. VUR, and recurrent UTI, low-dose antibiotic prophylaxis is recommended. It may also be used after an acute episode of UTI until the diagnostic work-up is completed. The most effective antimicrobial agents are: nitrofurantoin, TMP, cephalaxin and cefaclor (Evidence basis for these is rather obscure, no trials and none of the systematic reviews)

**National Institute for Health and Clinical Excellence. Urinary tract infection in children.** (August 2007) [38]
Antibiotic prophylaxis should not be routinely recommended in infants and children following first time UTI. Antibiotic prophylaxis may be considered in infants and children with recurrent UTI. Surgical management of VUR is not routinely recommended (good evidence base, a little out of date now with new trials being published since this guideline)

Antibiotic prophylaxis is recommended under the following circumstances:
1. Following treatment of: (i) the first UTI in all children below 2 years of age, and (ii) complicated UTI in children below 5 years old, while awaiting imaging studies.
2. Children with VUR.
3. Patients showing renal scars following a UTI even if reflux is not demonstrated. Prophylaxis may be stopped if a radionuclide cystogram or MCU repeated 6 months later is normal.
4. Children with frequent febrile UTI (3 or more episodes in a year) even if the urinary tract is normal. (Evidence base for this guideline is obscure, no references to trials or systematic reviews, no references in this section at all)

**American Academy of Pediatrics. Urinary tract infection: Clinical Practice guideline for the Diagnosis and Management of the initial UTI in febrile infants and children 2 to 24 months.** [40]
4. Although the effectiveness of antimicrobial prophylaxis for the prevention of UTI has not been demonstrated, the concept has biological plausibility. Virtually all antimicrobial agents used to treat or to prevent infections of the urinary tract are excreted in the urine in high concentrations. Barriers to the
Effectiveness of antimicrobial prophylaxis are adherence to a daily regimen, adverse effects associated with the various agents, and the potential for emergence of antimicrobial resistance. To overcome these issues, evidence of effectiveness with a well-tolerated, safe product would be required, and parents would need sufficient education to understand the value and importance of adherence. A urinary antiseptic, rather than an antimicrobial agent, would be particularly desirable, because it could be taken indefinitely without concern that bacteria would develop resistance. Another possible strategy might be the use of probiotics.


The child with VUR less than one year of age

Recommendation: Continuous antibiotic prophylaxis is recommended for the child less than one year of age with VUR with a history of a febrile urinary tract infection. This approach is based on the greater morbidity from recurrent urinary tract infections found in this population.
[Based on review of the data and Panel consensus]

Recommendation: In the absence of a history of febrile urinary tract infections, continuous antibiotic prophylaxis is recommended for the child less than one year of age with VUR grades III–V who is identified through screening.
[Based on review of the data and Panel consensus]

Option: In the absence of a history of febrile urinary tract infections, the child less than one year of age with VUR grades I–II who is identified through screening may be offered continuous antibiotic prophylaxis.
[Based on review of the data and Panel consensus]

Option: Circumcision of the infant male with VUR may be considered based on an increased risk of urinary tract infections in boys who are not circumcised compared to those who are circumcised. Although there are insufficient data to evaluate the degree of this increased risk and its duration, parents need to be made aware of this association to permit informed decision-making.
[Based on review of the data and Panel consensus]

The child with UTI and VUR more than one year of age

Recommendation: If clinical evidence of bladder/bowel dysfunction is present (see “Initial evaluation of the child with VUR” above) treatment of bladder/bowel dysfunction is indicated, preferably before any surgical intervention for VUR is undertaken.

There are insufficient data to recommend a specific treatment regimen for bladder/bowel dysfunction, but possible treatment options include behavioural therapy (see Glossary for description), biofeedback (appropriate for children more than age five), anticholinergic medications, alpha blockers, and treatment of constipation. Monitoring the response to bladder/bowel dysfunction treatment is recommended to determine whether treatment should be maintained or modified.
[Based on Panel consensus]

Recommendation: Continuous antibiotic prophylaxis is recommended for the child with bladder/bowel dysfunction and VUR due to the increased risk of urinary tract infection while bladder/bowel dysfunction is present and being treated (Table 1).
[Based on review of the data and Panel consensus]

Option: Continuous antibiotic prophylaxis may be considered for the child over one year of age with a history of urinary tract infections and VUR in the absence of bladder/bowel dysfunction (Table 1).
[Based on review of the data and Panel consensus]

Option: Observational management without continuous antibiotic prophylaxis, with prompt initiation of antibiotic therapy for urinary tract infections, may be considered for the child with VUR in the absence of bladder/bowel dysfunction, recurrent febrile urinary tract infections, or renal cortical abnormalities
(Table 1). While this approach is currently under investigation and therefore no firm recommendation can be made, preliminary data suggest that some groups of patients with VUR may do as well with this approach as with continuous antibiotic prophylaxis.

[Based on review of the data and Panel consensus]

**Kidney Disease Outcomes Quality Initiative**: No recommendation.

**UK Renal Association**: No recommendation.

**Canadian Society of Nephrology**: No recommendation.

**European Best Practice Guidelines**: No recommendation.

**International Guidelines**: No recommendation.

**SUGGESTIONS FOR FUTURE RESEARCH**

A large well designed randomised controlled trial of cranberry product in children who have experienced at least 2 UTIs.

**CONFLICT OF INTEREST**

Gabrielle Williams and Ian Hewitt have no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.

**REFERENCES**


APPENDICES

Table 1. Summary of included studies

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<th>Participants and Interventions</th>
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<tr>
<td><strong>Antibiotic treatment</strong></td>
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| Williams and Craig (2011)[10] | 12 studies. 1557 children | Systematic review of RCTs | Children < 18 years at risk of recurrent UTI. Studies were excluded if <50% of the participants had a predisposing cause such as renal tract abnormality. Interventions of long-term antibiotic use: 1. Antibiotic vs. placebo/no treatment 2. Comparison of two or more antibiotics | 10 weeks-12 months | Treatment vs. placebo/no treatment risk of symptomatic repeat UTI  
  • All studies (n=6) RR 0.75 (95%CI: 0.36, 1.53) [Control rate for recurrent UTI approximately 18%]  
  • Studies with low risk of bias (n= 2) RR 0.68 (95%CI: 0.48, 0.95)  
  • Children with VUR RR 0.65 (95%CI: 0.39, 1.07)  
  • Children without VUR RR 0.56 (95%CI: 0.15, 2.12)  
  Microbial resistance:  
  • Resistance to active treatment (n=2) RR 2.40 (95%CI: 0.62, 9.26)  
  Adverse events reported in 2 studies with inconsistent results. Limitations:  
  • Only 2 studies with low risk of bias. Smaller older studies gave highly variable and inconsistent results.  
  • Data suggests increased risk of symptomatic UTI caused by bacteria resistant to prophylactic agent however, this is not quantifiable.  
  • Limited and inconsistent data on adverse effects.  
  • Unable to evaluate selection bias.  
  • Variable definition for diagnosis of recurrent UTI. |
| Nagler et al (2011)[9]     | 22 studies. 2324 children | Antibiotic prophylaxis: 8 studies. 1039 children. Surgical or endoscopic correction of VUR. 10 studies 1141 | Males and females of any age with primary VUR diagnosed by VCUG with or without UTI. Excluded patients with VUR associated with urological abnormalities or kidney transplants. Interventions include all treatments of VUR including antibiotics, surgery, and non invasive techniques. | 1 month to 3 years | Long-term low dose antibiotic prophylaxis:  
  • Risk of repeat symptomatic UTI RR 0.68 (95%CI: 0.39, 1.17)  
  • Risk of febrile UTI RR 0.77 (95%CI 0.47, 1.24)  
  • Risk of bacterial drug resistance RR 2.94 (95%CI 1.39, 6.25)  
  • Risk of new or progressive renal damage RR 0.35 (95%CI 0.15, 0.80)  
  Long-term low dose antibiotic prophylaxis compared with surgical or endoscopic correction of VUR plus antibiotics:  
  • Risk of repeat symptomatic UTI not significantly different at any time point.  
  • Combined surgical and antibiotic treatment and risk of febrile UTI by 5 years - RR 0.43 (95%CI 0.27, 0.70) Limitations:  
  • Heterogeneity.  
  • Only 1 trial was adequately blinded. |
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  - All children RR 0.73 (95%CI 0.56, 0.95)  
  - Children with VUR RR 0.82 (95%CI 0.62, 1.08)  
  - Children without VUR RR 0.72 (95%CI 0.43, 1.20)  
Risk of adverse events including antibiotic resistance limited data and inconsistent results.  
Limitations:  
  - Variable definition of UTI.  
  - Limited trials with low risk of bias.  
  - Limited and inconsistent data on adverse effects.  
  - Limited methodological detail provided for systematic review. |
  - All children RR 0.83 (95%CI 0.66, 1.05)  
  - Children with VUR RR 0.94 (95%CI 0.70, 1.27)  
  - Children without VUR RR 0.76 (95%CI 0.45, 1.30)  
  - Trials with adequate allocation concealment RR 0.68 (95%CI 0.48, 0.95)  
Rate of new or deteriorated renal scars.  
  - All children (n=3) RR 0.95 (95%CI 0.51, 1.78)  
Limitations:  
  - Not able to evaluate effects of age and gender.  
  - Collection of urine samples poorly defined.  
  - Methodological limitations for most studies. |
  - All children RR 0.96 (95%CI 0.69, 1.32)  
Rate of new or deteriorated renal scars.  
  - All children (n=4) RR 1.15 (95%CI 0.75, 1.78)  
Limitations:  
  - No evaluation/discussion of impact of methodological quality on meta analysis.  
  - Limited study data presented or evaluated. |
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<tr>
<td>Le Saux et al (2000) [8]</td>
<td>265 children.</td>
<td>Systematic review of RCTs</td>
<td>Children with previous UTI including all abnormalities including neurogenic bladder. Excluded studies where urinary tract abnormality could not be characterised. Intervention: Antibiotic prophylaxis of at least 3 months duration vs. placebo or no treatment.</td>
<td>At least 3 months</td>
<td>No definitive conclusions made due to paucity of data and poor quality of trials. Limitations: • All studies of low quality and small size. • All studies of cross-over design.</td>
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<td>RIVUR Investigators 2014 [2]</td>
<td>607 children with VUR</td>
<td>RCT</td>
<td>Children 2-21 months of age with grade I - IV VUR, without urologic anomalies. Intervention: Antibiotic prophylaxis or placebo for 2 years</td>
<td>2 years</td>
<td>Relative risk 0.55 (95%CI 0.38 to 0.78) for repeat symptomatic UTI. Greater effect in children whose index UTI was febrile; hazard ratio; 0.5 (95% CI 0.34 to 0.74) and children with bowel and bladder dysfunction; hazard ratio 0.21 (95% CI 0.08 to 0.58).</td>
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<td>Nagler et al (2011) [9]</td>
<td>250</td>
<td>Retrospective review of consecutive cases. Single centre US.</td>
<td>Children (mean age 63 months) treated for primary unilateral VUR by open reimplantation surgery. Excluded children with significant comorbidity or additional concomitant procedures requiring admission.</td>
<td>1 month post operative.</td>
<td>Short complications occurred in 9 (3.6%). Three (1.2%) required postoperative hospital admission. Febrile UTI occurred in 8 (3.2%), 6 with persistent ipsilateral VUR. Limitations: • Retrospective case series from a single centre. • Limited patient data presented.</td>
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<td>Elmore et al (2008) [30]</td>
<td>69 open surgery, 40 Dx/HA implantation.</td>
<td>Retrospective review of records of consecutive cases. Single centre US.</td>
<td>Consecutive patients with history of febrile UTI and Grade II to IV VUR treated with either open surgery or Dx/HA implantation. Excluded: patients who were not cured of VUR, incomplete data; complicating factors, symptoms suggestive of voiding dysfunction.</td>
<td>3.2-4.4 years</td>
<td>Mean age 3.7 years (range 7 months to 12 years). Risk of recurrent UTI in open surgery compared to Dx/HA: • RR 2.53 (95%CI 1.06, 6.05) (rate in open surgery 38% of patients) Risk of recurrent UTI in open surgery compared to Dx/HA: • RR 4.83 (95%CI 1.08, 21.57) (rate in open surgery 24%) Limitations: • Single centre retrospective review. • Excluded those not cured by treatment. • Limited patient data presented. • Treatment selection bias likely.</td>
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<tr>
<td>Oberson et al</td>
<td>130</td>
<td>Retrospective</td>
<td>Consecutive patients with VUR</td>
<td>50 months</td>
<td>Risk of recurrent UTI in open surgery compared to SCIN:</td>
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<tr>
<td>Study ID</td>
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| (2007) [31]              | 56                 | endoscopic treatment (SCIN) 74 open surgery                   | treated by SCIN or Cohen implantation. No exclusions noted.                                     | (average) | • RR 0.86 (95%CI 0.47, 1.05) (rate in open surgery 23% of patients) Reflux after 6 months in open surgery compared to SCIN  
• RR 0.11 (95%CI 0.04, 0.36) (rate in open surgery 4% of patients)  
Limitations:  
• Single centre retrospective review.  
• Limited patient data presented.  
• Treatment selection bias likely.                                                                 |
| Venhola et al (2006) [21] | 3 RCTs (525 children) 2 Observation al (143 children) | Systematic review of RCTs and observational studies. | Children (1-18 years) with VUR. Included at least one treatment group with data on recurrence of UTI. Interventions: Surgery compared to conservative treatment | 36-60 months. | Risk of recurrent UTI in surgery compared to conservative treatment:  
• RR 0.90 (95%CI 0.72, 1.14) (rate in conservative treatment 38%)  
VUR disappearance in surgery compared to conservative treatment:  
• RR 0.09 (95%CI 0.06, 0.14) (rate in conservative treatment 67%)  
Limitations:  
• No assessment of reporting quality/risk of bias.  
• Limited descriptions of characteristics of included studies. No description of diagnosis of UTI.  
• Unclear description of literature search.                                                                 |
| Endoscopic subureteric injection |                     | See entry under antibiotic treatment.                                                                 |                                                                                             |           |                                                                                                                                                    |
| Nagler et al (2011) [9]  |                    | Systematic review of RCTs and prospective studies.             | Inclusion criteria are not stated. Articles sought related to endoscopic therapy of reflux.    | Not stated | Averaged post-operative UTI reported as 6.01 % (95% CI 3.0, 10.7)  
Limitations:  
• Limited descriptions of included studies.  
• No data tabulated.  
• Combination of prospective and retrospective studies.                                                                 |
• Recurrent UTI after treatment occurred in 52 (53%)  
• Reflux nephropathy occurred in 37 (37%).  
Limitations:  
• Single centre retrospective review.                                                                 |
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|           |            |                          | centre (US)                                                                                   | (median 40) | • Recurrent UTI after treatment occurred in 12 (27%)  
VUR after treatment occurred 10 (22%).  
Limitations:  
• Single centre retrospective review.  |
• Recurrent UTI after treatment occurred in 40 (24%)  
VUR after treatment occurred 7 (4%).  
Limitations:  
• Single centre retrospective review.  
• Reliance on parental recall.  |
| Stenberg et al (2007) [28] | 179       | Retrospective analysis using questionnaire. Single centre (Sweden)                           | Children with VUR treated with subureteric NASHA/DX gel.                                     | 7-12 years | Of the 179 children treated subureteric NASHA/DX gel:  
• Recurrent non-febrile UTI after treatment occurred in 39 (22%)  
• Recurrent febrile UTI after treatment occurred in 6 (3%).  
• No data on recurrent VUR.  
Limitations:  
• Single centre retrospective review.  
• Reliance on patient/parental recall.  
• Loss to follow-up 22%.  |
| Wadie et al (2007) [29] | 100       | Prospective case series. Single centre (Sweden)                                               | Children with VUR treated with subureteric Deflux.                                           | Mean 15 months (sd 0.7) | Of the 100 children treated subureteric NASHA/DX gel:  
• Recurrent UTI after treatment occurred in 13 (13%)  
VUR after treatment occurred in 6 (6%).  
Limitations:  
• Single centre.  
• Short follow-up period.  |
| Elder et al (2007) [24] | 152 (114 antibiotics, 38 Dx/HA) | Retrospective review of medical records database. Multi-centre (US)                          | Children with 2 reported cases of VUR (excluding those with bladder abnormalities) and treated with either antibiotics or endoscopic injection (those treated with both excluded). | 12 months | Of the 30 children treated subureteric Dx/HA:  
• Recurrent UTI after treatment occurred in 3 (8%)  
Of the 114 children treated with antibiotics:  
• Recurrent UTI after treatment occurred in 17 (15%).  
P=0.1 for difference between treatments.  
Limitations:  
• Retrospective review of database.  
• Short follow-up.  |
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| Puri et al (2007) [26]    | 276| Prospective case series. Single centre (Ireland) | Infants with VUR treated with subureteric Dx/HA.                                             | Not stated | Of the 276 children treated subureteric Dx/HA:  
  - Recurrent UTI after treatment occurred in 3 (92%)  
  - VUR after treatment occurred in 1 (0.4%)  
  Limitations:  
  - Single centre retrospective review.  
  - Unknown follow-up |
| Capozza et al (2007) [22] | 1732| Retrospective review over 20 years. Single centre (Italy) | Children and adults (<22 years) with VUR treated with endoscopic Teflon, cross-linked bovine collagen, or Dx/HA injection. | Not stated | No UTI or DMSA data reported.  
Over all success rate 79% of ureters (Grade II: 91%, Grade III, 78%, Grades IV-V: 62%).  
Limitations:  
- Single centre retrospective review.  
- Limited data reported |
Medical circumcision performed at time of birth or first 4 weeks vs. no circumcision.  
Primary outcome – occurrence of UTI | No trials identified. |
Circumcision vs. no circumcision  
Outcome: Diagnosis of UTI | NA | Association between circumcision and UTI:  
- RCT – OR 0.13 (95%CI: 0.01, 2.63)  
- Cohort studies OR 0.13 (95%CI: 0.07, 0.24)  
- Case-control studies OR 0.13 (95%CI: 0.07, 0.23)  
- All studies OR 0.13 (95%CI: 0.08, 0.20)  
- Number needed to treat to prevent 1 UTI:  
  - boys with normal risk of UTI – 111  
  - boys with past UTI – 11  
  - boys with high grade VUR - 4  
Limitations:  
- Based predominantly on observational studies.  
- Majority of studies reported episodes of UTI rather than number of patients. |
### Alternative Therapies

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<tr>
<th>Study ID</th>
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</table>
  - Cranberry compared to placebo or no treatment:  
    - RR: 0.48 (95% CI: 0.19, 1.22) – 2 studies  
  - Cranberry compared to antibiotics:  
    - RR: 0.69 (95% CI: 0.32 to 1.51) – 1 study  
  All groups at risk of UTI  
  - Cranberry compared to placebo or no treatment:  
    - RR: 0.86 (95% CI: 0.71, 1.04)  
Limitations:  
- Small sample size and frequency of events for children.  
- Moderate unexplained heterogeneity.  
- High attrition and limited studies undertaking intention-to-treat analysis. |
| Bauer et al (2002) [19] | 5 studies (601 women) | Meta-analysis | Adult women with UTI. Uro-Vaxom vs. placebo. | All 5 studies show the Uro-Vaxom treated group to have significantly lower recurrent UTI than the placebo group. | Limitations:  
- No details of review strategy, unclear whether it is a systematic review.  
- No trials in children.  
- Limited data provided in meta-analysis. For example, recurrent UTI rate not stated or able to be calculated.  
- Risk ratios or equivalent not provided. |
| Lee et al (2012) [17] | 13 studies (2032 participants); | Systematic review of RCTs | All populations at risk of UTI. Methenamine hippurate vs. placebo or no treatment. Outcomes: Symptomatic UTI, quantitative urine culture, adverse reactions. | Symptomatic UTI in patients with no renal tract abnormality:  
  - RR 0.24 (95% CI: 0.07, 0.89)  
Symptomatic UTI in patients with renal tract abnormality:  
  - RR 1.54 (95% CI: 0.38, 6.20)  
Symptomatic UTI in patients with no renal tract abnormality with <1 week treatment:  
  - RR 0.14 (95% CI: 0.05, 0.38)  
Limitations:  
- High degree of heterogeneity.  
- No studies in children. |
| Albrecht et al (2007) [34] | 219 (enrolled) 174 (ITT) | RCT – double blind placebo controlled. | Adults with a medical history of at least 3 recurrent UTIs at least 2 in 6 months | Mean UTI relapses per patient between 7 days and 6 months:  
  - Mean difference -0.34 (95% CI: -0.70, 0.02). [Control mean 0.77 UTI relapses per patient.] |
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<tr>
<td>Lee et al (2007) [35]</td>
<td>120</td>
<td>RCT. Single centre (South Korea)</td>
<td>Children with persistent primary VUR after antibiotic prophylaxis for 1 year. Probiotic prophylaxis (Lactobacillus acidophilus) vs. antibiotics prophylaxis. Outcome: recurrent UTI.</td>
<td>Not stated – possibly up to 2 years</td>
<td>Incidence of recurrent UTI in second year of follow-up; • RR 0.85 (95%CI: 0.41, 1.74) [Control rate 22%] Limitations: • Blinding and randomisation unclear. • Low power due to lower recruitment numbers than anticipated. • No treatment arm. • Unclear if designed as a non-inferiority trial.</td>
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<td>Danis et al (2002) [36]</td>
<td>585</td>
<td>RCT – double blind. Multi-centre (Italy)</td>
<td>New-born infants with gestational age &lt;33 weeks or birth weight &lt;1500 g admitted to NICUs. Probiotic (Lactobacillus acidophilus) in standard milk vs. placebo in standard milk. Primary outcome: reduction in necrotizing enterocolitis (NEC)</td>
<td>Not stated</td>
<td>Incidence of UTI; • RR 0.66 (95%CI: 0.30, 1.43) [Control rate 5.2%] Limitations: • UTI is a secondary outcome. • Limited to new born infants admitted to NICU.</td>
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<tr>
<td>Rudaitis et al (2009) [12]</td>
<td>148</td>
<td>Prospective case-control. Single centre (US)</td>
<td>Girls treated for cystitis (bacterial) and pyelonephritis. Excluded malformations, immunosuppression and pregnant girls. Case: Girls treated because of recurrent UTI. Control: Girls with non-recurrent UTI</td>
<td>Not stated</td>
<td>Recurrent UTI (case group) 104 (70%). Non-recurrent UTI (control group) 44 (30%). Independent risk factors for recurrent UTI by logistic regression: • Age ≤6.5 years at first UTI OR 0.9 (95%CI: 0.85, 0.96) • Abnormal voiding frequency OR 5.3 (95%CI: 1.1, 26.2) • Voiding postponement OR 3.8 (95%CI: 1.4, 10.1) • Poor fluid intake OR 9.2 (95%CI: 2.5, 33.6) • Residual urine &gt;20ml OR 1.1 (95%CI: 1.0, 1.1)</td>
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</table>
  - Single centre case-control study.  
  - Control group selected by omission from case group rather than by matching.  
  No trials identified on prevention of UTI. No UTI outcomes reported in bubble bath studies.  
  Limitations  
  - Limited methodological detail provided on review.  
  - Only observational studies identified by search.  
  - No studies include UTI as an outcome.  
  - Mixed adult and children. |