Preventing Urinary Tract Infections in Early Childhood

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Abstract

Urinary tract infection (UTI) is common in children, causes them considerable discomfort, as well as distress to parents and has a tendency to recur. Approximately 20 % of those children who experience one infection will have a repeat episode. Since 1975, 11 trials of long-term antibiotics compared with placebo or no treatment in 1,550 children have been published. Results have been heterogeneous, but the largest trial demonstrated a small reduction (6 % absolute risk reduction, risk ratio 0.65) in the risk of repeat symptomatic UTI over 12 months of treatment. This effect was consistent across sub groups of children based upon age, gender, vesicoureteric reflux status and number of prior infections. Trials involving re-implantation surgery (and antibiotics compared with antibiotics alone) for the sub-group of children with vesicoureteric reflux have not shown a reduction in repeat UTI, with the possible exception of a very small benefit for febrile UTI. Systematic reviews have shown that circumcision reduces the risk of repeat infection but 111 circumcisions would need to be performed to prevent one UTI in unpredisposed boys. Given the need for anaesthesia and the risk of surgical complication, net clinical benefit is probably restricted to those who are predisposed (such as those with recurrent infection). Many small trials in complementary therapies have been published and many suggest some benefit, however inclusion of children is limited. Only three trials involving 394 children for cranberry products, two trials with a total of 252 children for probiotics and one trial with 24 children for vitamin A are published. Estimates of efficacy vary

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widely and imprecision is evident. Multiple interventions to prevent UTI in children exist. Of those, long-term low dose antibiotics has the strongest evidence base, but the benefit is small. Circumcision in boys reduces the risk substantially, but should be restricted to those at risk. There is little evidence of benefit of re-implantation alone, and the benefit of this procedure over antibiotics alone is very small. Cranberry concentrate is probably effective.

18.1 Background

18.1.1 Frequency

Urinary tract infection (UTI) is a very common illness in children, affecting 2 % of boys and 8 % of girls by the age of 7 years [1]. It is also the most common serious bacterial infection in children with fever who present for assessment [2, 3] and causes an unpleasant acute illness with manifestations that include fever, lethargy, vomiting and cystitis symptoms.

18.1.2 Recurrence

Good evidence to quantify the risk of recurrence and identify factors that may predispose to repeat infections is quite scarce. Studies that follow children with UTI over time are required, and there have been only a few. Two studies of this design [4, 5] have demonstrated that about 12 % of children with first UTI experience a recurrence within one year. The placebo arm of a large, blinded trial [6] showed a recurrence rate of 19 % in 12 months, but eligibility criteria were not limited to the first infection, so this may be an over-estimate of the true risk.

18.1.3 Risk Factors for Recurrence

Some children are more at risk for future UTIs than others. Risk factors include an age less than six months at first UTI, grade III–IV vesicoureteric reflux and white race. Early observations that UTI and vesicoureteric reflux were associated with renal damage [7–9] led to the standard practice of performing voiding cystourethrography to identify reflux in children with a history of UTI [10, 11].

18.2 Antibiotic Treatment

Children with reflux were routinely given daily low-dose antibiotics for many years [12] with the aim of preventing further UTI and renal damage. Until 1997, only four trials [13–16] with 171 children and conflicting findings provided the evidence base for this treatment (Table 18.1). Since then seven trials [6, 17–22] have been published with broader criteria, including children with reflux and designs which are less prone to bias. Six of the seven trials showed a reduced risk of repeat symptomatic UTI with prophylactic antibiotics but the magnitude of the effect was small and in most studies the difference did not reach statistical significance (Fig. 18.1). In the largest ($n = 576$) and importantly the only blinded study [6], the benefit was statistically significant, and showed a 6 % absolute risk reduction for repeat symptomatic UTI in children taking trimethoprim sulphamethoxazole for 12 months. Benefits did not vary according to baseline characteristics such as age, gender and reflux status in *a priori* sub-group analysis. Five trials [6, 18, 20–22] also reported rates of bacterial resistance to the prophylactic drug and all showed substantial increases. Overall, there appears to be a small benefit from prophylactic antibiotics (6 % absolute risk reduction, or an overall number needed to treat of 16 over 1 year) but this must be weighed against the proven risk of increased bacterial resistance to antibiotic and with consideration for suggested but uncertain effects such as susceptibility to asthma and inflammatory bowel disease [23, 24].

Five trials have compared one antibiotic with another [25–29], two of which compared cotrimoxazole with nitrofurantoin [26, 29]. These two trials were small (N of 120 and 132) but both demonstrated statistically significant superiority of nitrofurantoin (risk ratios (RR) 0.57 (95 % CI

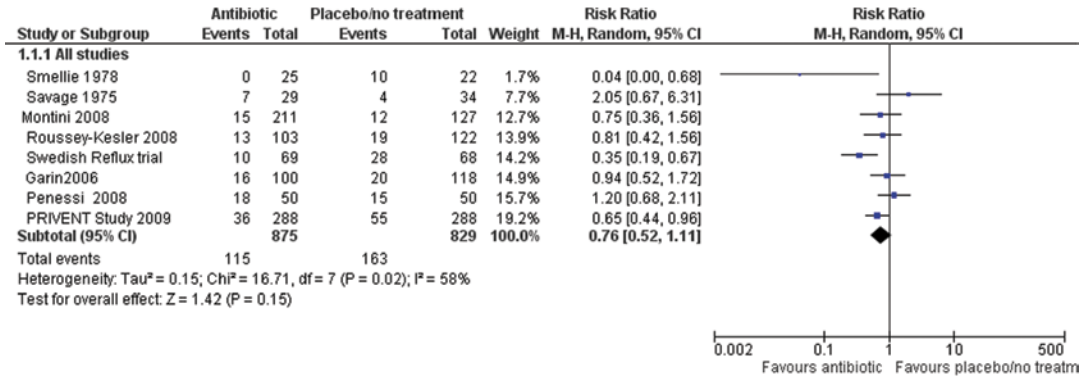

Fig. 18.1 Randomised controlled trials of antibiotic compared with placebo/no treatment for the prevention of repeat symptomatic UTI in children

0.35–0.92) and 0.32 (95 % CI 0.19–0.56)). However, one study [26] reported 30 % of patients withdrawing from the study due to side effects of nitrofurantoin suggesting the acceptability of this treatment may be poor.

18.3 Surgical Treatment

Surgical correction of the physical abnormality of reflux can involve open surgery to reimplant the ureters or endoscopic injection of agents at the vesicoureteric junction. A recent systematic review of these treatments [30] showed no convincing evidence of a reduced risk of repeat symptomatic UTI at 1–2, 4–5 or 10 years after surgery (and antibiotics) compared with antibiotics alone (1–2 years RR 0.88 (95 % CI 0.26–3.01), 5–10 years RR 0.79 (95 % CI 0.49–1.26), 10 years RR 1.06 (95 % CI 0.78–1.44)). These trials and the numerous case series found in the literature usually demonstrate a very high rate of surgical correction of reflux in treated children but without matching reduction in risk of UTI, suggesting that reflux only has a modest attributable risk for further UTI.

18.3.1 Circumcision

A systematic review of trials and observational studies of circumcision [31] to prevent UTI showed that circumcision reduces the risk of UTI but that 111 circumcisions would need to be performed to prevent one UTI in normal boys with a baseline risk of 1 %. Major complications occur in approximately 2 %. Circumcision could be considered in boys predisposed to UTI to achieve net clinical benefit, such as those with recurrent infection and/or those with high grade reflux. In this scenario the number needed to treat would be about 5–10.

18.4 Complementary Treatments

Systematic reviews and trials of complementary treatments for prevention of UTI have been conducted but most do not include a substantial number of children. A systematic review of cranberry products [32] suggests some benefit in preventing recurrent UTI in women but insufficient data were available for conclusions about efficacy in children. Since that review three trials in children have been published [33–35], two only in abstract form [34, 35], and all demonstrated apparent benefit in cranberry product use but only one reached statistical significance [33]. The smallest study ($n=51$) compared cranberry with antibiotic treatment trimethoprim and suggested that cranberry may be more effective (relative risk of 0.65 (95 % CI 0.34–1.25) while the larger, blinded study ($n=263$) gave a less favourable relative risk of 0.74 (95 % CI 0.44–1.25). Neither

Table 18.1 Randomised controlled trials for interventions to prevent urinary tract infection in children

First author	Year	Number	Participants			Intervention			Comparator	Blinded	Event rate (%)	Outcomes			Results
Low dose, antibiotic therapy compared with placebo/no treatment															
			Age (years)	N VUR	VUR grades	NF	TMP-SMZ	Other	Placebo			Symptomatic UTI	Positive culture	Abn DMSA	Risk ratio (95 % CI) symptomatic UTI, (*positive culture*)
Savage	1975	63	5–7.8	16	I–III	•	•		x	?	7/63 (11.1)	•	•		2.05 (0.67, 6.31) *0.93* (*0.74, 1.17*)
Stansfield	1975	45	0.5–14	13	NS		•		✓	✓	12/45 (26.7)		•		*0.05* (*0.00, 0.72*)
Lohr	1977	18#	3–13	0	NA	•			✓	✓	15/18 (83.3)				*0.13* (*0.04, 0.50*)
Smellie	1978	45	2–12	0	NA	•	•		x	x	11/47 (23.4)	•	•		0.04 (0.0, 0.68) *0.04* (*0.0, 0.52*)
Reddy	1997	43	NS	43	?	?	?	?	x	?	6/29 (20.7)		•	•	*0.25* (*0.03,1.85*)
Garin	2006	218	0.25–17	113	I–III	•	•		x	?	36/218 (16.5)	•	•	•	0.94 (0.52, 1.72) *0.74* (*0.43, 1.28*)
Montini	2008	338	0.08–8.4	128	I–III		•	•	x	x	27/338 (3.6)	•	•	•	0.75 (0.36, 1.56) *0.50* (*0.29, 0.86*)
Roussey-Kesler	2008	225	0.08–3	225	I–III		•		x	?	32/225 (14.2)	•	•		0.81 (0.42, 1.56) *0.67 (0.40, 1.11)*
Pennesi	2008	100	0–2.5	100	II–IV		•		x	x	33/100 (33.3)	•		•	1.20 (0.68, 2.11)
PRIVENT	2009	576	0–18	243	I–V		•		✓	✓	91/576 (15.8)	•		•	0.65 (0.44, 0.96)
Swedish Reflux Trial	2010	203	1–2	203	III–IV	•	•	•	x	x	49/203 (24.1)	•		•	0.39 (0.21 0.76)
Low dose, antibiotic A vs low dose antibiotic B															
Carlsen	1985	35#	1–13	17	I–III	•		Pivmecilliam	Alternative antibiotic	?	10/33 (30.3)		•		*0.68* (*0.28, 1.65*)
Brentstrup	1990	130	1–14	51	NS	•	•		Alternative antibiotic	✓	31/120 (25.8)		•		*0.32* (*0. 19, 0.56*)
Lettgen	2002	57	1–11	NS	NS	•		Cefixim	Alternative antibiotic	?	5/57 (8.8)	•			1.35 (0.24, 7.48)

Table 18.1 (continued)

First author	Year	Number	Participants			Intervention		Comparator	Blinded	Event rate (%)	Outcomes			Results
Belet	2004	80	0.5–15	0	NA	•	Cephadroxil/ cefprozil	Alternative antibiotic	x	12/80 (15.0)	•	•		0.69 (0.20, 2.39) *1.35* (*0.71, 2.56*) TMP_SMX vs cefprozil
														1.79 (0.33, 9.70) *5.95* (*1.46, 24.21*) TMP_SMX vs cephadroxil
														0.39 (0.09 to 1.71) *0.23* (*0.06, 0.92*) cephadroxil vs cefprozil
Falaflaki	2007	132	0.25–12	57	I–IV	• •		Alternative antibiotic	?	47/132 (35.6)	•			0.57 (0.35 to 0.92)
Alternative dose														
Baciulus	2003	33	0–16	8	?		Cefdroxil	Every vs alternate night dose	x	7/33 (21.2)		•		*1.11* (*0.29, 4.21*)
Complementary therapies														
Salo^	2010	263	NS	35	?	Cranberry juice		Placebo juice	✓	48/263 (18.3)	•			0.74 (0.44, 1.25)
Uberos^	2010	51	NS	NS	?	Cranberry syrup		Trimethoprim	✓	23/51 (45.1)	•			0.65 (0.34, 1.25) (cranberry vs trim)
Ferrara	2009	80	3–14	0	NA	Cranberry or probiotic		No treatment	x	34/80 (42.5)	•			0.28 (0.12, 0.64) cranberry vs no treatment
														0.63 (0.38, 1.07) probiotic vs no treatment
														0.44 (0.18, 1.09) cranberry vs probiotic
Lee^	2010	132	~0.08–0.8	132	?	Probiotic		TMP-SMX	?	47/128 (36.7)	•			0.81 (0.51, 1.28)
Lee	2007	120	1.08–3	120	I–V	Probiotic		TMP-SMX	?	24/120 (20.0)	•		•	0.85 (0.41 to 1.74)
Yilmaz	2007	24	>1–12	0	NA	Vitamin A (single dose)		Placebo	✓	?		•		RR not calculable, *Vit A 0.29/mo vs 0.44/mo 6–12 mo*

Cross over trial
^ Published only in abstract form

study demonstrated statistical significance. This evidence suggests cranberry products may reduce the risk of repeat UTI in children but there is considerable uncertainty. None of these trials reported adverse events, however trials in adults suggest most adverse events are minor gastrointestinal issues.

A systematic review of methenamine hippurate [36] for preventing UTI concluded that the intervention may be effective in patients without renal tract abnormalities but no children were included in the trials. No new trials have been published to help resolve the uncertainty. A blinded, randomised placebo controlled trial of herbal products *Tropaeoli majoris* and *Armoraciae rusticanae* [37] in adults showed no difference in average number of recurrences between the two groups using intention to treat analysis. Two randomised trials of probiotics compared with cotrimoxazole treatment to prevent UTI in children with vesicoureteric reflux have been published [38, 39]. Neither study demonstrated a statistically significant difference but the point estimates favoured probiotics 0.85 (95 % CI 0.41–1.74) and 0.81 (95 % CI 0.51–1.28) [36, 37]. There remains uncertainty and imprecision about the efficacy of this intervention to prevent recurrent UTI in children.

A meta-analysis of trials [40] of the immune active agent, Uro-Vaxom showed it to be an effective treatment for preventing recurring UTIs, however none of the five included trials were large or optimally designed and each included only adults. Several treatment studies in children have been published [41, 42] but without randomisation nor a comparator these are not a firm basis for decision making.

A randomised, placebo controlled trial of vitamin A to prevent recurrent UTI in children [43] showed a reduced rate of UTI in the follow-up period, but only 24 children participated so the estimate of efficacy is imprecise and there are also concerns over selection bias.

18.5 Conclusion

Good quality evidence demonstrates that low dose antibiotics reduce the risk of repeat UTI in children by approximately 6 %, and is consistent across all groups of children. Clinicians now have a clear estimate of risk reduction along with details on adverse effects with which to discuss treatment options with parents. Given the relatively small absolute benefit, clinicians and families may opt for prophylactic antibiotics when the risk of recurrence is relatively high (e.g. in those with recurrent infection) or when the potential seriousness of an additional event is very significant (e.g. in a very young infant). Circumcision reduces the risk of repeat UTI but is best limited to those at higher risk of recurrence. Complementary therapies have been explored using randomised controlled trials and usually found to be effective but study design is generally poor and studies are small, leading to potential bias and imprecision. However, most of these interventions are usually free of adverse events and parents may elect to try them. They should be reminded to be alert to further infections and seek treatment when appropriate.

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