

Reflux nephropathy

Date written: July 2005

Final submission: September 2005

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GUIDELINES

- a. **Standard surgical intervention is not superior to medical management in preventing the progression to end-stage kidney disease (ESKD) in children with severe reflux disease. (Level I evidence)**
- b. **Antibiotic prophylaxis is not superior to supportive care in preventing urinary tract infections or renal parenchymal injury in children with vesicoureteric reflux (VUR). (Level II evidence)**

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **A rationale for any intervention is only provided by the risk for adverse outcomes resulting from non-intervention. While young children with stage I or II VUR (reflux to the ureter or renal pelvis without ureteral dilatation) occasionally form new scars despite medical therapy (Arant 1992), these children are not at risk for severe renal disease and spontaneous resolution of the reflux occurs in approximately 80% in 5 years. As a consequence, there is no indication for intervention in this setting to prevent progressive kidney impairment.**
- **The optimal treatment (surgical vs medical) of gross reflux, with or without scarring, is uncertain. Given the general lack of direct evidence that any treatment option is superior to another, the clinician should provide parents with information about the known benefits and harms of available options and facilitate discussion regarding the intervention. At present, it is not clear whether any intervention for children with primary VUR confers any benefit. Moreover, it is not clear whether antibiotics alone or reimplantation surgery alone are most effective in reducing the risk of urinary tract infections (UTI) and renal parenchymal abnormality. Because of this data and the tendency for many cases of reflux to resolve, many patients with reflux are initially treated on an observation medical protocol including periodic urine cultures to detect asymptomatic bacteriuria. Algorithms based on parental preference have been devised (Capozza et al 2003) but not as yet tested in clinical trials.**
- **Although UTI does not appear to influence progression of reflux disease, urosepsis can account for partially reversible (acute on chronic) renal impairment. Patients with renal impairment have an increased frequency**

of septicaemia, complications and poor outcomes with urinary infection. Higher proportions of women with pyelonephritis have been reported to heal with renal scarring if initiation of therapy is delayed (Roberts 1999). Consequently, urosepsis should be treated early and aggressively in patients with renal impairment (taking into account the toxicity of antibiotic treatments). Bacteriological clearance should also be confirmed, as relapse is also more common in patients with VUR.

Background

Vesicoureteric reflux is a common problem in childhood that results in urine passing, in a retrograde manner, into the ureter during voiding. In some cases, this is associated with chronic renal scarring and hypertension (Martinell et al 1996, Wennerstrom et al 2000). The exact mechanisms for renal damage remain to be fully delineated, although recurrent urinary infection may have a role (Huland & Busch 1984). However, some researchers (Sreenarasimhaiah & Hellerstein 1998) have suggested that renal parenchymal abnormalities instead reflect underlying renal dysplasia rather than damage following UTI (Hellerstein 2000). Consequently, there is considerable disagreement regarding the best treatment to prevent renal scarring. The objective of this guideline is to summarise evidence for the utility of interventions to prevent chronic renal impairment in patients with primary VUR. This guideline does not address secondary VUR, which results from increased bladder pressure because of neurogenic bladder, anatomical abnormality, or outlet obstruction.

Search strategy

Databases searched: MeSH terms and text words for reflux nephropathy. This search was carried out in Medline (1966 to September Week 1, 2004). The Cochrane Renal Group Trials Register was also searched for reflux nephropathy trials not indexed in Medline.

Date of searches: 7 September 2004.

What is the evidence?

Surgery vs antibiotics

There have been 7 trials comparing long-term antibiotics and surgical correction of VUR with antibiotics in 847 children (Weiss et al 1992, Holland et al 1982, Capozza et al 2002, Hjalmas et al 1992, Morris et al 1991, Smellie et al 2001, Birmingham Reflux Study Group 1987). A recent meta-analysis of these studies assessed the utility of these interventions in preventing UTI, renal parenchymal abnormalities, hypertension and renal function impairment (Wheeler et al 2004).

Risk of UTI by 1, 2 and 5 years was not significantly different between surgical and medical groups (by 2 years RR 1.07, 95%CI: 0.55–2.09; by 5 years RR 0.99; 95%CI: 0.79–1.26). A significant reduction in the frequency of febrile UTI was observed in the combined therapy groups of the International Reflux Study (8–10%) and antibiotic only groups (22%) (RR 0.43, 95%CI: 0.27–0.70). However, the overall incidence of

symptomatic UTI (febrile and non-febrile) showed no significant difference in risk between groups.

Renal parenchymal abnormalities were examined in 5 of the 7 randomised controlled trials (RCTs) comparing long-term antibiotics and surgical correction of VUR with antibiotics (Hellerstein 2000, Weiss et al 1992, Capozza et al 2002, Morris et al 1991, Smellie et al 2001). As for UTIs, the frequency of new renal parenchymal abnormalities or progression of existing scan abnormalities did not differ at 4–5 years between the two groups. In addition, there was no significant difference in the rate of renal growth between study groups.

ESKD and hypertension were reported by the two UK studies (Morris et al 1991, Smellie et al 2001). Six children developed ESKD and 11 developed hypertension during follow-up. There was no significant difference in the risk for ESKD (RR 1.07, 95%CI: 0.23–5.04) or hypertension (RR 0.93, 95%CI: 0.25–3.42) between treatment groups. None of these studies were powered to detect these endpoints and follow up time was short, meaning that late effects cannot be excluded. Four studies (Holland et al 1982, Hjalmas et al 1992, Morris et al 1991, Smellie et al 2001) reported data on glomerular filtration rates (GFR). None of these studies individually reported any significant difference between groups.

Antibiotics vs no treatment

There has been only one small RCT comparing antibiotic prophylaxis with no treatment.

- Reddy et al (1997) randomised 43 children with newly diagnosed VUR grade to receive no treatment, daily antibiotic prophylaxis or prophylaxis given on three days each week. There was no significant difference in risk for UTI between daily antibiotic prophylaxis and no prophylaxis (RR 0.25, 95%CI: 0.03–1.83) or between intermittent prophylaxis and no prophylaxis (RR 0.46, 95%CI: 0.10–2.00). Similarly, there was no significant difference in the risk for renal parenchymal injury between daily antibiotic prophylaxis and no prophylaxis (RR 0.40, 95%CI: 0.02–9.18) or between intermittent prophylaxis and no prophylaxis (RR 0.38, 95%CI: 0.02–8.59).

Summary of the evidence

Reflux-correction surgery has no effect on kidney size, scarring, proteinuria, or the GFR when compared with patients managed conservatively. The long-term outcome of renal status and renal function of patients with severe reflux appears to be independent of treatment modality. In addition, the clinical course of patients with established glomerulosclerosis is not altered by late surgical correction or by infection. While the severity of reflux is the single most important determinant of whether renal impairment will occur, persistent reflux or recurrent infection does not appear to be a risk factor for progressive glomerulosclerosis. At this time, there is no evidence to indicate clear superiority of either medical or surgical management for the prevention of progressive kidney disease.

What do the other guidelines say?

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:

Paediatric Vesicoureteric Reflux Guidelines Panel summary report on the management of primary vesicoureteric reflux in children (Elder et al 1997).

Guidelines for management of children with urinary tract infection and vesicoureteric reflux. Recommendations from a Swedish state-of-the-art conference. Swedish Medical Research Council (Jodal et al 1999).

American Academy of Pediatrics: The Diagnosis, Treatment, and Evaluation of the Initial Urinary Tract Infection in Febrile Infants and Young Children (AC9830) [AAP 1999].

Implementation and audit

No recommendation.

Suggestions for future research

No recommendation.

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Appendices

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Birmingham Reflux Study Group, 1987	179	Randomised controlled clinical trial	GP, paediatrician referrals, hospital casualty	179 children under 15 yrs with primary reflux	Surgical reimplantation and antibiotics	Trimethoprim or nitrofurantoin 1-2 mg/kg	24	
Capozza et al, 2002	61	Randomised controlled clinical trial	University hospital, Italy	61 children over 1 yr with primary reflux	Subureteric implantation of Dx/HA copolymer (Deflux and antibiotics)	Antibiotic	12	
Hjalmas et al, 1992	321	Randomised controlled clinical trial	University teaching hospitals, Europe	321 children 6 days – 11 yrs with primary reflux	PL, Cohen, LGe and antibiotics	Nitrofurantoin or trimethoprim 1-2 mg/kg	60	
Holland et al, 1982	10	Randomised controlled clinical trial	US	10 children between 2 mo – 10 yrs with primary reflux	Surgical reimplantation and antibiotics	Trimethoprim-sulfamethoxazole or nitrofurantoin 1 mg/kg	24	
Morris et al, 1991 (abstract)	138	Randomised controlled clinical trial	New Zealand	138 children 6 mo – 10 yrs	Cohen reimplantation and antibiotics	Antibiotic	24	
Reddy et al, 1997 (abstract)	43	Randomised controlled clinical trial	University teaching hospital, US	43 children with primary reflux	Intermittent antibiotics 3 x week, daily urine nitrate testing	Antibiotic continuous prophylaxis	12	3-arm trial with third arm of no antibiotics, surveillance

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Smellie et al, 2001	53	Randomised controlled clinical trial	University teaching hospitals, UK	53 children with primary reflux	Cohen procedure and antibiotics	Nitrofurantoin or trimethoprim or trimethoprim-sulfamethoxazole 1-2 mg/kg	48	
Weiss et al, 1992	142	Randomised controlled clinical trial	University teaching hospitals, US	142 children with primary reflux	PL, Cohen, or other reimplantation and antibiotics	Nitrofurantoin or trimethoprim 1-2 mg/kg	60	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Birmingham Reflux Study Group, 1987	Sealed envelope	No	No	Radiological outcomes only	unclear	14.0
Capozza et al, 2002	Computer generated	No	No	Not stated	No	2.0
Hjalmas et al, 1992	Sealed envelopes	No	No	Not stated	Unclear	11.0
Holland et al, 1982	Not stated	No	No	Radiological outcomes only	unclear	0.0
Morris et al, 1991 (abstract)	Not stated	No	No	Not stated	Unclear	10.0
Reddy et al, 1997 (abstract)	Not stated	No	No	Not stated	Unclear	0.0
Smellie et al, 2001	Sealed envelope	No	No	Not stated	No	6.0
Weiss et al, 1992	Sealed envelope	No	No	Not stated	No	9.0

Table 3 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Birmingham Reflux Study Group, 1987	UTI	16/73	23/80	0.76 (95%CI: 0.44, 1.33)	-0.07 (95%CI: -0.21, 0.07)
	Renal parenchymal defects IVP at 2 yrs	4/77	5/84	0.87(95%CI: 0.254, 3.13)	-0.01 (95%CI: -0.08, 0.06)
	ESRD	1/51	1/53	1.04(95%CI: 0.07, 16.18)	0.00 (95%CI: -0.05, 0.05)
	Hypertension	1/51	3/53	0.35 (95%CI: 0.04, 3.22)	-0.04 (95%CI: -0.11, 0.04)
Capozza et al, 2002	UTI	6/39	0/21	7.15 (95%CI: 0.42, 121.04)	0.15 (95%CI: 0.02, 0.28)
	Renal parenchymal defects on DMSA scan	1/39	3/21	0.18 (95%CI: 0.02, 1.62)	-0.12 (95%CI: -0.27, 0.04)
Hjalmas et al, 1992	UTI	59/147	59/150	1.02 (95%CI: 0.77, 1.35)	0.01 (95%CI: -0.10, 0.12)
	Febrile UTI	15/147	33/150	0.46 (95%CI: 0.26)	-0.12, (95%CI: -0.20, - 0.04)
	Renal parenchymal defects on IVP	35/149	30/153	1.20 (95%CI: 0.78, 1.85)	0.04 (95%CI: -0.05, 0.13)

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	Renal parenchymal defects on DMSA scan	23/140	25/147	0.97 (95%CI: 0.58, 1.62)	-0.01 (95%CI: -0.09, 0.08)
	Renal scarring on IVP	21/149	19/153	1.13 (95%CI: 0.64, 2.02)	0.02 (95%CI: -0.06, 0.09)
Holland et al, 1982	UTI	1/5	2/5	0.50 (95%CI: 0.06, 3.91)	-0.20 (95%CI: -0.75, 0.35)
	Renal parenchymal defects on IVP	1/5	0/5	3.00 (95%CI: 0.15, 59.89)	0.20 (95%CI: -0.21, 0.61)
Morris et al, 1991 (abstract)	UTI	13/60	8/58	1.57 (95%CI: 0.70, 3.51)	0.08 (95%CI: -0.06, 0.22)
Reddy et al, 1997 (abstract)	UTI (continuous vs. surveillance)	1/13	5/16	0.25 (95%CI: 0.03, 1.85)	-0.24, (95%CI: -0.50, 0.03)
	UTI (intermittent vs. surveillance)	2/14	5/16	0.46 (95%CI: 0.10, 2.00)	-0.17 (95%CI: -0.46, 0.12)
	Renal parenchymal abnormalities (continuous vs. surveillance)	0/13	1/16	0.40 (95%CI: 0.01, 9.18)	-0.06 (95%CI: -0.23, 0.10)
	Renal parenchymal abnormalities (intermittent vs. surveillance)	0/14	1/16	0.38 (95%CI: 0.02, 8.59)	-0.06 (95%CI: -0.23, 0.10)

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Smellie et al, 2001	UTI	6/24	11/26	0.59 (95%CI: 0.26, 1.35)	-0.17 (95%CI: -0.43, 0.08)
	ESRD	2/24	2/26	1.08 (95%CI: 0.17, 7.10)	0.01 (95%CI: -0.14, 0.16)
	Hypertension	4/24	3/26	1.44 (95%CI: 0.36, 5.80)	0.05 (95%CI: -0.14, 0.24)
Weiss et al, 1992	UTI	21/64	20/68	1.12 (95%CI: 0.67, 1.85)	0.03 (95%CI: -0.12, 0.19)
	Febrile UTI	5/64	15/68	0.35 (95%CI: 0.14, 0.92)	-0.14 (95%CI: -0.26, -0.02)
	Renal parenchymal defects on IVP	18/51	23/65	1.00 (95%CI: 0.61, 1.64)	0.00 (95%CI: -0.18, 0.17)
	Renal scarring on IVP	16/51	14/65	1.46 (95%CI: 0.79, 2.70)	0.10 (95%CI: -0.06, 0.26)