3. Evaluation of Proteinuria in Children

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Guidelines

No recommendations possible based on Level I or II evidence

Suggestions for clinical care
(Suggestions are based on level III and IV sources)

- Protein/creatinine and albumin/creatinine ratios on a single voided urine sample correlate well with 24 hour urine collections and can be used to detect and monitor proteinuria/albuminuria in children.

- Measurement of total urine protein is recommended for screening in normal children and for monitoring in children with chronic kidney disease. Total urine protein should also be measured in diabetic children who do not meet the criteria detailed below.

- Measurement of urinary albumin is recommended for screening and monitoring of diabetic children as detailed below:

  I. Prepubertal onset of diabetes: 5 years after onset or at age 11 years, or at puberty (whichever is earlier), and annually thereafter.
  II. Pubertal onset of diabetes: 2 years after onset, and annually thereafter.

Background

Proteinuria in a single urine specimen is relatively common in children, with a reported prevalence between 1%-10% (Hogg et al 2000; K/DOQI guidelines, Guideline1, Part 4). However, persistent proteinuria is much less common, with one American study of nearly 9000 school children reporting proteinuria in 1 out of 4 samples in 10.7% of children, but proteinuria in all 4 samples in only 0.1% (Vehaskari et al (1982)). A screen of 9355 South Australian school children reported a low prevalence of proteinuria (0.25%). One third of these children were found to have significant renal disease (Hogg et al 1998).

Search strategy

Databases searched:

The Renal Health Library (2004), Cochrane Renal Group:
'Trials in Nephrology and Cochrane Reviews in Nephrology' were searched using the terms child / paediatric/ pediatric/ proteinuria / albuminuria / microalbuminuria.

No suitable studies were identified.

Medline (1966 – June Week 2 2004):
1. proteinuria or albuminuria or microalbuminuria.mp. [mp = title, original title, abstract, name of substance, MeSH subject heading
2. limit 1 to (human and diagnosis <optimized> and all child <0 to 18 years>)

A total of 213 studies were identified and the titles examined to determine relevant studies. Abstracts of 16 studies were reviewed.

Date of search/es: 16 July 2004.

What is the evidence?

No randomised controlled trials were found on this topic.

Summary of the evidence

Study quality

All studies were observational; no randomised controlled trials were identified. Study characteristics are summarised in Tables 1 and 2 and show that study numbers were small in most trials. Statistical anaylsis of individual series was limited with comparison between methods of urine collection usually assessed by correlation, rather than more stringent methods such as Bland-Altman plots.

Screening

Screening for proteinuria in children is usually performed using urinary dipstick testing. One study by Abitbol et al (1990) was performed in children and tested the ability of dipsticks to correctly designate patients as either nephrotic (> 1 g/m^2/day) or non-nephrotic (< 0.1 g/m^2/day). The authors reported a sensitivity and specificity of 70% and 68%, respectively. However, this calculation is flawed, unless the sensitivity and specificity for nephrotic and non-nephrotic samples are equivalent. The positive predictive value of 3-4+ on the dipstick to predict proteinuria > 1 g/m^2/day was 89% and the negative predictive value of 0/trace on the dipstick to predict proteinuria < 0.1 g/m^2/day was 60%.

Quantitation

Physiological proteinuria varies with the age and size of the child, but when expressed as mg/m^2/24 hours, is relatively constant after the first year of life. The normal rate of protein excretion is < 4 mg/m^2/hr or < 100 mg/m^2/24hr throughout childhood in both boys and girls (Hogg et al 2000). Nephrotic range proteinuria, as defined by the International Study of Kidney Disease in Children (ISKDC), is > 40 mg/m^2/hr in an overnight specimen of urine. This is equivalent to the rather low value of 1.7 g/24hr in adults, and Glassock (1988) has suggested a uniform value of 3.5 g/1.73m^2/24hr as the preferred value.

In young children, accurate timed collections are difficult to obtain and the protein/creatinine (Pr/Cr) ratio on an untimed urine specimen has been the accepted standard for many years. A review of published studies (Table 1) shows a high correlation between the Pr/Cr ratio and 24 hr urine protein collections. Although the absolute values vary according to the laboratory method used, for children over 2 years of age, values < 20-25 mg protein/mmol creatinine correlate with the normal 24 hr value of < 4 mg/m^2/hr. Physiological proteinuria is greater in children aged 6 months to 2 years and values < 50 mg/mmol can be considered normal. Nephrotic range proteinuria (> 40 mg/m^2/hr) is equivalent to a Pr/Cr ratio of 200-250 mg/mmol.

Postural or orthostatic proteinuria is common in children and adolescents. In this disorder, the 24 hr urine protein excretion is usually less than 1 g, although higher values have been reported. A number of long term follow-up studies strongly suggest that this is a benign condition with an excellent prognosis (Robinson 1980; Rytand and Spreiter 1981; Springberg et al 1982; Thompson et al 1970).

Timing of collection

The Pr/Cr ratio on both first morning/early morning and random urine specimens correlate well with the 24 hr protein excretion (Table 1). Thus, for ease and consistency of collection, a random urine specimen for Pr/Cr ratio is acceptable. However, abnormally elevated values should be confirmed with a first morning urine sample to exclude the diagnosis of orthostatic proteinuria.

Microalbuminuria in children

Congenital structural abnormalities and tubular disorders occur much more commonly in children than in adults, while diabetes and hypertension are rare. Structural and tubular diseases may be characterised by significant excretion of low molecular weight proteins that would not be detected by testing exclusively for albumin. Therefore, it is recommended that total protein is measured for those children with renal disorders other than diabetes.

Urinary albumin rather than total protein should be measured in diabetic children and adolescents who meet certain age criteria (see below). Normal values for albumin excretion in children are not well established, but overall, the values appear similar to the reference ranges reported for adults (K/DOQI guidelines, Guideline 1, Part 4). Recommendations for age of microalbuminuria screening are detailed in the ISPAD Consensus Guidelines, 2000.

From the above data, a summary of normal reference ranges that can be applied to paediatric patients is:

	First morning specimen	Overnight urine protein
Infants and children < 2 years of age	< 50 mg protein/mmol	Not established
Non-diabetic children (> 2 years of age) and adolescents	< 20-25 mg protein/mmol	< 4 mg protein/m^2/hr
Diabetic	< 3.5 mg albumin/mmol*	< 20μg protein/min

* Pugia et al (1999)

Note:

- The same reference range can be applied to both males and females.
- Initial positive dipstick tests should be confirmed by an overnight collection. 24 hr collections are not recommended for initial diagnosis due to the high incidence of postural proteinuria in children and adolescents.
- 24 hr collections are recommended for monitoring disease activity in those children with known renal disease.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative:
Specific guidelines for children without diabetes
When screening children for chronic kidney disease, total urine protein should be measured in a spot urine sample using either:
– standard urine dipstick
– total protein-to-creatinine ratio.

Orthostatic proteinuria must be excluded by repeat measurement on a first morning specimen if the initial finding of proteinuria was obtained on a random specimen.

When monitoring proteinuria in children with chronic kidney disease, the total protein-to-creatinine ratio should be measured in spot urine specimens.

Specific guidelines for children with diabetes
Screening and monitoring of post-pubertal children with diabetes of 5 or more years of duration should follow the guideline for adults.

Screening and monitoring of other children with diabetes should follow the guidelines for children without diabetes.

British Renal Association:
No recommendation.

Canadian Society of Nephrology:
No recommendation.

European Best Practice Guidelines:
No recommendation.

Implementation and audit

See “Suggestions for Clinical Care”.

Suggestions for future research

No recommendation.

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Appendices

Table 1. Summary of urine protein/creatinine ratios versus timed urine collections in children

Author, Year	No. (measurements)	Study population		Comparison	Correlation (r^2)	Comments
		Age (years)	Proteinuria range			
Chahar, 1993	20 healthy, 30 renal disease (50/50)	2.5-14	10-6,000 mg/ h/m^2	Random vs 24 hr	0.99 normal 0.98 renal disease	
Chang, 2000	1072 random samples, 125 24 hr samples	Taiwanese 7-18	Mean: 86 mg/24 h/m^2	Random vs 24 hr	0.95	
Abitbol, 1996	16 (23/23)	Children with HIV nephropathy Mean age 3	NA	Random vs timed urine (1-6 hrs)	0.98	$p < 0.0001$
Mir, 1992	50 (50/50)		20 - 70 mg/24 h/kg	First morning vs 24 hr		$p < 0.01$
Houser, 1984	15 (+ 5 adults) (20/20)	5-17	15 – 8,500 mg/24 h/m^2	Random vs 24 hr	0.99	$p < 0.001$
Tsai, 1991	5 healthy, 28 renal disease (61/61)	2-14	NA	Random vs 24 hr	0.97	4 mg/h/m^2 ~ 25 mg/mmol 40 mg/h/m^2 ~ 260 mg/mmol
Iyer, 1991	25 healthy, 25 nephrotic in remission, 50 nephrotic (100/100)	NA	0-9,600 mg/day	Random vs 24 hr	0.81 [0.25 (normal & acute GN), 0.66 (nephrotic)]	$p < 0.001$
Yoshimoto, 1990	44 (44/44)	4-16	NA	Early morning vs 24 hr	NA	Smallest coefficient of variation in early morning samples
Abitbol, 1990	64 145 collections (125/125)	1.5 -16 Relapsing nephrotic syndrome	NA	NA	0.95 (NB: statistical analysis appears flawed)	Sensitivity of dipsticks also tested - see below (Sochett et al 1988)
Elises, 1988	66 (71/71)	3-23 (mean 12.5)	0 - 2,400 mg/24h/m^2	Early morning vs 24 hr	0.93	4 mg/h/m^2 ~ 20 mg/mmol 40 mg/h/m^2 ~ 200 mg/mmol
Kim, 2001	53 (23/23)	2 months - 15 (mean 7)	[1] 30, 5-57 mg/day/m^2 [2] 23, 114-6,431 mg/day/m^2	Early morning vs 24 hr	Group 1 – r = 0.04 Group 2 – r = 0.88	

Table 2. Summary of urine albumin/creatinine ratios versus timed urine collections in children

Author, Year	No. (measurements)	Study population			Comparison	Correlation (r^2)	Comments
		Age (years)	Diabetic vs Non-diabetic	Proteinuria range			
(Sanchez-Bayle, 1995)	2224	2-18	Non-diabetic		Overnight vs early morning urine	0.958	
(Bangstad, 1993)	150 (NS)	10-18.5	Non-diabetic	0.2-34.0 µg/min	Overnight (same specimen used for Alb/Cr ratio)	0.90	Alb/Cr > 2.5 mg/mmol, PPV 88%, NPV 99%
Barratt, 1970	8 (71/71)	4-8 days	Non-diabetic	Alb/Cr < 1-300 mg/g	Random vs 24 hr	0.94	
Davies, 1984	374 (374/374)	4-16	Non-diabetic	Mean: 6.6-8.3 mg/1.73m^2/24h	First morning vs overnight	0.79	
Houser, 1986	17 (17/17)	2 months - 62	Non-diabetic	3.4 -4700 mg/m^2/d	First morning vs 24 hr	0.92	
Cowell, 1986	111 (111/111) 64 (64/64)	3.5-15 1 week-13	Non-diabetic Diabetic	1-45 mg/24 hr 1-38 mg/24 hr	First morning vs 24 hr	0.59 0.86	
Gibb, 1989	73 (171/171) 119 (406/406	Mean = 13.5 Mean = 11.9	Non-diabetic Diabetic	NS	First morning vs overnight	0.81	
Assadi, 2002	97 (124 samples)	8-19	Diabetic	7-108 mg/24 hr	24 hr vs early morning urine	0.89	30 mg/24 hr ~ 20 µg/mg
Shield, 1995	104 (247/247)	10.6 -23.5	Diabetic	NS	Overnight (same specimen used for Alb/Cr ratio)	NS	Alb/Cr ratio ≥ 2.5 mg/mmol had sensitivity 94%, specificity 94%, PPV 66%, NPV 99%
Sochett, 1988	41 (41/41)	6-18	Diabetic	NS	Random vs 24 hr	0.17	
Jefferson, 1985	40 (40/40)	8-16	Diabetic	1.4-43.0 mg/24 hr	Random vs 24 hr	0.69-0.78	

* NS = not stated