3. Evaluation of Proteinuria in Children

Date written: February 2003  
Date submitted: June 2004

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 analysis 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/m²/day) or non-nephrotic (< 0.1 g/m²/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/m²/day was 89% and the negative predictive value of 0/trace on the dipstick to predict proteinuria < 0.1 g/m²/day was 60%.

**Quantitation**

Physiological proteinuria varies with the age and size of the child, but when expressed as mg/m²/24 hours, is relatively constant after the first year of life. The normal rate of protein excretion is < 4 mg/m²/hr or < 100 mg/m²/24hr 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/m²/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/1.73m²/24hr 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/m²/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/m²/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:
**Urine Protein as Diagnostic Test**

(Tenber 2004)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>First morning specimen</th>
<th>Overnight urine protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants and children &lt; 2 years of age</td>
<td>&lt; 50 mg protein/mmol</td>
<td>Not established</td>
</tr>
<tr>
<td>Non-diabetic children (&gt; 2 years of age) and adolescents</td>
<td>&lt; 20-25 mg protein/mmol</td>
<td>&lt; 4 mg protein/m²/hr</td>
</tr>
<tr>
<td>Diabetic</td>
<td>&lt; 3.5 mg albumin/mmol</td>
<td>&lt; 20 µg protein/min</td>
</tr>
</tbody>
</table>


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.

Out of date
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.
References


The CARI Guidelines – Caring for Australians with Renal Impairment


Urine Protein as Diagnostic Test
(October 2004)


## Appendices

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

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>No. (measurements)</th>
<th>Study population</th>
<th>Comparison</th>
<th>Correlation ($r^2$)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chahar, 1993</td>
<td>20 healthy, 30 renal disease (50/50)</td>
<td>2.5-14</td>
<td>10-6,000 mg/ h/m²</td>
<td>Random vs 24 hr</td>
<td>0.99 normal 0.98 renal disease</td>
</tr>
<tr>
<td>Chang, 2000</td>
<td>1072 random samples, 125 24 hr samples</td>
<td>Taiwanese, 7-18</td>
<td>Mean: 86 mg/24 h/m²</td>
<td>Random vs 24 hr</td>
<td>0.95</td>
</tr>
<tr>
<td>Abitbol, 1996</td>
<td>16 (23/23)</td>
<td>Children with HIV nephropathy</td>
<td>Random vs timed urine (1-6 hrs)</td>
<td>0.98</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Mir, 1992</td>
<td>50 (50/50)</td>
<td>20 - 70 mg/24 h/kg</td>
<td>First morning vs 24 hr</td>
<td>0.97</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Houser, 1984</td>
<td>15 (+ 5 adults) (20/20)</td>
<td>5-17</td>
<td>15 – 8,500 mg/24 h/m²</td>
<td>Random vs 24 hr</td>
<td>0.99</td>
</tr>
<tr>
<td>Tsai, 1991</td>
<td>5 healthy, 28 renal disease (61/61)</td>
<td>2-14</td>
<td>NA</td>
<td>Random vs 24 hr</td>
<td>0.97</td>
</tr>
<tr>
<td>Iyer, 1991</td>
<td>25 healthy, 25 nephrotic in remission, 50 nephrotic (100/100)</td>
<td>NA</td>
<td>0-9,600 mg/day</td>
<td>Random vs 24 hr</td>
<td>0.81</td>
</tr>
<tr>
<td>Yoshimoto, 1990</td>
<td>44 (44/44)</td>
<td>4-16</td>
<td>NA</td>
<td>Early morning vs 24 hr</td>
<td>NA</td>
</tr>
<tr>
<td>Abitbol, 1990</td>
<td>64 (145 collections (125/125))</td>
<td>1.5 -16 Relapsing nephrotic syndrome</td>
<td>NA</td>
<td>NA</td>
<td>0.95</td>
</tr>
<tr>
<td>Elises, 1988</td>
<td>66 (71/71)</td>
<td>3-23 (mean 12.5)</td>
<td>0 - 2,400 mg/24h/m²</td>
<td>Early morning vs 24 hr</td>
<td>0.93</td>
</tr>
<tr>
<td>Kim, 2001</td>
<td>53 (23/23)</td>
<td>2 months - 15 (mean 7)</td>
<td>[1] 30, 5-57 mg/day/m², [2] 23, 114-6,431 mg/day/m²</td>
<td>Early morning vs 24 hr</td>
<td>Group 1 – r = 0.04 Group 2 – r = 0.88</td>
</tr>
</tbody>
</table>
### Table 2. Summary of urine albumin/creatinine ratios versus timed urine collections in children

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>No. (measurements)</th>
<th>Study population</th>
<th>Proteinuria range</th>
<th>Comparison</th>
<th>Correlation ($r^2$)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Sanchez-Bayle, 1995)</td>
<td>2224</td>
<td>2-18</td>
<td>Non-diabetic</td>
<td>Overnight vs early morning urine</td>
<td>0.958</td>
<td></td>
</tr>
<tr>
<td>(Bangstad, 1993)</td>
<td>150 (NS)</td>
<td>10-18.5</td>
<td>Non-diabetic</td>
<td>Overnight (same specimen used for Alb/Cr ratio)</td>
<td>0.90</td>
<td>Alb/Cr &gt; 2.5 mg/mmol, PPV 88%, NPV 99%</td>
</tr>
<tr>
<td>Barratt, 1970</td>
<td>8 (71/71)</td>
<td>4-8 days</td>
<td>Non-diabetic</td>
<td>Alb/Cr &lt; 1-300 mg/g</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>Davies, 1984</td>
<td>374 (374/374)</td>
<td>4-16</td>
<td>Non-diabetic</td>
<td>Mean: 6.6-8.3 mg/1.73m²/24h</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Houser, 1986</td>
<td>17 (17/17)</td>
<td>2 months - 62</td>
<td>Non-diabetic</td>
<td>3.4 -4700 mg/m²/d</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Cowell, 1986</td>
<td>111 (111/111)</td>
<td>3.5-15</td>
<td>Non-diabetic</td>
<td>1-45 mg/24 hr</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>Gibb, 1989</td>
<td>73 (171/171)</td>
<td>Mean = 13.5</td>
<td>Non-diabetic</td>
<td>NS</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Assadi, 2002</td>
<td>97 (124 samples)</td>
<td>8-19</td>
<td>Diabetic</td>
<td>7-108 mg/24 hr</td>
<td>0.89</td>
<td>30 mg/24 hr – 20 µg/mg</td>
</tr>
<tr>
<td>Shield, 1995</td>
<td>104 (247/247)</td>
<td>10.6-23.5</td>
<td>Diabetic</td>
<td>NS</td>
<td>NS</td>
<td>Alb/Cr ratio ≥ 2.5 mg/mmol had sensitivity 94%, specificity 94%, PPV 66%, NPV 99%</td>
</tr>
<tr>
<td>Sochett, 1988</td>
<td>41 (41/41)</td>
<td>6-18</td>
<td>Diabetic</td>
<td>NS</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Jefferson, 1985</td>
<td>40 (40/40)</td>
<td>8-16</td>
<td>Diabetic</td>
<td>1.4-43.0 mg/24 hr</td>
<td>0.69-0.78</td>
<td></td>
</tr>
</tbody>
</table>

* NS = not stated