The Renal Biopsy

Indications

Influence on Management
Why do we do a biopsy?

• To make a diagnosis
Why do we do a biopsy?

• To make a diagnosis
• To inform prognosis
  – Grade
  – Severity
Why do we do a biopsy?

• To make a diagnosis
• To inform prognosis
  – Grade
  – Severity
• To assess response to treatment
  – Progression
  – Regression
  – Drug toxicity
Scenario 1

- 4 year old boy
- Typical nephrotic syndrome
  - Normal renal function, BP, immunology
- In remission after 9 days of pred
- 6 month initial tapering Rx
- 3 relapses in next 7 months
- Decision:
  - To have 8 wk course of cyclophosphamide
Would you do biopsy first?

Y = YES

N = NO

U = UNSURE
Childhood steroid-sensitive nephrotic syndrome: does the histology matter?


- **Webb NJ, Lewis MA, Iqbal J, Smart PJ, Lendon M, Postlethwaite RJ**.
- Renal biopsy in 51 children with FRSSNS
- performed prior to course of cyclophosphamide
- reviewed by two histopathologists
- Pre-biopsy clinical course did not predict histologic diagnosis
- no correlation between pre-biopsy course or histology and post-cyclophosphamide course.
- steroid sensitivity rather than histology the major determinant of prognosis
- frequency of relapse alone is not an indication for biopsy.
Do current recommendations for kidney biopsy in nephrotic syndrome need modifications?


The decision to administer cyclophosphamide should be based on steroid response pattern without requiring a prior routine biopsy.
Is biopsy required prior to cyclophosphamide in steroid-sensitive nephrotic syndrome?


- Stadermann MB, Lilien MR, van de Kar NC, Monnens LA, Schröder CH.

Aim: How did histology influence treatment decision?

- 85 children with FRSSNS / SDSSNS
- All had normal C3, normal creat, normal BP
- Biopsy before the start of 8-week cyclophosphamide treatment.

Histology:
- MCNS in all (and 1 who showed FSGS on repeat 3 yrs later)

Conclusion:
- no biopsy required prior to cytotoxic therapy in uncomplicated SSNS
A biopsy is usually not necessary in patients with frequent relapses or steroid dependence before starting treatment with levamisole, cyclophosphamide, or MMF
CLINICAL STUDY

Renal biopsy in children with steroid-dependent nephrotic syndrome

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Department of Paediatrics, Charles University in Prague, Medical Faculty Hradec Králové, Czech Republic.

- Biopsy in 18 patients with SDSSNS
- Then 12-week course of cyclophos ± pred
- Histology
  - MCNS: 14
  - MCNS + IgM: 4
- No influence on Rx
- Conclude biopsy not indicated prior to cyclophos
Indication for kidney biopsy

Routine biopsies in FR or SD SSNS before using corticosteroid sparing therapy:
• not indicated
Scenario 2

- 7 year old boy
- Typical nephrotic syndrome diagnosed aged 4
  - Normal renal function, BP, immunology
- In remission after 9 days of pred
- 6 month initial tapering Rx
- 3 relapses in next 7 months
- Decision:
  - To have 8 wk course of cyclophosphamide
Scenario 2

• 7 year old boy
• Typical nephrotic syndrome diagnosed aged 4
  – Normal renal function, BP, immunology
• In remission after 9 days of pred
• 6 month initial tapering Rx
• 3 relapses in next 7 months
• Decision:
  – To have 8 wk course of cyclophosphamide
• Relapse free for 14 months, then 2 relapses in 4 months
• Still steroid sensitive; normal creat and BP
• Decision:
  – To start tacrolimus
Would you do biopsy first?
A biopsy is usually not necessary in patients with frequent relapses or steroid dependence before starting treatment with levamisole, cyclophosphamide, or MMF, but should be performed before therapy with calcineurin inhibitors.
Indication for kidney biopsy

Routine biopsies in FR or SD SSNS before using corticosteroid sparing therapy:
• not indicated
ECH Biopsy meeting 13.06.2013

• Debate over this question
• Variation in practice
  – Some would
  – Some would not (including me)

• What effect is biopsy going to have on management?
Scenario 3

- 9 year old boy
- Typical nephrotic syndrome diagnosed aged 4
  - Normal renal function, BP, immunology
- In remission after 9 days of pred
- 6 month initial tapering Rx
- 3 relapses in next 7 months
- Decision:
  - To have 8 wk course of cyclophosphamide
- Relapse free for 14 months, then 2 relapses in 4 months
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Scenario 3

- 9 year old boy
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- 6 month initial tapering Rx
- 3 relapses in next 7 months
- Decision:
  - To have 8 wk course of cyclophosphamide
- Relapse free for 14 months, then 2 relapses in 4 months
- Still steroid sensitive; normal creat and BP
- Decision:
  - To start tacrolimus
- Has been controlled on tacrolimus for 24 mths
Would you do biopsy?
Two-year cyclosporin treatment in children with steroid-dependent nephrotic syndrome

*Ped Nephrol* 1999

- Renal biopsies before CyA treatment all showed MCNS without tubulointerstitial lesions.
- Creatinine clearance during CyA treatment normal in all patients, but biopsies after CyA treatment revealed chronic CyA nephrotoxicity in 7/13 patients.

- Conclusions:
  - Renal function is not a reliable indicator of chronic Cya nephrotoxicity
  - Renal biopsy is therefore necessary to monitor chronic CyA nephrotoxicity
CyA nephrotoxicity
• late failure to respond following initial response to corticosteroids
• **decreasing kidney function** in children receiving CNIs
• annual biopsy if CNI therapy is continued beyond 2 years
• *But*, no data whether benefits of regular biopsies exceed the harm
Scenario 4

• 9 year old girl presents with 4 mths puffy eyes
• GP treats her with antihistamine
  → no improvement
• locum GP tests her urine: protein +++
• referred to local hospital:
  – albumin 24 g/l
  – creatinine 76 μmol/l
  – BP 128/88
• commenced on prednisolone 60 mg/m²/day
Scenario 4

- 9 year old girl presents with 4 mths puffy eyes
- GP treats her with antihistamine → no improvement
- locum GP tests her urine: protein +++
- referred to local hospital:
  - albumin 24 g/l
  - creatinine 76 μmol/l
  - BP 128/88
- commenced on prednisolone 60 mg/m²/day
- no response after 4 weeks:
  - urinalysis = prot ++
- C₃,₄: normal; ANA, anti-dsDNA: neg
- Hep B,C: neg
Would you do biopsy?
This document relates only to the management of **idiopathic nephrotic syndrome**. Children who present with the typical features of nephrotic syndrome (see below) are generally responsive to steroid treatment and a renal biopsy, were it performed, would be likely to show minimal change nephrotic syndrome. Those with atypical features are more likely to be unresponsive to steroid treatment, and a biopsy more likely to show FSGS or one of the other forms of nephrotic syndrome.

Therefore children with typical features are started on steroids without recourse to renal biopsy. Those with atypical features should therefore undergo renal biopsy before receiving steroid treatment.
Do current recommendations for kidney biopsy in nephrotic syndrome need modifications?

1. biopsies in children should be restricted
   (a) to a subgroup with two or more clinical and biochemical parameters (↑BP, haematuria, ↑ creat, ↓ C₃)
   (b) in steroid non-responders
A biopsy is usually not necessary in patients with frequent relapses or steroid dependence before starting treatment with levamisole, cyclophosphamide, or MMF, but should be performed before therapy with calcineurin inhibitors.

### Table 3
### Indications for kidney biopsy

**At onset**
- Age of onset <1 year.
- Gross hematuria, persistent microscopic hematuria or low serum C3.
- Sustained hypertension.
- Renal failure not attributable to hypovolemia.
- Suspected secondary causes of nephrotic syndrome.

**After initial treatment**
- Proteinuria persisting despite 4-weeks of daily corticosteroid therapy.
- Before treatment with cyclosporin A or tacrolimus.

**Revised guidelines for management of steroid-sensitive nephrotic syndrome**

KDIGO Clinical Practice Guideline for Glomerulonephritis 2012
Chapter 4: Steroid-resistant nephrotic syndrome in children

• Renal biopsy recommended in initial assessment
But...

- What treatment would you recommend for this patient?
- How would a biopsy help or influence this decision?
Scenario 5

- 9 year old girl presents with red/brown urine
- sore throat which started 3 days earlier
- also complains of headache and malaise, sore feet
- O/E: rash on legs, arms, ears
  - P: 108/min
  - JVP: + 3 cm
  - BP: 134/92
- slight swelling of feet and ankles
Scenario 5

9 year old girl presents with red/brown urine
sore throat which started 3 days earlier
also complains of headache and malaise, sore feet
O/E: rash on legs, arms, ears
P: 108/min
JVP: + 3 cm
BP: 134/92
slight swelling of feet and ankles

Ix:
urinalysis: blood ++++ prot+++ 
Hb: 10.7g/dl
urea: 24 mmol/l
creat: 119 µmol/l
albumin: 22 g/L
C₃, C₄: normal
ANA, ANCA: neg
Would you do biopsy?
What might it show?
When to biopsy in acute GN?

- Diagnosis uncertain
- Progressive deterioration to, or condition at presentation with:
  - GFR <50%
  - Nephrotic syndrome
ISKDC Classification of HSP

I  minimal changes

II pure mesangial
   a) focal   b) diffuse

III mesangial proliferative GN, <50% crescents
   a) focal   b) diffuse

IV mesangial proliferative GN, 50-75% crescents
   a) focal   b) diffuse

V mesangial proliferative GN, >75% crescents
   a) focal   b) diffuse

VI mesangiocapillary GN
Clinical Outcome

A  normal

B  minor urinary abnormalities
   prot:creat ratio = 21-200 mg/mmol
   ± microscopic haematuria

C  active renal disease
   prot:creat ratio > 200 mg/mmol
   hypertension
   impaired renal function, GFR 60-80

D  renal failure
   GFR < 60; ESRF; or death
Haycock G
Oxford
Textbook of
Clinical Nephrology
Scenario 6

- 8 year old boy
- Sees GP because abdo pain and fever
- Urinalysis shows 3+ haematuria, trace proteinuria
- Repeat urinalysis x 3 over 6 months: 3+ haematuria
- Referred to local paediatrician:
  - Normal creat; normal BP; normal US; normal Urine Ca:creat
- Referred to you after 12 months:
  - One episode of visible haematuria for 48 hrs associated with URTI
  - 3+ haematuria
  - Parents urine: NAD
  - No family history
  - BP and creatinine: normal
Would you do biopsy?
How would biopsy help?

- Will probably (but not definitely) explain haematuria
  - Thin membrane
  - IgA
  - Alport’s
How would biopsy help?

• Will probably (but not definitely) explain haematuria
  – Thin membrane
  – IgA
  – Alport’s

• Benefits:
  – Can discuss more clearly the condition and prognosis
  – Removes uncertainty from family
How would biopsy help?

• Will probably (but not definitely) explain haematuria
  – Thin membrane
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  – Alport’s

• Benefits:
  – Can discuss more clearly the condition and prognosis
  – Removes uncertainty from family

• Does it alter management?
  – Does he need treatment?
How would biopsy help?

- Will probably (but not definitely) explain haematuria
  - Thin membrane
  - IgA
  - Alport’s
- Benefits:
  - Can discuss more clearly the condition and prognosis
  - Removes uncertainty from family
- Does it alter management?
  - Does he need treatment?
  - Would you still recommend long-term follow-up whether or not biopsy done?
Prof Frances Flinter e-mail

• Most people would prefer a genetic test to a renal biopsy!
• may have TBM with a single mutation in one of the autosomal genes - would recommend lifelong follow-up to check BP and urine for proteinuria
• he could also have Alport's
Prof Frances Flinter e-mail

- Most people would prefer a genetic test to a renal biopsy!
- may have TBM with a single mutation in one of the autosomal genes - would recommend lifelong follow-up to check BP and urine for proteinuria
- he could also have Alport's
- Suggest you send DNA and request
  - COL4A3/4 screen first (£1,400)
  - COL4A5 screen if negative (£860)
- hoping to be able to bring the costs < £800 for screening all 3 genes simultaneously plus COL4A6 by the introduction of Next Generation Sequencing
- I've just got a grant from Kidney Research UK to set this up..
Scenario 6

- 5 year old boy receives 48 hours IV cefotaxime for chest infection, then discharged on oral cefadroxil
- Also given Nurofen at home
- Readmitted with low grade fever, joint pains, rash, malaise, anorexia
Scenario 7

- 5 year old boy receives 48 hours IV cefotaxime for chest infection, then discharged on oral cefadroxil
- Also given Nurofen at home
- Readmitted with low grade fever, joint pains, rash, malaise, anorexia
- Urine: protein 1+, glucose 2++
- Urea 18mmol/L, creatinine 139μmol/L
- Urine output 1.8 ml/kg/hr
Would you do biopsy?
<table>
<thead>
<tr>
<th>Normal Complement</th>
<th>Reduced Complement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Renal Disease</strong></td>
<td><strong>Primary Renal Disease</strong></td>
</tr>
<tr>
<td>Membranous</td>
<td>Acute post-strept GN</td>
</tr>
<tr>
<td>IgA</td>
<td>($C_3 \downarrow; C_4$ norm)</td>
</tr>
<tr>
<td>anti GBM</td>
<td>MPGN type I</td>
</tr>
<tr>
<td>FSGS</td>
<td>(both low)</td>
</tr>
<tr>
<td><strong>Systemic Disease</strong></td>
<td><strong>Systemic Disease</strong></td>
</tr>
<tr>
<td>HSP</td>
<td>SLE (both low)</td>
</tr>
<tr>
<td>PAN</td>
<td>cryoglobulinaemia</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>systemic infection</td>
</tr>
<tr>
<td></td>
<td>SBE</td>
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<tr>
<td></td>
<td>shunt nephritis</td>
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# Biopsy audits 2000-1, and 2012

<table>
<thead>
<tr>
<th></th>
<th>Native</th>
<th>Transplant</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2000-1:</strong></td>
<td>91 (42%)</td>
<td>126 (58%)</td>
<td>217</td>
</tr>
<tr>
<td><strong>2012:</strong></td>
<td>79 (62%)</td>
<td>48 (38%)</td>
<td>126</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>2000-1</th>
<th>2012</th>
</tr>
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<tbody>
<tr>
<td>Native Bx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haem.</td>
<td>31</td>
<td>21</td>
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<tr>
<td>Prot</td>
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<td>10</td>
</tr>
<tr>
<td>NS</td>
<td>33</td>
<td>21</td>
</tr>
<tr>
<td>Acute GN</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Other</td>
<td>18</td>
<td>15</td>
</tr>
</tbody>
</table>

**Native Bx %**
- 2000-1: 31%
- 2012: 27%

**Transplant %**
- 2000-1: 12%
- 2012: 13%

**Total %**
- 2000-1: 12%
- 2012: 14%

**Other**
- 2012: 19%