Diagnostic evaluation of patients with hematuria

<B. Hoppe>
Hematuria

- Transient finding, e.g. after infections
- Indicator of kidney or urinary tract diseases
- Microscopic / Macroscopic hematuria
  - Alert situation for parents!
- Often non-problematic
- Hematuria + Proteinuria
  - Significant disease
  - CNI?
Big variety of diagnosis in patients with microscopic or macroscopic hematuria, e.g.

- benign familial hematuria <> patients with Alport syndrome
- hypercalcuria and urinary crystals <> severe kidney stones or nephrocalcinosis due to inborn error of metabolism
- cystitis <> urological anomalies
Low price

Diagnostic evaluation

Expensive
Normal red blood cell excretion?

- Few red blood cells can be normal
  - Squeezed through capillary basement membrane
  - More after exercise
- Small amount of blood will color the urine
- Brown color after period of standing
  - Oxidized heme pigment => metheme derivate
- Further discoloration by
  - hemolysis, rhabdomyolysis, metabolic disorders, foods and drugs
Definition

- 5 red blood cells/µL of fresh uncentrifuged midstream urine
- 3 red blood cells/high power field in centrifuged midstream urine (10 mL)
- Controversy on how much cells in how much midstream urine and centrifugation spun used

- Cofactors:
  - Hypertension
  - Proteinuria
  - Urinary casts
  - Family history

Non glomerular hematuria
Urine collection

<table>
<thead>
<tr>
<th>Urine bag</th>
</tr>
</thead>
<tbody>
<tr>
<td>After careful examination of the genitals</td>
</tr>
<tr>
<td>No bag placement via the parents</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Midstream urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclude balanitis, vulvovaginitis</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Catheter</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Bladder punction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold standard?</td>
</tr>
</tbody>
</table>
Dipstick

- Briefly dipped into urine
  - Tapp off excess fluid
- Pay attention to interval indicated by manufacturer before „reading“ the color charts
- Cave: delayed reading produces false positive results!
- Test uses peroxidase like activity of hemoglobin present in urine
- Test is very sensitive!
Dipstick analysis

Correct, but watch the time

More reliable
Dipstick => don‘t rely on one analysis

False positive results in
- Hemoglobinuria (intravascular hemolysis)
- Myoglobinuria (rhabdomyolysis)
- Oxidative agents in urine

False negative results in
- Large amount of reducing agents (ascorbic acid)
- Urine with high specific gravity

Dipstick => further evaluation if persistently > 1+
Microscopy

Red blood cells are easy to identify
  More difficult when scanty
  Use ultracentrifuged urine for examination
  False negative in diluted urine or in high pH

Morphology
  Normal from the lower urinary tract
  Variation in size and morphology from the upper urinary tract => phase contrast microscopy
Microscopy

Phase contrast microscopy

> 30% dysmorphic red blood cells glomerular origin
90-95% isomorphic => lower urinary tract

Further pathology

Red blood cell casts (fresh or acidified urine) => GN
White blood cell casts => infection
Eosinophils => interstitial nephritis
Crystals => stones or nephrocalcinosis
Phase contrast microscopy

- Should be available in a (pediatric) nephrology setting!
- Use freshly voided urine
- Search for
  - (red) blood cells
  - Blood cell casts
  - Crystals

Mickey Mouse like pictures
Diagnostic evaluation

- Repeated dipstick with ongoing hematuria
- Microscopy with isomorphic or dysmorphic red blood cells
- Micro-Macrohematuria
- Proteinuria

Evaluation

Lower UT

Upper UT
Clinical approach

- Serious condition?
  - E.g. RPGN
- Avoidance of unnecessary and expensive testings
- Just the first menarche?
- Follow guidelines
- Careful patients history and physical examination before extensive evaluation!

} Be quick with decisions!
History

- Deafness, Rhinitis sicca
- Abdominal pain, diarrhea, blood in stool
- Failure to thrive => CKD?
- Purpura, Butterfly erythema
- Face and/or leg swelling
- Arthritis, joint pain, joint swelling
- Uveitis, loss of vision
History

- Recurrent streptococcal infections
- Viral infections (e.g. Hepatitis => MN)
- Hemoptoe (Goodpasture)
- Surgery, Immobilization
- Sexual activity (urethritis, cystitis)
- Medication (Vitamins, suppositories?)
Family history

- Hematuria (benign familial)
- Kidney stones
- Cystic kidney diseases
- Rheumathoid diseases
- Collagenosis
- Hypertension
- Hardness of hearing
- Eye disease
Patients history

- Dysuria, Pollakisuria
- Fever
- Flank pain, recurrent abdominal pain
- Recurrent UTI
- Family history with nephrologic, urologic, gynecologic diseases
  - (Schistosomiasis)
Patients history

- Hypertension
- Dysuria, Pollakisuria
- Fever
- Flank pain, recurrent abdominal pain
- Recurrent UTI
- Skin, Purpura
- Family history
Macrohemosumaria

<table>
<thead>
<tr>
<th>With fever</th>
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<tbody>
<tr>
<td>Cystitis</td>
</tr>
<tr>
<td>IgA nephritis</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Sudden</th>
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<tbody>
<tr>
<td>Renal vein thrombosis</td>
</tr>
<tr>
<td>Kidney stone</td>
</tr>
<tr>
<td>Bleeding (Cysts)</td>
</tr>
<tr>
<td>Trauma</td>
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</tbody>
</table>
Patients examination

<table>
<thead>
<tr>
<th>Male:</th>
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<tbody>
<tr>
<td>Varicosis testicularis</td>
</tr>
<tr>
<td>Orchitis, torsion</td>
</tr>
<tr>
<td>Epididymitis</td>
</tr>
<tr>
<td>Balanitis</td>
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<table>
<thead>
<tr>
<th>Female</th>
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<tbody>
<tr>
<td>Vulvovaginitis</td>
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V. lienalis
V. renalis sinistra
Colored urine

- Ascorbic acid supplementation
- Vitamin A/D excess
- Rifampicin (dark yellow or orange urine)
- Foods (beetroot, blackberries)
- Drugs (chloroquine, phenazopyridine)
- Myoglobin
- Phorphyrins
- Hemoglobinuria
Urology

- Bleeding
- Frenulum
- Bladder
- Upper urinary tract
- Three glasses assay
- Always red = upper UT
- Stone passage
- Trauma / Misuse
Urology

- Bleeding
- Frenulum
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Urology - procedures

- Ultrasound
- Low enhanced CT
- Stones?
- No intravenous pyelography
- Only indication for IVP in childhood is Megacalycosis
- Cystoscopy
- Genocology evaluation
Algorithm?

- Depends on origin of red blood cells!
- Can be different according to reference....
Algorithm
according to Yap and Lau, in
Comprehensive Pediatric
Nephrology, Eds.: D.F. Geary & F.
Schäfer

STEP 1
Confirm hematuria with
• Urine dipstick
• Urine microscopic examination

STEP 2
Significant red blood cells (RBC) seen
Symptoms and signs of acute nephritic syndrome, e.g., edema, hypertension, oliguria

STEP 3
Yes
Macroscopic hematuria: exclude preceding exercise.
Isolated microscopic hematuria: repeat urinalysis weekly x 2 (without exercise). Investigate if persistent hematuria.

STEP 4
Urine phase contrast microscopy
Urine protein/creatinine ratio

STEP 5
NON-GLOMERULAR
Isomorphic RBC, no casts, no proteinuria

GLOMERULAR
Dysmorphic RBC, RBC casts, proteinuria

• Urine calcium/creatinine ratio
• Urine culture
• Urine adenosine virus culture
• Renal ultrasound and Doppler
• Coagulation screen (full blood count, PT, PTT)
• Abdominal X-ray (in cases of urinary tract calculi)
• 24-hour urine calcium, uric acid, oxalate, cystine (in cases of renal calculi)
• CT abdomen (in cases of trauma or tumor)
• Magnetic resonance angiography (if nutcracker syndrome is suspected)

• Serum urea, creatinine, electrolytes
• 24-hour urine protein and creatinine clearance
• Serum complements C3 and C4
• Serum IgA
• Renal ultrasound
• Test parents and siblings for hematuria
• Consider audiology
• Consider renal biopsy if indicated

Follow up with yearly urinalysis

? Ultrasound first?
non-glomerular hematuria

**Chronic**
- Nutcracker/vascular malformations
- Nephrolithiasis/Nephrocalcinosis
- Crystalluria
- Munchhausen by proxy / Misuse

**UTI**
- Recurrent
- With Crea increase
- With scars

**Acute**
- Trauma
- Tumor
- Cystitis
- Exercise
- Medications
- Menarche
Chronic glomerular hematuria

Chronic GN
- persistent events of macrohematuria
- persisting proteinuria
- increase in serum creatinine
- Hypertension

Alport-Syndrome
- Hardness to hear
- RRT in family
- +/- Proteinuria
- +/- Hypertension

Benign familial hematuria/isolated microhematuria
- No deafness
- no RRT in family
- no proteinuria
- no Hypertension
- Sonographically normal kidneys
- No increase in serum creatinine

Kidney biopsy

Renal protective treatment

Yearly controls
Questions??