HEMATURIA EVALUATION: AN OPPORTUNITY TO ENHANCE THE VALUE OF CARE?

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Hematuria as a Marker of Occult Urinary Tract Cancer: Advice for High-Value Care From the American College of Physicians

Matthew Nielsen, MD, MS, and Amir Qaseem, MD, PhD for the High Value Care Task Force of the American College of Physicians

Background: The presence of blood in the urine, or hematuria, is a common finding in clinical practice and can sometimes be a sign of occult cancer. This article describes the clinical epidemiology of hematuria and the current state of practice and science in this context and provides suggestions for clinicians evaluating patients with hematuria.

Methods: A narrative review of available clinical guidelines and other relevant studies on the evaluation of hematuria was conducted, with particular emphasis on considerations for urologic referral.

High-Value Care Advice 1: Clinicians should include gross hematuria in their routine review of systems and specifically ask all patients with microscopic hematuria about any history of gross hematuria.

High-Value Care Advice 2: Clinicians should not use screening urinalysis for cancer detection in asymptomatic adults.

High-Value Care Advice 3: Clinicians should confirm heme-positive results of dipstick testing with microscopic urinalysis that demonstrates 3 or more erythrocytes per high-powered field before initiating further evaluation in all asymptomatic adults.

High-Value Care Advice 4: Clinicians should refer for further urologic evaluation in all adults with gross hematuria, even if self-limited.

High-Value Care Advice 5: Clinicians should consider urology referral for cystoscopy and imaging in adults with microscopically confirmed hematuria in the absence of some demonstrable benign cause.

High-Value Care Advice 6: Clinicians should pursue evaluation of hematuria even if the patient is receiving antiplatelet or anticoagulant therapy.

High-Value Care Advice 7: Clinicians should not obtain urinary cytology or other urine-based molecular markers for bladder cancer detection in the initial evaluation of hematuria.

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For author affiliations, see end of text. This article was published at www.annals.org on 26 January 2016.

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<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Year</th>
<th>Reference</th>
<th>Case Definition</th>
<th>Components of Evaluation</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dipstick</td>
<td>Microscopic Urinalysis Results, erythrocytes/HPF</td>
</tr>
<tr>
<td>American Urological Association guideline</td>
<td>2012</td>
<td>12</td>
<td>Inadequate</td>
<td>≥3</td>
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<td>2008</td>
<td>32</td>
<td>≥1 heme</td>
<td>Not required</td>
</tr>
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</table>

CT = computed tomography; HPF = high-powered field; IVP = intravenous pyelography.
Areas of uncertainty (Table 1)

- Age threshold for urology evaluation (35-50)
- Imaging modality of choice (CT for all vs. risk-stratified approach to CT vs. ultrasound for all)
- Nephrology evaluation as concurrent vs. alternative pathway
Limitations of Evidence

- Health Technology Assessment (2006, UK National Institute for Health Research)
  - 79 different diagnostic algorithms relevant to hematuria, none of which formally evaluated in terms of effect on patient outcomes

- 2012 AUA Guideline on AMH
  - None of 22 specific recommendations supported by evidence higher than Grade C
Uncertainty regarding indications for referral and components of evaluation identified as major gap in current practice / policy

Concerns about harms of CT urogram

- Major difference between guidelines
- Substantially differential effectiveness / yield?
- Highest radiation dose of common CT protocols
- Harm>>benefit for large subgroups
- Emerging evidence base supporting risk-stratified approach
Stratifying Risk of Urinary Tract Malignant Tumors in Patients With Asymptomatic Microscopic Hematuria

Ronald K. Loo, MD; Stephen F. Lieberman, MD; Jeff M. Slezak, MS; Howard M. Landa, MD; Albert J. Mariani, MD; Gary Nicolaen, MD; Ann M. Aspia, MD; and Steven J. Jacobsen, MD, PhD

FIGURE. Comparison of cancer detection rates in test and validation cohorts.
Overall cancer diagnosis: 2.9%
  - AUA Guidelines’ pooled data analysis: 3.3%

Upper tract findings:
  - Loo et al (n=4414): 0.3% RCC; zero upper tract TCC
  - Edwards et al (n=4020, 46.8% GH)
    - 3.7% bladder cancer, 1% RCC
    - 0.2% upper tract TCC (n=10; 7=GH, 3=NVH)
      - none in men <50, women <70

Edwards et al, *BJU Int* 2006; 97:301
Area Under the Curve

Comparison of ROC Curves for Hematuria Risk Index and AUA Guideline

Sensitivity
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
100
1-Specificity

AUA
Hematuria Risk Index
KP Risk Index—Implemented 2012

Low risk: 33%
Moderate risk: 53%
High risk: 14%

3782/4414 patients in MCP study would avoid CT in current protocol
What are the tradeoffs?

Table 1. Organizational Recommendations for the Initial Evaluation of Average-Risk Patients With Asymptomatic Microscopic Hematuria

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Year</th>
<th>Reference</th>
<th>Dipstick</th>
<th>Microscopic Urinalysis Results, erythrocytes/HPF</th>
<th>Positive/Total Test Results, n/N</th>
<th>Age Threshold, y</th>
<th>Cystoscopy</th>
<th>Preferred Imaging Method</th>
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</thead>
<tbody>
<tr>
<td>American Urological Association guideline</td>
<td>2012</td>
<td>12</td>
<td>Inadequate</td>
<td>≥3</td>
<td>1</td>
<td>≥35</td>
<td>All patients</td>
<td>CT urography</td>
</tr>
<tr>
<td>American Urological Association best practice policy</td>
<td>2001</td>
<td>16</td>
<td>Inadequate</td>
<td>≥3</td>
<td>2/3</td>
<td>≥40</td>
<td>All patients</td>
<td>CT urography or IVP/ultrasoundography</td>
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<tr>
<td>Canadian Urological Association guideline</td>
<td>2008</td>
<td>30</td>
<td>Inadequate</td>
<td>≥2</td>
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<td>All patients</td>
<td>Renal ultrasoundography</td>
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<td>≥50</td>
<td>All patients</td>
<td>Renal ultrasoundography</td>
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CT = computed tomography; HPF = high-powered field; IVP = intravenous pyelography.

Gross or Microscopic Hematuria in Primary Care Setting

Order Lab Tests
- Urine C&S
- Osmolality

Gross hematuria?

Age 35-49
- NO
- Gross hematuria?
  - NO
  - Age ≥ 50
    - Risk factors (male or smoker)
    - Renal sono Urology
    - CT urogram Urology
  - NO
  - Renal sono Urology
  - CT urogram Urology

- YES
  - CT KUB Urology

- YES
  - Global pain

- NO
  - Global pain

- NO
  - Global pain

- NO
  - Global pain

- NO
  - Global pain

- NO
  - Global pain

- NO
  - Global pain

- NO
  - Global pain
“A model is a lie that helps you see the truth.”
Howard Skipper, PhD
Hypothetical cohort

Assign:
- Sex
- Age
- Cancer status
- Cancer location
- History of gross hematuria
- Smoking status
- Urine RBC count

Risk stratification (KP/HRI)
- Low risk: no further work-up
- Moderate risk: cystoscopy + renal ultrasound
- High risk: cystoscopy + CT

Canadian guidelines
- Patients aged ≥ 40 years: cystoscopy + renal ultrasound

Dutch guidelines
- Patients aged ≥ 50 years: cystoscopy + renal ultrasound

Assess outcomes:
- Costs
- Cancer detection rates
- Missed cancer cases
- False positive cases
- Short-term complications
  - Contrast allergy
  - Contrast nephropathy
  - Dysuria
  - UTI
- CT radiation-induced harms
  - Secondary cancers
  - Attributable deaths

Patient characteristics
- Model-based comparison of alternatives
- Initial encounter
- Post-encounter events
- Hematuria cohort studies
- Clinical guidelines
- Literature review
### Incremental cost-effectiveness results

Cost-effectiveness of different evaluation strategies of AMH patients (N=100,000)

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Total costs to cohort</th>
<th>Cancer cases detected*</th>
<th>Incremental costs</th>
<th>Incremental cancer cases detected</th>
<th>ICER (cost per cancer case detected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch</td>
<td>$42,470,698</td>
<td>3,234</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Canadian</td>
<td>$44,303,924</td>
<td>3,288</td>
<td>$1,833,227</td>
<td>54</td>
<td>$34,072</td>
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<td>KP/HRI strategy</td>
<td>$46,623,885</td>
<td>3,358</td>
<td>$2,319,960</td>
<td>70</td>
<td>$32,939</td>
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<tr>
<td>AUA</td>
<td>$81,640,142</td>
<td>3,495</td>
<td>$35,016,257</td>
<td>137</td>
<td>$254,745</td>
</tr>
</tbody>
</table>

*Total number of detected cancer cases (bladder, renal, and ureteral/renal pelvis).

ICER - incremental cost-effectiveness ratio.

@mivlage @StephWheelerUNC
Potential harms

Note: KP-HRI - Kaiser Permanente recommendations using the Hematuria Risk Index

- False positive cases from all test evaluations (CT, cystoscopy, renal ultrasound)
- Initial evaluation costs of multiphase abdominal/pelvic CT,
Cancer risks are not trivial

Smith-Bindman, Arch Int Med 2009 169(22): 2078-86
Typical summary of Cancer Risks by Age at Exposure
Cancer Risk: Actually a U-Shaped Distribution

Preston Radiation Research 2007; 168(1)1-64
Health economic outcomes for the simulated cohort (N=100,000)

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<tr>
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<th>Canadian guidelines</th>
<th>Dutch guidelines</th>
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<tbody>
<tr>
<td>Total diagnosed cancer cases</td>
<td>3,492</td>
<td>3,358</td>
<td>3,290</td>
<td>3,237</td>
</tr>
<tr>
<td>Missed cancer cases</td>
<td>26</td>
<td>160</td>
<td>228</td>
<td>281</td>
</tr>
<tr>
<td>Radiation-induced cancer cases</td>
<td>780</td>
<td>91</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Deaths from radiation-induced cancer</td>
<td>441</td>
<td>51</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Short-term complications from CT</td>
<td>2,595</td>
<td>310</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total false positive cases(^a)</td>
<td>16,390</td>
<td>8,254</td>
<td>6,728</td>
<td>6,441</td>
</tr>
<tr>
<td>Total costs per patient(^b)</td>
<td>$1,159</td>
<td>$507</td>
<td>$443</td>
<td>$424</td>
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</table>

Note: KP-HRI - Kaiser Permanente recommendations using the Hematuria Risk Index
\(^a\)False positive cases from all test evaluations (CT, cystoscopy, renal ultrasound)
\(^b\)Initial evaluation costs of multiphase abdominal/pelvic CT, renal ultrasound, and cystoscopy
Medicine used to be simple, ineffective and relatively safe. Now it is complex, effective, and potentially dangerous.

Sir Cyril Chantler,
Dean of Guy’s Hospital, London
5.1 For each recommendation provide:

- A summary of relevant available evidence, description of the quality, quantity and consistency of aggregate available evidence
- A clear description of the potential benefits and harms
- An explanation of the part played by values, opinion, theory and clinical experience in deriving the recommendation
- A description of any differences of opinion regarding the recommendation
Acknowledgements

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Thank You

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