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Renal Ultrasound in the Evaluation of Acute Kidney Injury: Developing a Risk Stratification Framework

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Renal Ultrasound in the Evaluation of Acute Kidney Injury: Developing a Risk Stratification Framework. Adam Licurse (Yale School of Medicine, New Haven, CT), Michael Kim (Yale College, New Haven, CT), Howard Forman (Yale Department of Radiology, Yale University, School of Medicine, New Haven, CT), Richard Formica and Chirag Parikh (Section of Nephrology, Department of Internal Medicine, Yale University, School of Medicine, New Haven, CT), Danil Makarov (Robert Wood Johnson Clinical Scholars Program, Yale University, School of Medicine, New Haven, CT), James Dziura (Yale Center for Clinical Investigation, Yale University, School of Medicine, New Haven, CT), Cary Gross (Section of General Medicine, Yale University, School of Medicine, New Haven, CT)

Background: In adult inpatients with acute kidney injury (AKI), clinicians routinely order a renal ultrasound (RUS). It is unclear how often this test provides clinically useful information.

Specific Aims: We aimed to develop a simple decision rule that will identify those patients with AKI who are at low risk of hydronephrosis (HN) on RUS, or HN requiring an intervention (HNRI; defined as nephrostomy tube or stent placement). Using this classification scheme, we also aimed to evaluate the effectiveness of RUS evaluation in each group, in terms of number needed to screen (NNS).

Methods: We conducted a cross-sectional study, divided into derivation and validation samples. Our sample consisted of 997 U.S. adult inpatients who were admitted to Yale-New Haven Hospital (YNHH) from January 1, 2005 to May 1, 2009, diagnosed with AKI, and received diagnostic RUS in the evaluation of their elevated Creatinine. Pregnant women, renal transplant recipients, and patients with recently diagnosed HN were excluded. Demographic and clinical characteristics were abstracted from the medical records, including pre-existing comorbidities, inpatient course (e.g. use of pressors) and exposures (e.g. contrast or nephrotoxic medications). A multivariable logistic regression model was used to create risk strata for HN and HNRI; a separate sample was used for validation. We assessed the presence of incidental findings on RUS for each stratum (i.e. other clinically useful findings other than presence of HN). In the validation sample, patients were classified according to their risk of HN; this system was assessed in terms of its sensitivity, specificity, negative predictive value (NPV), NNS, and cost of RUS evaluation per positive study.

Results: In the derivation sample of 200 patients, seven factors were found to be associated with HN: history of HN, recurrent urinary tract infections, diagnosis consistent with obstruction, non-black race; and *absence* of – exposure to nephrotoxic medications, congestive heart failure, or pre-renal status prior to AKI. Patients were assigned to the low risk group when 0-2 risk factors were present, medium risk group when 3 factors were present, and high risk group when 4 or

more factors were present or when there was a documented history of HN. Among 797 patients in the validation sample (mean age of 65.6 years), 10.6% had HN and 3.3% had HNRI. Of the 223 patients assigned to the low risk group, seven (3.1%) had HN and one (0.4%) had HNRI (223 patients needed to screen to find one HNRI). In this group, there were no incidental findings on RUS unknown to the clinical team. In the higher risk group, 15.7% had HN and 4.7% had HNRI. The NNS to find one case of HN in the low risk group is 32, or $6,371 per positive study (at a cost of $200 per study). For HNRI, the NNS for the low risk group in the same model was 223, at a cost of $44,600 per positive study.

Conclusions: In adult inpatients with acute kidney injury, specific factors can identify patients who are unlikely to have hydronephrosis, or hydronephrosis requiring an intervention, on renal ultrasound.

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Introduction

The problem of high healthcare spending in the U.S. is a familiar one in this year of healthcare reform: we pay more for our care than any other country and aren't healthier as a result. [1, 2] The case for cost-control is persuasive – rising costs degrade employer-sponsored insurance, reduce access to care leaving more Americans without insurance, and displace spending on other societal priorities. [3, 4] Cost-control has received much attention from policy-makers in this first year of the Obama administration, who have stressed the importance and cost-saving potential of comparative-effectiveness research, preventive care, disease management, and health information technology in the recent push for reform. [5]

At the heart of the debate surrounding cost-control are two questions: how are we spending our healthcare dollars and what are we getting in return? Much of the most relevant and frequently cited research that has helped answer these questions at a national level comes from the Dartmouth Atlas of Health Care. [6] The Dartmouth group evaluates Medicare spending by "hospital referral region", a unit of analysis which breaks down the nation according to patterns of use of local hospitals. By considering utilization in this way, regional variation in spending and clinical outcomes can be assessed.

What the Dartmouth data show is marked variation in healthcare spending by geographic area. In some areas, the results are staggering. Between 1992 and 2006, for example, the difference in Medicare spending between East Long

Island and San Francisco was approximately one billion dollars. [7] These differences remain after adjustment for regional differences in patient health. In the setting of this marked regional variation, much attention has been paid to finding out where the money is going.

One key area of focus has been the use of imaging services by physicians. Expenses for high technology imaging, including magnetic resonance imaging (MRI), computed tomography (CT), and sonography have grown more than almost any type of health care service in recent years. [8-10] According to a recent report from the Government Accountability Office (GAO), from 2000 to 2006, Medicare spending on radiology services under the physician fee schedule more than doubled. [11]

Evidence from regional variation research suggests that much of this spending is unnecessary. In the GAO report, substantial variation was noted in imaging utilization. For example, in-office imaging spending per Medicare beneficiary varied from $62 in Vermont to $472 in Florida. [11] The Dartmouth data shows similar trends: compared to Medicare patients in the lowest-spending regions, patients in the highest-spending regions have more frequent physician visits and undergo more MRI procedures (21.9 vs. 16.6 per 100 beneficiaries) and CT scans (61.4 vs. 46.9 per 100). [7] As previous studies have suggested that as high as 30% of imaging services may be inappropriate, marked variation in utilization by region raises the question of whether a large portion of radiology services are unnecessary. [12]

One explanation that likely accounts for much of this marked variation is discretionary decision-making: how physicians decide to allocate diagnostic and therapeutic modalities in caring for their patients. [13] In hospital settings, these decisions are shared both by clinicians caring for patients and radiologists advising imaging choices. Radiologists, for their part, have contributed significantly to the literature on evidence-based support of imaging decisions. For instance, the American College of Radiology (ACR) publishes comprehensive appropriateness criteria to inform decision-making surrounding specific clinical questions, such as the proper initial imaging of a palpable breast mass in a woman 30 years or older. [14] These guidelines are based on outcomes data as well as broad-based empiric consensus among physician committees and societies. The ACR criteria have been increasingly utilized by both institutions and payers, including the largest private insurance company in the U.S., UnitedHealth Group. [15] When implemented, these guidelines have the potential for significant reductions in imaging use, with some studies reporting reductions of 40-50%. [16]

Another important form of decision support that may improve resource utilization as well as clinical outcomes is the use of clinical decision rules (CDRs). [17] Like appropriateness criteria, these algorithms are designed for specific clinical questions and help guide clinicians through diagnostic and management decisions. However, CDRs go a step further, by allowing clinicians to use clinical factors to assess the likelihood of a particular result, diagnosis, or other outcome, rather than just the appropriateness of a certain test. In certain situations, CDRs

can help determine the pretest probability of a diagnostic test, identify the most beneficial treatment modality, or predict a patient's prognosis. [18-21] Many have become commonplace in clinical medicine, helping clinicians decide when to treat sore throats, establishing the likelihood of pulmonary embolus, screening for common conditions that often go unnoticed such as alcohol abuse, and estimating risk of future conditions such as the development of delirium in hospitalized patients. [22-25]

A number of high impact studies have produced CDRs that guide decision-making around imaging. One important study examined the use of computed tomography (CT) of the head by clinicians before performing lumbar puncture for adult patients with suspected meningitis. [26] In this prospective study of 301 adults in the YNHH Emergency Department, clinical features such as a history of central nervous system disease or seizure within one week before presentation were found to be associated with an abnormal finding on CT. Using these features, a subgroup of patients could be identified who were unlikely to have an abnormal CT result. In principle, these patients could be managed without CT testing and thus avoid the unnecessary radiation exposure of the study and a prolonged stay in the emergency department.

Perhaps the best-known CDR in imaging decision support is the Ottawa Ankle Rule. In the original study from which the rule was developed, 750 adults with acute ankle injuries were assessed for 32 standardized clinical variables, such as bony tenderness at pre-specified locations. [27] These variables were used to design decision rules to predict the presence of fractures on foot and

ankle radiographic series. In the main study, the two rules correctly predicted all significant fractures to achieve a sensitivity of 100%. The “cut-point” was constructed to achieve as high a sensitivity as possible at the expense of a high specificity (40% in the main study) because the authors assumed that clinician use would be optimized if there was little concern about missing fractures without imaging. After a second large study to refine these rules, they were prospectively validated in two other emergency departments and remained 100% sensitive. [28]

Though CDRs are common and continuously developed, there remain important and frequently encountered clinical questions for which little decision support exists. Acute kidney injury (AKI) is one major example. AKI is a common problem in hospitalized patients, with an incidence that has increased from approximately 10 to 25 per 1000 discharges over the last 15 years. [29] Conceptually defined as an abrupt decline in renal function, AKI is significantly associated with increased mortality. [30] Early epidemiologic work assessed hospital-acquired disease through cohort studies. In one of the first prospective cohort studies of AKI, published in 1983, hospital-acquired disease was most often caused by decreased renal perfusion (42%), with less likely precipitating factors including major surgery, contrast exposure, and aminoglycoside use. [31] These findings were replicated in more recent cohorts, with compromises in renal perfusion remaining the most common causes (including congestive heart failure, cardiac arrest, and volume contraction) [32]. Multi-center cohort studies and administrative database studies have showed similar epidemiological patterns.

[33, 34] In one recent study which included both hospital- and community-acquired AKI, the most common cause of acute tubular necrosis (45%) followed by pre-renal disease (21%, defined as a decline in renal function rapidly reversed by fluid administration) and urinary tract obstruction (10%). [33]

One of the diagnostic modalities used in the initial evaluation of AKI is a renal (or retroperitoneal) ultrasound (RUS). It is often ordered to exclude an obstructive etiology. [35, 36] If diagnosed, patients with an obstruction may require further interventions that can treat the underlying cause of the AKI. However, as described above, the vast majority of AKI is not caused by obstruction. [29] In fact, hydronephrosis (HN), the evidence of obstruction on imaging, is a rare finding in patients with AKI, present on between one and 10% of ultrasound studies ordered in this setting. [33, 37-39] As a result, RUS does not change clinical management in the majority of AKI patients who undergo the test. Additionally, it has been suggested that obtaining a RUS might yield additional information that is clinically useful, yet little is known about how frequently this occurs. [39, 40]

Because RUS is relatively expensive, costing approximately $200 per study, targeting RUS evaluation towards patients with a higher risk of HN would not only be clinically useful, but could potentially conserve resources. [41] This type of patient-centered decision making, and targeting of testing towards those most likely to benefit, has been recently recommended by the Institute of Medicine and is a central component of comparative effectiveness research. [42]

Further information is needed in order to stratify patients with AKI according to the likelihood that a RUS will yield clinically meaningful results. We sought to create a stratification system that would help clinicians ascertain a patient's risk of renal obstruction among those with AKI. This approach would improve the pre-test probability of a positive finding on RUS, and hence the likelihood of influencing the post-test management of patients most likely to benefit. Specifically, we designed and validated a decision rule that would identify those patients at low risk of obstruction, as well as those patients at low risk for an obstruction requiring surgical intervention. As a secondary analysis, we evaluated the additional value of RUS by assessing the presence of other non-HN, but clinically useful findings. Finally, we assessed RUS utilization at YNHH and the effectiveness of RUS screening in terms of NNS.

Hypothesis

Our hypothesis is that clinical and demographic factors can be used to develop a decision rule to classify AKI patients according to their risk of HN. Moreover, for patients at low risk of HN, RUS would offer little value to the diagnostic workup of their AKI, even when incidental findings were revealed.

Specific Aims

1. To assess the association between baseline patient characteristics and:
    a. HN on renal ultrasound
    b. HN on renal ultrasound that required an intervention;
2. To develop a simple, transportable decision rule (based on demographic and clinical factors found to be associated with HN in Aim 1) for identifying patients with AKI who are unlikely to benefit from a RUS;
3. To validate the decision rule in a separate group of patients;
4. To determine the prevalence of other non-HN findings on RUS according to risk group;
5. To assess the effectiveness of RUS screening in terms of NNS.

Methods

Adam Licurse contributed to each stage of this study, including conception and design, acquisition of data, analysis and interpretation of data, statistical analysis, and drafting of the thesis.

Study Design

We conducted a cross-sectional study of hospitalized patients with AKI, using separate derivation and validation samples. For patients with AKI who met inclusion criteria, we abstracted demographic and clinical data, as well as the results of their RUS study. A derivation sample was analyzed using the presence of HN on RUS as the dependent variable of interest. Strata were created based on presence of risk factors associated with HN in the derivation sample. A validation sample was developed using all RUS studies performed over a one-year period, and the presence of HN and HNRI was assessed in each risk group. This study was approved by the Yale Human Investigation Committee in April of 2008.

Patients

A two-step approach was used to create samples of inpatients with AKI who undergo RUS. First, patients were identified by searching the YNHH imaging database for RUS studies performed on hospitalized adults ($\geq$ 18 years of age) with suspected AKI from January 1, 2005 to May 1, 2009. Suspicion of

AKI was defined by a list of terms we piloted in a three-month analysis of RUS studies, including “hydronephrosis,” “creatinine,” and “arf” (for complete list, see appendix). The strategy was designed to create a sample of patients who received an RUS in the workup of elevated Creatinine, rather than simply any indication (e.g. we excluded studies ordered to assess stone disease without concern for compromised renal function). On the other hand, only those patients who received a RUS were included, rather than all AKI patients, in order to construct an enriched sample of patients whose clinicians were concerned enough about an obstructive etiology to order a RUS (i.e. patients at such low risk for obstruction that they never received a RUS were not included).

Second, patients were excluded who did not meet the definition of AKI: an absolute rise in serum creatinine (CR) of 0.3 mg/dL from baseline, based on the peak serum CR during an inpatient admission. Though AKI is a complex disorder with a changing definition, we operationalized it according to a recent recommendation from the *Acute Kidney Injury Network*, whose members represent key societies in nephrology. [43] Baseline serum CR was defined as the lowest value in the three months prior to admission (if unavailable, then in order: the lowest value 12 months prior to admission, the baseline value described in the admission note, and finally the lowest value during the current admission). Additional exclusion criteria included pregnancy, history of a renal transplant, and a previous diagnosis of HN within the 30 days prior to the study date (these were considered follow-up studies, rather than primary diagnostic evaluations).

Separate derivation and validation samples were constructed from those eligible studies (Figure 1). In the derivation sample, 100 studies with HN on RUS and 100 randomly selected normal studies were included. This approach was used to maximize power in the derivation sample, as HN is a relatively rare finding. In the validation sample, all eligible studies from January 1, 2008 to May 1, 2009 were included. In both derivation and validation, one study per patient was included.

Figure 1. Study flow diagram

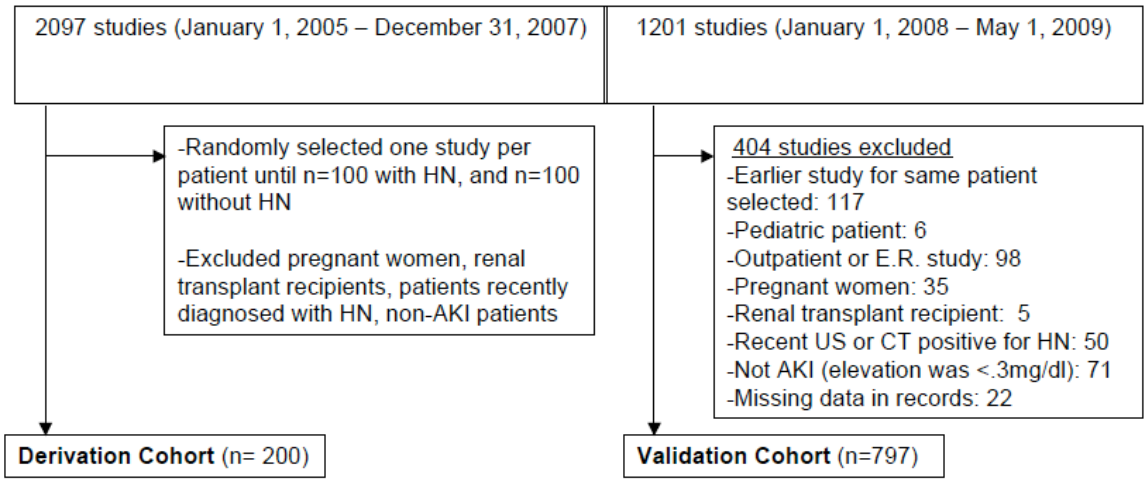

Figure 1: Sampling strategy in derivation and validation cohorts, including selection criteria.

Assessment of Risk Factors and Outcomes

We chose candidate risk factors based on clinical relevance and description in the salient medical literature. [38-40] All data was abstracted from medical records (discharge summaries and clinical notes) by four trained reviewers. The abstraction form was piloted and refined on a sample of 50 patients before use in the study sample. Inter-observer agreement was calculated for 10% of the derivation sample, and was found to be 95% overall. Chart reviewers were blinded to the RUS result for each patient. [19, 44] Demographic data included race, age, and sex. Clinical data was abstracted in two general categories: those factors predisposing a patient to obstructive AKI, such as history of abdominal or pelvic cancer, and factors making another etiology more likely (e.g. hemodynamic instability or pressor use for pre-renal AKI and acute tubular necrosis, or exposure to intra-arterial contrast for contrast-induced nephropathy). Other variables included laboratory data (e.g. granular casts on urinalysis) or certain inpatient exposures (e.g. radiographic contrast). Clinical variables were only coded if they were available and known by the clinical team prior to the maximum serum CR value *and* RUS date (for full list of variables, see Table 1).

All data were constructed as categorical variables, except for the mean rise in CR, age and white blood cell count, which were constructed as continuous variables. Age and white blood cell count were then dichotomized based on preliminary bivariate analysis. Inpatient exposure to contrast was defined as any

angiography or cardiac catheterization, owing to their association with contrast-induced nephropathy. [45, 46] Hospital-acquired AKI was defined as AKI for which the maximum serum CR occurred greater than two days after the date of admission. One variable was coded two ways. In our primary model “No history of pre-renal status prior to AKI” only included history of sepsis during current admission or use of pressors, while in a second model (designed for sensitivity analysis), this variable *also* included history of hypotension prior to the onset of AKI, defined as at least two consecutive episodes of systolic blood pressure below 80 mm Hg or diastolic pressure below 60 mm Hg.

The study outcomes were HN, and HN requiring intervention (HNRI). Any RUS report which described “hydronephrosis” in the findings section was considered an outcome event. HNRI was defined as a RUS-diagnosed HN followed by either a urologic stent or nephrostomy tube placement performed after the RUS date. As a secondary analysis, we also assessed the prevalence of incidental non-HN findings on RUS. These were defined as anatomic abnormalities or masses described in the RUS report we included in our study (for a list of search terms, see appendix). To determine whether these findings were previously known to the clinical team, we searched for prior documentation in the patient’s chart or imaging history, dating back to the beginning of the patient’s medical information available at YNHH.

Statistical analysis

The association between candidate risk factors and presence of HN on RUS was initially assessed for the derivation sample using bivariate logistic regression analysis . Clinically relevant variables with a p-value < 0.1 from the bivariate analysis were used to generate a logistic regression model in the derivation sample. A “history of HN” was defined as a documented history of HN in the medical record or any previous imagining history of HN in the prior two years. In multivariable logistic regression, variables were removed in order of decreasing p-value and the model’s quality was assessed at each step. We calculated the AIC and C-statistic for each iteration. Stepwise regression was continued until the model’s quality was optimized (according to the C-statistic and AIC). We selected the model with the best accuracy (i.e. discrimination), and applied it to the validation sample. For a sensitivity analysis, we evaluated a second model, which differed from the main model only in the definition of a single clinical variable (“pre-renal status”) which showed poorer discrimination between HN and normal patients, but had a lower AIC than the primary model.

A risk score was developed based on the individual odds ratio (OR) of each variable in the model. As all but one risk factor had similar ORs, they were each awarded a risk point of one. Any patient with a known history of HN was assigned *a priori* to the high risk group, as these patients were considered most likely to need a RUS in the setting of AKI. In fact, this variable was the only one with an OR greatly different from the others (approximately 11, compared to 2-3). Using this scoring system, we segregated patients into three risk groups based

on the prevalence of HN among patients with each risk score. This stratification was then applied to a validation sample, the necessary size of which was calculated to be 800 patients. This sample size would provide 80% power in the validation sample to detect a prevalence of HNRI in the low risk group of 0.3-0.5%.

Finally, we calculated the number needed to screen (NNS) to find one case of HN or HNRI for each risk group (i.e. the total number of patients in each group divided by number of outcome events). To estimate cost associated with a positive finding, we multiplied the NNS by the approximate cost per study according to Medicare reimbursement. [41]

Results

Derivation sample and bivariate analysis

Our derivation sample consisted of 100 patients with HN and 100 patients without HN. The mean age 65.6 years, 56.5% were male and 25.5% were black; none of these characteristics was significantly related to HN status. Overall, HN patients were more likely to have a previous diagnosis of HN (on RUS or abdominal/pelvic CT; 3% of normal patients vs. 28% of HN patients, $p < 0.001$), a history of abdominal or pelvic cancer (14% vs. 38%, $p <0.001$), previous pelvic surgery (10% vs. 19%, $p=0.11$), a single functional kidney (1% vs. 6%, $p=0.054$), or hematuria (4% vs. 13%, $p=0.023$) during the selected admission (Table1). A past history of urologic dilatation on imaging not considered HN, described as “pelvicaliectasis” or “caliectasis”, was not significant, nor was an imaging history of anatomic abnormalities, stones, masses, or cysts.

Conversely, patients with a normal RUS were more likely to have granular casts on urinalysis (28% vs. 18%, $p=0.09$), a white blood cell count greater than 16,000 cells/mm^3 (48% vs. 24%, <0.001), a history of congestive heart failure (22% vs. 13%, $p=0.094$), documented hypotension during the current admission (55% vs. 39%, $p=0.011$); or exposure to either aspirin (>81mg/day), a diuretic or ACE-inhibitor, or intravenous vancomycin during the current admission (63% vs. 39%, $p=0.001$). Use of *any* IV antibiotic was also assessed, but was not significant.

Table 1. Patient characteristics and HN status, derivation sample

Candidate predictor	Patients without HN, % (n=100)	Patients with HN, % (n=100)			P-Value[a]
		Total HN	No intervention	Intervention	
Demographics					
Age <55	**28**	**17**	14	3	0.063
Race, non-black	**69**	**80**	59	21	0.074
Male sex	**56**	**56**	42	14	1.00
Laboratory data					
Granular casts on urinalysis (3 days before or after maximum serum CR value)	**28**	**18**	16	2	0.093
White blood cell count > 16,000 cells/mm^3	**48**	**24**	15	9	<0.001
Mean absolute rise in serum CR (md/dL)	**1.97**	**2.67**	4.05	2.23	0.11
Urine output (<500 ml/day)	**11**	**12**	7	5	0.76
Clinical history consistent with obstructive AKI					
Documented history of HN	**1**	**9**	4	5	0.0097
History of HN on previous imaging (CT or RUS)	**3**	**28**	16	12	<0.001
Abdominal or pelvic Cancer	**14**	**38**	24	14	<0.001
Recurrent UTIs (mentioned by name in chart, or $\geq$ 2 in year prior to current	**6**	**19**	15	4	<0.001

Recurrent UTIs (mentioned by name in chart, or ≥ 2 in year prior to current admission)	**6**	**19**	15	4	<0.001
BPH	**10**	**14**	13	1	0.38
One functional kidney	**1**	**6**	4	2	0.054
Neurogenic bladder	**0**	**7**	6	1	0.0071
Pelvic surgery	**11**	**19**	16	3	0.11
Flank pain	**2**	**6**	5	1	0.15
Hematuria	**4**	**13**	10	3	0.023
Clinical history consistent with non-obstructive AKI					
Congestive heart failure	**22**	**13**	9	4	0.094
Hypotension (≥ 2 measurements of either SBP<100 or DBP<80 within 5 days prior to maximum serum CR level)	**55**	**39**	30	9	0.011
Sepsis (mentioned directly in chart)	**19**	**10**	7	3	0.071
Cirrhosis	**5**	**3**	0	0	0.47
Hypertension	**68**	**61**	45	16	0.30
Diabetes	**45**	**33**	27	6	0.082
Chronic kidney disease	**34**	**28**	18	10	0.36
Hospital-acquired AKI (AKI for which the maximum serum CR value was reached > 2 days after admission date)	**46**	**35**	27	8	0.005
Medications and nephrotoxic exposures (within 10 days prior to maximum serum CR value)					
IV Contrast (angiography or cardiac catheterization)	**1**	**6**	6	0	0.054

Diuretic or ACE-inhibitor	**42**	**20**	14	6	<0.001
Pressor	**18**	**6**	4	2	0.024
Vancomycin	**44**	**25**	20	5	0.005
Any IV antibiotic	**59**	**55**	51	4	0.57

[a]value for pairwise comparison of patients with vs. patients without HN

NNS = number needed to screen, HN = hydronephrosis, CT = computed tomography, RUS = renal ultrasound, UTI = urinary tract infection
BPH = benign prostatic hyperplasia, SBP = systolic blood pressure (DBP = diastolic), CR = creatinine
AKI = acute kidney injury, NSAID = non-steroidal anti-inflammatory, ACE = angiotensin-converting enzyme

Derivation of classification schemes

The final model was selected based on its high accuracy and low AIC (Table 2). It consists of 7 variables: history of HN (high risk group), recurrent urinary tract infections (1 point), diagnosis consistent with possible obstruction (1 point), non-black race (1 point); and *absence* of the following – exposure to inpatient nephrotoxic medications (1 point), congestive heart failure (1 point), or pre-renal status prior to AKI (1 point). This system was applied to the derivation sample and the prevalence of HN was assessed for each risk score. Three distinct risk groups emerged: low ($\leq$2 points, 1-20% prevalence of HN), medium (3 points, 20-40% HN) and high (>3 points, >40% HN).

Table 2. Multivariable model, derivation sample

Patient characteristic	% with HN	Adjusted Odds Ratio (95% CI, adjusted p-value)	
		Model 1 (primary)	**Model 2**
Race			
Non-black	53.7	2.1 (0.1-4.4, 0.060)	2.2 (1.0-4.6, 0.046)
Black	39.2	1.0	1.0
History of recurrent urinary tract infections			
Yes	76.0	2.7 (0.8-8.5, 0.10)	2.3 (.7-7.1, 0.16)
No	46.3	1.0	1.0
Diagnosis consistent with possible obstruction[a]			
Yes	67.4	2.4 (1.2-4.6, 0.010)	2.4 (1.2-4.7, 0.009)
No	36.0	1.0	1.0
History of HN[b]			
Yes	90.3	11.1 (3.0-41.3, <0.001)	11.7 (3.0-45.2, <0.001)
No	42.6	1.0	1.0
History of CHF			
No	52.7	2.1 (0.8-5.2, 0.12)	2.0 (0.8-5.0, 0.14)
Yes	37.1	1.0	1.0
History of pre-renal status prior to AKI (use of pressors or history of sepsis)			
No	53.0	2.3 (0.9-6.2, 0.10)	
Yes	35.3	1.0	
History of pre-renal status prior to AKI (use of pressors, history of sepsis, or hypotension)			
No	60.2		2.1 (0.9-3.6, 0.041)
Yes	40.2		1.0

Exposure to nephrotoxic medications prior to AKI[c]			
No	62.2	2.1 (1.0-3.85, 0.053)	1.8 (0.9-3.6, 0.092)
Yes	38.2	1.0	1.0
Model Characteristic		**Model 1 (primary)**	**Model 2**
AIC		237	235
Accuracy		74%	73%

[a]Diagnosis consistent with possible obstruction = benign prostatic hyperplasia, abdominal or pelvic cancer, neurogenic bladder, single functional kidney, or previous pelvic surgery.
[b]History of HN = documented history of HN in the medical record or any previous imagining history of HN in the two years prior to the current RUS.
[c]Nephrotoxic medications = aspirin (>81mg/day), diuretic, ACE-inhibitor, or intravenous vancomycin.

HN = hydronephrosis , CHF = congestive heart failure, AKI = acute kidney injury
AIC = Akaike information criterion

Validation of classification schemes

Our validation sample consisted of 797 patients (mean age=65.6). Of these, 54.6% were male and 22.8% were black. Overall, 10.6% had HN, of which 31.7% required an intervention (3.3% of total sample).

Two models were used in this sample. Model 1 was our primary model, and differed from model 2 only in its definition of pre-renal status. It was more sensitive for HN, but included fewer patients in the low risk group (i.e. less specific). Out of 797 patients, 223 (27.8%) were assigned to the low risk group, of whom 3.1% had HN [1 patient, or 0.4% (0.01-2.5) had HNRI]. The prevalence of HN in the middle risk group was 10.7%, and 16.1% in the high risk group (Figure 2).

Figure 2. Prevalence of HN and HNRI in validation sample

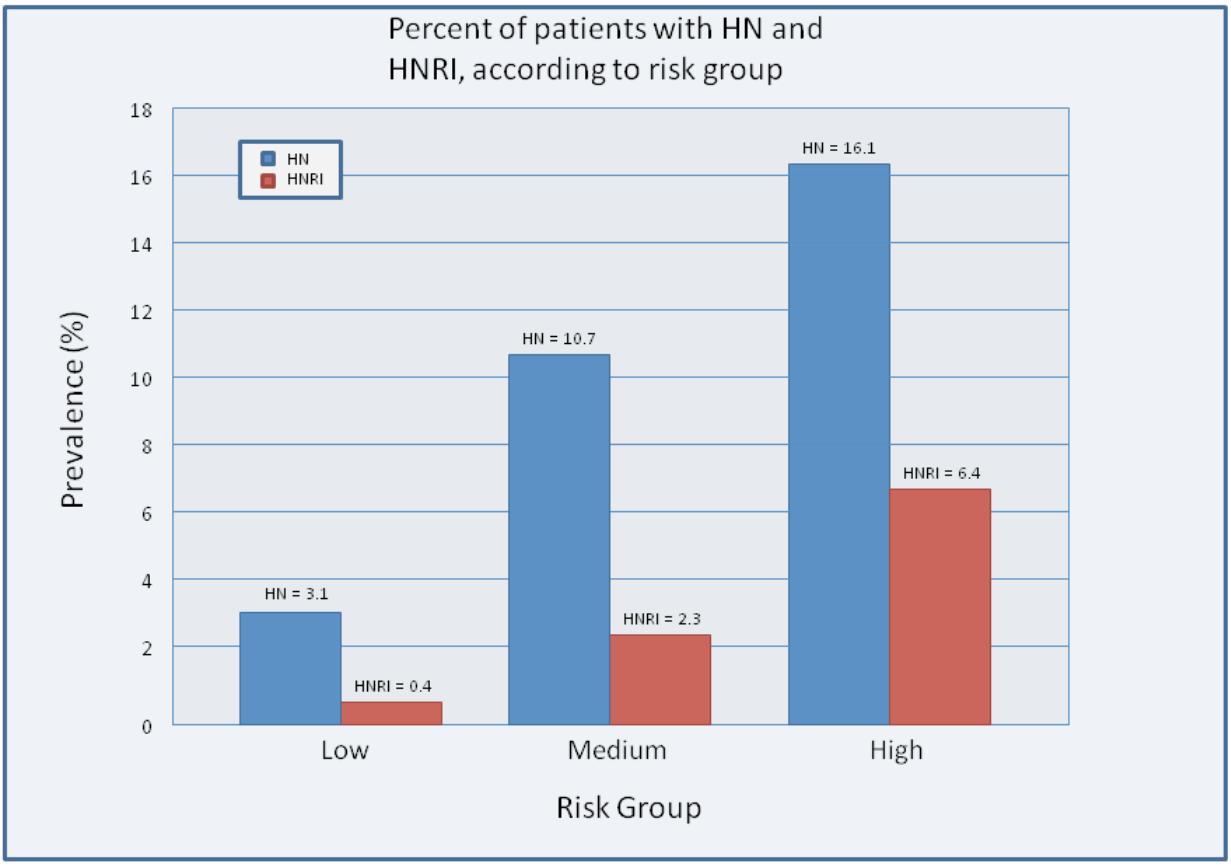

Figure 2: Prevalence of patients with HN and HNRI in the validation sample (n=797).

HN = hydronephrosis
HNRI = hydronephrosis requiring intervention

When dichotomized to low risk vs. all others, the NPV of the stratification was 96.9% (95.7-98.1) for HN and 91.8% (89.9-93.7) sensitive, with a negative likelihood ratio (NLR) of 0.27. When the outcome was HNRI, the NPV increased to 99.6 (99.1-100.0) and the sensitivity increased to 96.3 (94.9-97.6), with a NLR of 0.13 (Tables 3, HN as outcome; Table 4, HNRI as outcome).

Table 3: Performance of stratification in validation sample, HN as outcome

Risk stratification				
	Model 1 (primary), no. of patients		Model 2, no. of patients	
Model classification	HN	Normal	HN	Normal
Low risk	7	216	17	314
Medium or high risk	78	496	68	398
Test performance				
Negative predictive value	96.9 (95.7-98.1)		94.9 (93.3-96.4)	
Sensitivity	91.8 (89.9-93.7)		80.0 (77.2-82.8)	
Specificity	30.3 (27.2-33.5)		44.1 (40.7-47.6)	
Negative likelihood ratio	0.27		0.45	
Prevalence of HN in low risk group	3.1		5.14	

HN = hydronephrosis
HNRI = hydronephrosis requiring intervention

Table 4: Performance of stratification in validation sample, HNRI as outcome

Risk stratification				
	Model 1, no. of patients		Model 2, no. of patients	
Model classification	HNRI	Normal	HNRI	Normal
Low risk	1	222	1	330
Medium or high risk	26	548	26	440
Test performance				
Negative predictive value	99.6 (99.1-100.0)		99.7 (99.3-100.1)	
Sensitivity	96.3 (94.9-97.6)		96.3 (94.9-97.6)	
Specificity	28.8 (25.7-32.0)		42.9 (39.4-46.3)	
Negative likelihood ratio	0.13		0.09	
Prevalence of HN in low risk group	0.4 (0.01-2.5)		0.3 (0.008-1.7)	

HN = hydronephrosis
HNRI = hydronephrosis requiring intervention

We assessed the presence of incidental findings on RUS, other than presence of HN (e.g. masses, anatomic abnormalities) in the entire validation sample. Among the 797 patients, there were eight incidental findings (1%) unknown to the clinical team: two horseshoe kidneys, four extra-renal pelvises, and two complex cysts. Of these, none were found in patients in the low risk group.

Model 2 was less sensitive for HN, but more specific. In the low risk group there were 331 (41.5%) patients, of whom 5.1% had HN (1 patient had HNRI, or 0.3%). The NPV for HN was 94.9 (93.3-96.4) [99.7% (99.3-100.1) for HNRI], with a sensitivity of 80.0% (77.2-82.8) [96.3% (94.9-97.6) for HNRI] and a NLR of 0.45 (0.09 for HNRI).

Number needed to screen and cost savings estimate

The NNS to find one case of HN in the low risk group for model 1 is 32; compared to HNRI, which required an NNS of 223 (Figure 3). If no RUS studies were ordered for low-risk patients, Models 1 and 2 would permit reduced utilization of 27.8% and 41.5%, respectively, of RUS studies. At YNNH in 2008, approximately 700 RUS studies were performed in the setting of AKI on adult inpatients who met our inclusion criteria; 30% of these patients would be in the low risk group. At an approximate cost of $200 per study, a 30% reduction in RUS imaging would result in an annual savings of $42,000 at one institution. To

find one case of HN in the low risk group for model 1 cost $6,371 per positive study; for HNRI in the same model, the cost is $44,600 per positive study.

Figure 3. Number needed to screen and cost in validation sample

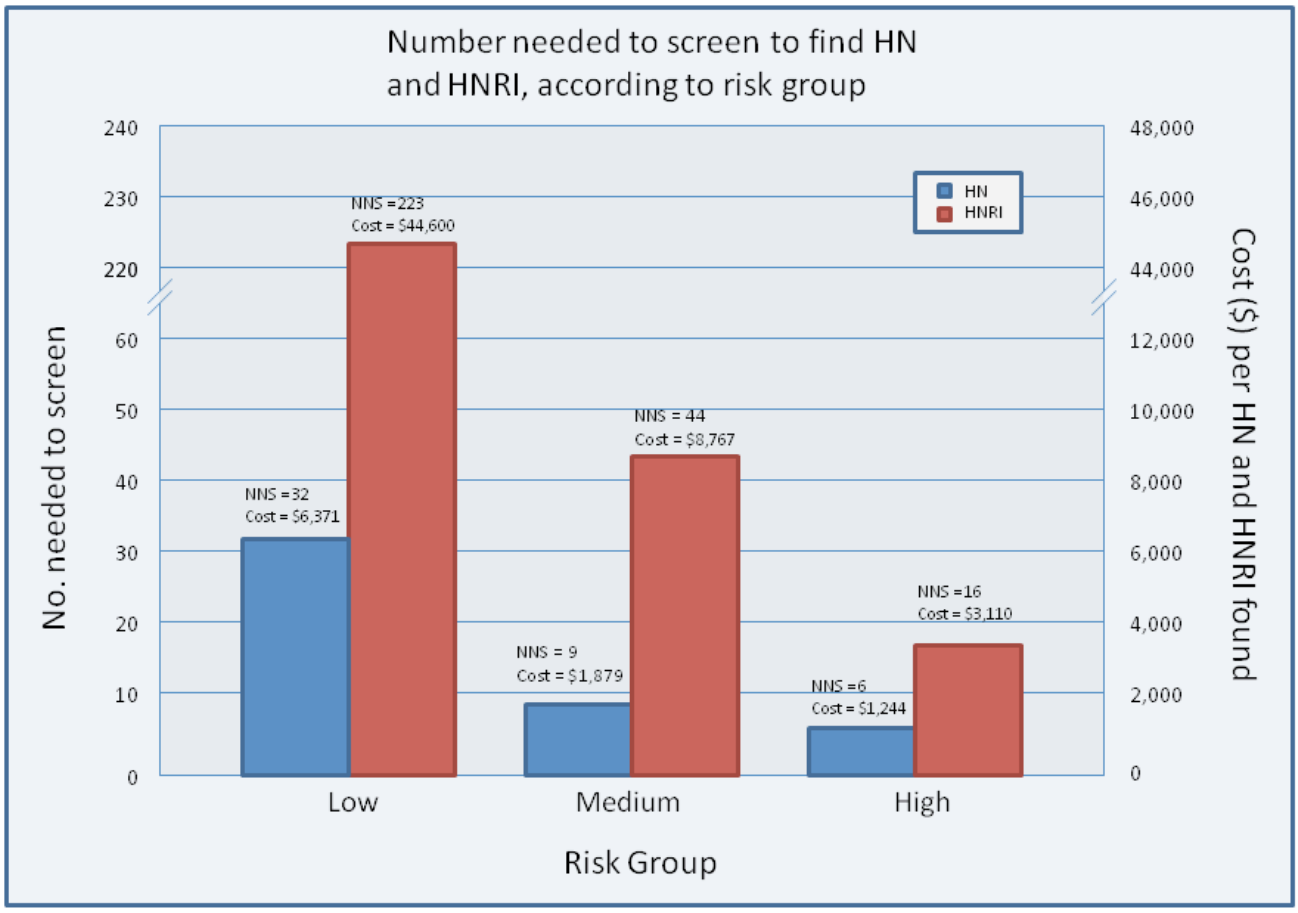

Figure 3: Number needed to screen (NNS) and cost per positive result of renal ultrasound evaluation, according to risk group. NNS = number of outcome events (HN or HNRI) / number of patients risk group. Cost = NNS (HN or HNRI) x $200 (approximate cost of ultrasound study).

NNS = number needed to screen
HN = hydronephrosis

Discussion

In this retrospective study, we found that approximately 10% of patients who had RUS ordered in the setting of AKI had HN on RUS, and 3% had HNRI. This prevalence estimate of HN is similar to previous studies. [33, 37-39] We also derived and validated a decision rule to stratify inpatients with acute kidney injury by risk of having HN. It is based entirely on common clinical information and can be easily applied, as recommended by reviews of methodological standards. [18] Our primary model was 91.8% sensitive and had a NPV of 96.9% for HN. To our knowledge, no such decision model exists in the literature. [38-40]

In addition to considering all cases of HN, we also assessed those which required an intervention (HNRI). It is these cases which are most important to identify, since they represent patients for whom a renal ultrasound affected their management. Our primary model was highly sensitive for HNRI (96.3%) with an NPV of 99.6%. We defined our outcome HNRI as an acute surgical intervention most likely to be performed in the setting of HN, which 27 (31.8%) of the HN patients received in our validation sample. Each model had a negative likelihood ratio of near 0.1 for HNRI, a value which affects the pre-test probability of a positive finding to a large degree. [47] There were other interventions performed on the HN patients, but these were less likely to be a direct result of finding obstruction on RUS: 60% of patients received a Urology consult, 13% had a Foley placed, 2% had a cystoscopy, and 1% had lithotripsy performed (all performed after the RUS study). Our model stratified all but one of the 27 HNRI patients as either medium or high risk, with a NPV approaching 100%. They each

assigned the same HNRI patient to the low risk group, a woman admitted with urosepsis and a history of a colectomy, nephrolithiasis, and a CT consistent with cirrhosis, who was diagnosed with hepatocellular carcinoma after the time of the RUS (beyond our window of analysis, which ended at the time of the RUS study).

We also considered the value of RUS in terms of its ability to reveal clinically useful information other than the presence of HN. Though the primary reason a clinician orders a RUS is to identify an obstructive etiology, there are other incidental findings that may be important to discover, including cysts, masses, or anatomic abnormalities. In our validation sample of nearly 800 patients, there were no previously unknown incidental findings found in patients the low risk group. For many patients, the test result was not important enough to even be noted in the medical record. In the low risk groups of both models there were 20 unique HN patients, of whom 19 did not receive an intervention. In five of these 19 cases, there was no mention of the RUS result in the patient's progress notes. For another seven, the result was not mentioned in their discharge summaries.

The evaluation of AKI is a nuanced process, one that likely requires clinical judgment not currently captured by our model. We were not able to include all possible risk factors for obstruction, either to maintain model parsimony or because of a lack of statistical evidence (i.e. the variables were clearly not associated with HN in derivation), or both. However, as with the one HNRI patient in the low risk group, there are likely risk factors not included in this model that should be incorporated into clinical decision-making (or explicitly included by future refinements of this rule). Since as many as 40% of adult inpatients with AKI may be assigned to the low risk group by our model, there is

room for studies to be ordered for patients whose risk of obstruction is likely higher than calculated, while still markedly decreasing over-utilization. Patients who are at higher risk for obstruction according to this model should always receive sonographic evaluation, while the vast majority of the patients at low risk should not.

The cost savings we estimate are substantial. To find one case of HNRI among low risk patients, we estimate that approximately $45,000 needs to be spent on RUS studies. Moreover, this analysis was conservative. We did not take into account all the potential savings of improved RUS utilization, such as the effect on length of hospitalization. As unnecessary diagnostic imaging contributes significantly to rising healthcare costs, this rule may lead to significant potential savings for healthcare institutions and payers. [48-50] By establishing evidence-based guidelines, the marked geographic variation in spending on imaging may also be improved. [11, 13, 51]

One likely objection against this recommendation of selective RUS use is that ultrasound will still need to be ordered, regardless of a patient's risk of obstruction, under certain clinical circumstances. For instance, for those patients whose serum creatinine continues to rise after intravenous hydration and removal of nephrotoxic medications. In these situations, a RUS evaluation should likely be undertaken. However, anecdotal experience suggests that many studies are not strictly ordered in this setting after an attempt at management has been made, but rather as part of an initial work-up of increased creatinine. Indeed, for many of the patients included in our study, a RUS was ordered at the first sign of AKI, often concurrently or prior to the initiation of hydration or the removal of certain medications. If our decision rule, at the

least, causes clinicians to delay ordering a RUS until their patients' AKI persists in the face of medical management, the utilization of RUS will still be markedly improved.

Four previous studies have explored the association between clinical factors and presence of HN on RUS. [38-40, 52] In two older studies, the prevalence of HN was characterized in cohorts of hospitalized patients. One of these studies excluded patients with known risk factors for HN, and the other stratified HN by severity of obstruction without assessing risk factors. [38, 39] In one recent study, 2854 patients underwent RUS evaluation over a three-year period, of whom 1.6% were found to have an obstructive etiology. Obstruction was associated with male sex, age over 65, history of BPH, or history of nephrolithiasis. [52] In a similar study from 1988, 394 patients with acute kidney were assessed for a short list of risk factors determined *a priori,* including history of pelvic or abdominal cancer and previous pelvic surgery, and placed patients in one of two risk groups if any factor was present.

This work builds on the existing literature in a number of important ways. First, we employed a recently recommended definition of AKI and use it as an exclusion criterion. By doing so, we created a sample which we believe accurately represents a group of hospitalized patients on whom clinicians would order RUS studies. Previous studies used much older definitions of acute renal failure, or simply considered all cases of RUS studies without limiting by reason for ordering. Second, by creating a large number of demographic and clinical variables and assessing their independent association with HN, we were able to develop a decision rule that accurately stratified patients according to risk of HN. No other study devised such a rule or used uni- or multivariate analysis to assess the association between risk factors and HN. Third, ours

is the only study to validate a risk stratification system in a separate sample of patients. By doing so, we were able to increase the external validity of our rule, and assess it according to a number of important criteria, including its characteristics as a diagnostic test (i.e. sensitivity and NPV), and as well as its effectiveness, in terms of NNS. Finally, we attempt a preliminary cost-savings analysis if our rule were implemented, a further step not taken by previous studies.

Once a CDR like ours is derived, it must be validated and refined to ensure its reliability and accuracy. However, CDR use requires the time and energy of clinicians, so if implementation is not practical then systemic use will likely not be achieved. Studies assessing the impact of these rules in clinical practice (i.e. impact analysis) are a critical step towards widespread adoption. Unfortunately, these studies are often not performed so little is known about many of the CDRs that have been developed. [19] In the case of the Ottawa ankle rules, an impact analysis study used an implemented strategy to assess the effect of the rule on actual practice. The intervention was a practical one: the rule was introduced at a general staff meeting, summarized and distributed in the form of pocket cards, posted through the emergency department, and included along with a pre-printed data collection form in each chart. Compared to the control group, there was a 20% reduction in foot and ankle imaging without a single missed fracture leading to an adverse outcome. Thus, a positive resource utilization was demonstrated with adverse clinical outcomes. [53]

However, implementation is often a significant challenge. Studies suggest that systemic adoption may require local, effective, and proven implementation strategies to ensure widespread use. [54, 55] In one study assessing the problem of clinicians not

following practice guidelines, the most common reasons for non-use were lack of familiarity and awareness, and the presence of external barriers, including guideline-related (i.e. rule was cumbersome), patient-related (i.e. rule was difficult to apply to individual patients or to reconcile with their wishes), and environmental (i.e. lack of time or support from staff, or reimbursement concerns). [56]

One strategy that may improve the odds of successful implementation is the use of healthcare information technology in decision support. As electronic medical records become more prevalent, CDRs can be incorporated into digital order entry systems and can prompt physicians to follow the rule when appropriate. [57, 58] In one study, a computerized physician order entry system was used to improve medication ordering and reduce adverse drug events. [59] The system performed drug-allergy checking, drug-drug interaction checking, and drug-laboratory checking and, together with a team-based intervention, resulted in a 55% reduction in serious medical errors. For our decision rule, a prompt could appear in a hospital's order entry system asking clinicians to enter in their reason for ordering an RUS. If the reason matched with a list representing words and phrases consistent with AKI, the clinician could be asked to input the information contained in our rule before completing the order and, if appropriate, may be advised to consider delaying sonographic evaluation. As a key focus of the Obama administration's efforts in health reform is the improvement and dissemination of technology in healthcare settings, these types of order-entry systems may play an increasingly important role in evidence-based care. [5]

Another likely necessary step towards improving imaging utilization is increased communication between physicians. In our study, the strongest predictor of HN on RUS

was a history of HN, either as documented in the medical chart or seen on previous imaging. However, in many of these patients with HN on previous imaging there was no documentation in the chart, likely indicating that the clinical team was unaware of the patient's previous HN status. As more evidence becomes available to guide clinical decision-making, both in the form of appropriateness criteria and CDRs, conversations between radiologists and clinicians will be increasingly more necessary. In fact, early studies have shown that this type of communication leads to more informed decision-making. In two, direct consultation between clinicians and radiologists resulted in a substantial decrease in utilization of costly tests such as ultrasound and CT. [60, 61] However, this effect was not reproduced in a more recent randomized-controlled trial. [62]

Our study has limitations. The decision rule was derived and validated in a retrospective fashion in the same institution. Future refinement and validation of the model should be pursued in prospective studies in other patient populations. In addition, our study population represents only those patients who received a RUS while admitted. As such, our sample likely represents a population enriched with obstruction (i.e. those patients at such low risk of obstruction who never received a RUS were not included). Therefore, the inclusion of all patients admitted with AKI, not just those with AKI who received a RUS, would likely skew our HN prevalence data downward (and improve the NPV of our model).

We have derived and validated a decision rule to help clinicians identify those patients at low risk of obstruction on ultrasound, and specifically those patients whose ultrasound result will likely affect their management. If further refined and validated,

these models may allow clinicians to both order ultrasound studies for those patients at high risk for obstruction, and delay or decide not to order a study on the roughly one-third of patients at low risk. As more attention is paid to the cost-effectiveness of diagnostic modalities, prioritizing testing for those at higher risk of abnormal findings will result in more informed diagnostic approaches. For inpatients with AKI, directing RUS studies towards those at greater risk of obstruction will both aid clinical decision-making and decrease the cost of evaluation.

Appendix

To find RUS studies, the YNNH imagining database was queried for these words and phrases: “creatinine” or “cr” (when used as an abbreviation), “renal failure,” “stone,” “nephrolithiasis,” “flank pain,” “arf,” “obstruction,” “hydronephrosis,” and “retention.

Incidental findings were found by searching the radiologist’s report text for these words: “solitary” or “single” (kidney), “extra-renal” or “double” (pelvis), “complex” (cyst), “polycystic” (kidney disease), “angiomyolipoma”, and “horseshoe” (kidney).

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