Issues in Emerging Health Technologies

## NephroCheck: A Bedside Biomarker Test to Identify Patients at Risk for Acute Kidney Injury

Summary

✓ **NephroCheck is a point-of-care urine test that flags two biomarkers that indicate if a critically ill patient is at risk for acute kidney injury (AKI).**

✓ **Currently, serum creatinine is the main test used to detect AKI, but it may take a day or more for serum creatinine levels to accumulate in the blood of a patient with a kidney injury — consequently, it may not reflect real-time kidney damage or loss of function. Results of the NephroCheck test are available within 20 minutes — before clinical signs of kidney failure are apparent.**

✓ **The evidence suggests that the NephroCheck test has good sensitivity (89% at the 0.3 cut-off value) for detecting critically ill patients at risk for AKI; however, its specificity (at approximately 50%) is relatively poor.**

✓ **Aging patient populations, with more complex comorbidities yet typically shorter hospital stays, make early detection of AKI important.**

✓ **Further studies are needed to determine the value of NephroCheck across different patient populations and its place (and that of other emerging biomarkers for AKI) within current decision support frameworks for patient care.**

The Technology

Acute kidney injury (AKI) occurs when the kidneys are unable to filter wastes and excess fluid from the blood, control blood pressure, and regulate the balance of salt and water in the body.[1] Formerly called acute renal failure; AKI is common in critically ill and surgical patients. A recent meta-analysis of 154 AKI studies from around the world (n = 3,585,911 patients) estimated that 1 in 5 adults (21.6%) and 1 in 3 children (33.7%) experience AKI during hospitalization.[2] Similarly, a study at five Canadian hospitals (n = 603 patients), during a 30-day period, found that 26.7% of intensive care unit (ICU) patients developed AKI.[3]

The incidence of AKI is increasing. This is partly because of a greater awareness of the condition, but it is also due to an aging population and increasing rates of diabetes, cardiovascular disease, and chronic kidney disease. The use of drugs that are toxic to the kidneys (including nonsteroidal anti-inflammatories) and contrast media in diagnostic imaging procedures may also be contributing to the increasing incidence of AKI.[4,5]
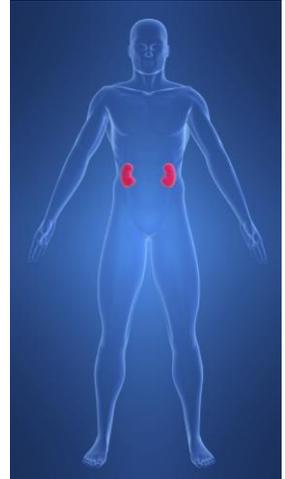
AKI is associated with increased morbidity, longer length of hospital stay, increased health care costs, and increased mortality.[2,4,6-9] A recent UK report estimates that AKI costs their National Health Service (NHS) more than £1 billion (just over 1% of the NHS budget) each year.[10] UK estimates suggest that an estimated 20% to 30% of AKI cases could be prevented.[10,11]

Unless a clear cause is evident (e.g., traumatic injury), the onset of AKI is difficult to identify.[12] Current tests detect AKI after kidney function has already declined. Earlier detection through biomarkers that detect precursors to kidney injury could allow more timely changes in patient care, such as discontinuing the use of nephrotoxic drugs, avoiding the use of radiocontrast agents in imaging studies, providing earlier assessment by a nephrologist, and other interventions to prevent disease progression.[7]

NephroCheck is a urine test that detects two biomarkers:
- Insulin-like Growth Factor Binding Protein 7 (IGFBP-7)
- Tissue Inhibitor of Metalloproteinase 2 (TIMP-2).[12,13]

Both biomarkers are proteins expressed by healthy human kidneys that contribute to a cell-cycle arrest of the tubular cells in the kidneys in response to injury.

For the NephroCheck test, a urine sample is mixed with a reagent and added to a single-use test cartridge, which is inserted into the portable Astute140 Meter. The test uses a fluorescent immunoassay to measure levels of the IGFBP-7 and TIMP-2 biomarkers in the urine.[14] Test results (an algorithm of both biomarkers) are shown as an AKI risk score on the meter display, and are available within 20 minutes.[13,15] Higher scores indicate a patient is at greater risk for developing moderate to severe AKI within 12 hours of testing.[14]

Compared with serum creatinine, the standard blood test for kidney function, biomarkers can detect AKI one or more days before serum creatinine levels increase.[8]

Regulatory Status

The NephroCheck Test System (Astute Medical, Inc., San Diego) received US Food and Drug Administration (FDA) approval as a Class II device in September 2014.[15] The FDA-approved indication for the test specifies it is "… to be used in conjunction with clinical evaluation in patients who currently have, or have had within the past 24 hours, acute cardiovascular and / or respiratory compromise and are ICU patients, as an aid in the risk assessment for moderate or severe acute kidney injury (AKI) within 12 hours of patient assessment…" The test is intended for use in adult patients, in conjunction with other clinical and laboratory tests, and it is not intended to be used as a standalone test.[15]

The NephroCheck test system (the NephroCheck test kit, liquid controls kit, calibration verification kit, and Astute 140 Meter) will be marketed by Ortho Clinical Diagnostics, Inc. in the US and in some parts of Europe.[16] Each test kit can be used for 25 tests.[15]

As of March 2015, NephroCheck was not licensed by Health Canada, and the anticipated time to licensing in Canada is unknown.

Patient Group

Clinical indications of AKI may include edema (swelling due to excess fluid), hypertension, confusion, and a decrease in urine production. However, early AKI often has no clear clinical signs or symptoms.[17]

Many patients are at particular risk for AKI, including the elderly, those with other health comorbidities (such as cardiovascular disease, chronic obstructive pulmonary disease, or diabetes), and patients who receive nephrotoxic drug therapies or radiocontrast dyes for diagnostic imaging studies.[18] A recent study at one US academic hospital (more than 31,000 hospitalizations during a one-year period) found that the highest incidence rates of AKI were in patients hospitalized for vascular surgery (50.2%), cardiac surgery (52.2%), hematopoietic stem cell transplantation (55.9%), critical care (60.3%), mechanical ventilation (63.9%), and sepsis (68.4%).[9]

Severe AKI can lead to chronic kidney disease requiring lifelong dialysis or multi-organ failure resulting in death.[6]

Current Practice

In the past, many different definitions of AKI were used, which made it difficult to compare study results or determine disease incidence.[4,8] The main classifications of AKI currently used categorize the severity of AKI by either risk, injury, or failure, or by stage 1, 2 or 3, as follows:

- The Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria define risk for AKI as an increase in serum creatinine ≥ 1.5 times the baseline value within seven days, or a measurement of urine output of < 0.5 mL/kg per hour over six hours, or a combination of both measures.
- The Acute Kidney Injury Network (AKIN) criteria uses a modified RIFLE classification that defines risk for AKI as an increase in serum creatinine by 0.3 mg/dL (27mmol/L) or ≥1.5 times the baseline value in 48 hours.[8,17]
- The Kidney Disease Improving Global Outcomes (KDIGO) working group recently combined RIFLE and AKIN into a single classification system for AKI. Their definition is an increase in serum creatinine of ≥ 0.3 mg/dL within 48 hours, or of ≥ 1.5 times that of baseline within seven days, or a urine volume of < 0.5 mL/kg per hour for six hours.[8] Moderate to severe AKI is defined as stage 2 or 3 in the KDIGO classification.[7,19]

Serum creatinine measurement and urine output have been the standard diagnostic tests for AKI for many years. Creatinine is a waste product produced by the muscles during the break down of creatine that produces energy for muscle contraction. Elevated levels of creatinine indicate impaired kidney function.[20]

Determining the duration of AKI helps to distinguish it from chronic kidney disease (CKD), identify possible underlying causes, and guide the treatment of patients.[17] This requires baseline measurements of serum creatinine or urine output, or both, to compare with subsequent test results.[17] However, these baseline levels are not always available.[4] Hospitalized patients usually have serum creatinine tested regularly as part of routine blood work.

Unfortunately, serum creatinine measurement is an imperfect reference standard test — both its sensitivity and specificity are affected by age, sex, muscle mass, exercise, and diet, as well as by certain drugs and underlying clinical conditions.[6,21,22] In addition, because of kidney reserves, levels of serum creatinine may not increase until as much as 50% of kidney function has been lost.[23] Serum creatinine levels rise after the kidney injury has occurred and the level may not reflect current kidney function.[12] It may not be appropriate to compare biomarkers that flag precursors to kidney injury with tests that show "functional change," such as serum creatinine.[24]

Low urine volume, another measure of kidney function, can also be an unreliable indicator because the volume may be affected by bleeding and other factors, such as the use of diuretic drugs, and it is difficult to measure accurately.[6,8,17]

An estimated glomerular filtration (eGFR) rate may be used to assess kidney function, but this also involves serum creatinine concentration and clearance rates, which vary in patients with AKI, and are also affected by age, body weight, ethnicity, and other factors.[17]

Relatively few advances have occurred in the treatment of AKI, but early identification is important to allow supportive interventions and prevent further harm. Supportive interventions include avoiding nephrotoxic drugs and contrast agents, maintaining fluid balance, and using dialysis.[25]

Methods

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, and The Cochrane Library (2014, Issue 12). Grey literature was identified by searching relevant sections of the Grey Matters checklist (http://www.cadth.ca/resources/grey-matters). No methodological filters were applied. The search was limited to English language documents published between January 1, 2010 and January 9, 2015. Regular alerts were established to update the search until March 10, 2015.

The Evidence

The primary evidence on the NephroCheck test comes from four multi-centre studies conducted in Europe and North America that sought to identify AKI risk biomarkers and then to validate IGFBP-7 and TIMP-2. These studies were named Discovery, Sapphire, Opal, and Topaz.[26-29] (A fifth study, Ruby, is examining the use of biomarkers in monitoring recovery from AKI, but results from this trial have not yet been published.[30])

Discovery was an exploratory study to select the most promising biomarkers for AKI risk from 340 potential biomarkers first identified through a literature search for biomarkers of kidney injury. The trial was conducted at three clinical sites in Austria and the US, and included 522 patients. The biomarkers were ranked both individually and in combination according to their ability to predict moderate or severe AKI (RIFLE stages I or F) within 12 to 36 hours. The two top biomarkers for AKI risk were IGFBP-7 and TIMP-2, with slightly better results when both biomarkers were combined: an area under the receiver operator characteristic curve (AUC) of 0.80 (95% confidence interval (CI), 0.75 to 0.84).[26]

The Sapphire study ran from 2010 to 2012 at 35 centres and included 744 patients.[26-28] It compared IGFBP-7 and TIMP-2 with seven other biomarkers for AKI (KDIGO stages 2 to 3) and confirmed that the two NephroCheck biomarkers outperformed the others. The NephroCheck biomarkers had a combined AUC of 0.80 (95% CI, 0.75 to 0.84) within 12 hours of testing, while the other biomarkers had AUCs of ≤ 0.71 (95% CIs ranging from 0.57 to 0.81). Risk stratification also improved when the IGFBP-7 and TIMP-2 biomarkers were added to a nine-factor clinical model.[26] The results of the Sapphire study were used to establish a cut-off threshold for detecting AKI risk as 0.3 $[ng/mL]^2/1{,}000$, which was prospectively confirmed in the Opal study.[26,27]

The Opal study, which ran from 2012 to 2013, was intended to validate the biomarker cut-off values (0.3 and 2.0 $[ng/mL]^2/1{,}000$) for sensitivity, specificity, and relative risk to predict development of moderate or severe AKI (KDIGO stages 2 or 3) within 12 hours of testing. The study compared data from the Sapphire study with that from a new cohort of 154 critically ill

adult patients at six US hospitals.[27] Results were comparable for both groups: the AUC was 0.80 (95% CI, 0.74 to 0.84) for Sapphire, and 0.79 (95% CI, 0.69 to 0.88) for Opal.[27] Estimates of sensitivity were 89% at the 0.3 cut-off in both studies (95% CI, 82 to 94), while specificity estimates were 50% (Sapphire, 95% CI, 47 to 53) and 53% (Opal, CI not provided). At the 2.0 cut-off, estimates of sensitivity were 42% (Sapphire, 95% CI, 33 to 51) and 44% (Opal), while specificity estimates were 95% (Sapphire, 95% CI, 93 to 96) and 90% (Opal).[27]

The Topaz study, a prospective trial that included 420 critically ill patients with severe respiratory or cardiovascular disease at 23 US hospitals, assessed the ability of NephroCheck biomarkers to predict those at risk of developing moderate to severe AKI within 12 hours of testing.[29] AKI was determined based on clinical evidence by a panel of three nephrologists who were blinded to the biomarker test results. At the 0.3 cut-off value, biomarker test sensitivity was 92% (95% CI, 85 to 98). When the biomarker results were combined with clinical variables, the AUC was 0.86 (95% CI, 0.80 to 0.90) versus 0.70 (95% CI, 0.63 to 0.76) for clinical variables alone, and 0.82 (95% CI, 0.76 to 0.88) for the biomarker test alone.[29] At the 0.3 cut-off value, specificity for the biomarker test was 46% (95% CI, 41 to 52).[29]

A follow-up study of a subset of 692 patients from the Sapphire study found patients with AKI and early TIMP-2 plus IGFBP-7 scores of > 2.0 had an increased risk of death or of requiring dialysis during the following nine months when compared with patients with a score of ≤ 0.3.[28]

Beyond the four primary studies described above, several smaller studies of these AKI biomarkers have been published. A German study of 42 patients undergoing cardiac bypass surgery at one centre found urinary TIMP-2 plus IGFBP-7 tests using cut-off thresholds of 0.3 $(ng/mL)^2/1,000$ for high sensitivity and 2.0 for high specificity were able to distinguish between no AKI and moderate AKI risk on the first day post-surgery, but not when measured within the first four hours of surgery.[31] This trial was not restricted to patients at high risk for AKI, their surgical fluid management practices differed, and the study had a small sample size. These factors may explain the different sensitivity (53%) and specificity (54%) reported at the lower threshold (CIs not reported).[31]

A second, single-centre German study of 50 patients undergoing cardiac bypass surgery measured urinary TIMP-2 plus IGFBP-7 at 4, 12, 24, 48, and 72 hours after cardiopulmonary bypass.[7] The investigators found a marked rise in the biomarker values at all points in time in the 26 patients who subsequently developed AKI. A composite of the maximum urinary biomarker concentration during the first 24 hours was superior to measures at individual time points, with an AUC of 0.90 (95% CI, 0.79 to 1.00). At a single time point of four hours, the biomarker test AUC was 0.81 (95% CI, 0.68 to 0.93). By comparison, another urinary biomarker test, neutrophil gelatinase-associated lipocalin (NGAL) at four hours, had an AUC of 0.68 (95% CI, 0.53 to 0.84).[7]

Other recent trials have examined the use of either IGFBP-7 or TIMP-2 alone, or in combination with other biomarkers for AKI, such as NGAL, but not the NephroCheck duo.[32-34]

The cut-off value established for NephroCheck in the published trials and as specified in the US FDA-approved indication has not been validated in patient populations beyond the ICU and cardiac surgery, such as in patients with pre-existing kidney disease.[14] Optimal test threshold values may vary for different clinical conditions and settings.[35,36]

The US FDA approval noted the relatively low specificity of NephroCheck (i.e., some patients who are not at risk of AKI will have a positive test result) and emphasized that the test should be used in conjunction with other clinical criteria to assess AKI risk.[15]

Adverse Effects

No adverse effects were reported with the use of the NephroCheck test.

Administration and Cost

Health professionals will need training in the use, interpretation, and limitations of the NephroCheck test.[15]

No information on the cost of the NephroCheck test system was available. NephroCheck will be an additional cost on top of that for existing tests and clinical assessments to detect AKI.

In the patient populations where NephroCheck has been used to date (i.e., critically ill, cardiac surgery), AKI is so common that optimization of hemodynamic status and avoiding nephrotoxic drugs and contrast agents, where possible, are standard practice. This is also true for patients with other risk factors for AKI, such as pre-existing kidney disease or diabetes. These patients are assumed to be at risk of AKI until proven otherwise. It is not yet obvious what a positive NephroCheck test would add to the care of these patients [personal communication: Dominic Carney, Grey Nuns Community Hospital / University of Alberta Hospital, Edmonton (AB), 11 Feb 2015]. For this reason and those mentioned above, whether NephroCheck will eventually reduce overall costs through earlier detection and prevention of AKI is unknown.

Concurrent Developments

Many new biomarker tests for AKI have recently been developed or are under investigation. Some biomarkers detect changes in kidney function while others signal kidney damage. Consequently, both types may be needed to cover the span of AKI.[36] NGAL is one example. This protein biomarker is elevated in response to kidney inflammation or injury and can be measured in either blood or urine.[6,35] The NGAL assay takes approximately 10 minutes to process.[6] Several different commercial NGAL tests are available in Canada, including the NGAL ELISA kit (BioPorto) and the Triage NGAL test (Alere Ltd.).

Other biomarkers under investigation for AKI include cystatin C, kidney injury molecule-1 (KIM-1), liver fatty acid-binding protein (L-FABP), and interleukin-18 (IL-18).[17,22,25] Italian and US researchers recently found that preoperative levels of ouabain, a stress hormone, are also predictive of AKI risk; this has been incorporated into a risk prediction model for mild to severe post-operative AKI in cardiac surgery patients.[37,38]

A small clinical trial is under way to compare the ultrasound-based Renal Resistive Index of kidney blood flow with NephroCheck to predict AKI in post-cardiac surgery patients.[39]

Another trial will assess the use of NephroCheck as a marker of kidney function in emergency department patients who receive contrast agents during computed tomography scans.[40]

The increasing use of bedside monitoring devices, integrated with decision support tools, will provide a further avenue for improved detection and monitoring of patients at risk for AKI.[4]

Rate of Technology Diffusion

NephroCheck is not currently in clinical use in Canada.

Implementation Issues

The increasing age of patient populations, their rising number of comorbidities, and their typically shorter hospital stays all make earlier detection of AKI and timely intervention important for patient care.[22]

Although the NephroCheck biomarkers performed better than other biomarker tests for AKI in the 12-hour time frame, whether they continue to perform better during the longer KDIGO guideline time frame of 48 hours is unknown.[14,41]

NephroCheck may detect only one of the various pathways of kidney injury — a panel of different biomarkers may be needed to detect both functional change and damage in different patients and clinical settings.[11,22,36,37] NephroCheck will not replace existing tests, such as serum creatinine, which indicate the severity of kidney injury.[14]

Studies are still needed to demonstrate the cost-effectiveness of biomarker tests for AKI and, most importantly, the impact of these tests on patient management and outcomes.[31,41-43] Some of this evidence may be captured through a UK study, now under way, which will assess the evidence on AKI biomarker tests, identify care pathways, and collect the data needed to determine their clinical utility and cost-effectiveness.[44]

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