The Validity of the Quick Renal MRI in Pediatric Kidney Disease

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- **The Validity of the Quick Renal MRI in Pediatric Kidney Disease**

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PROJECT SUMMARY

Children born with congenital anomalies of the urinary tract are susceptible to kidney infections and scarring. They form a high risk group for developing renal insufficiency in adulthood. A basic tenet in pediatric urology is that kidney infections should be prevented and otherwise promptly identified to minimize the risk of acquiring renal scars and permanent tissue damage.

The current radiologic standard for renal infection and scarring is the 99mTechnetium-dimercaptosuccinic acid (99mTc- DMSA) renal scan. This exam requires an intravenous injection, occurs over a 3 hour period, involves exposure to radiation, and can require sedation of young children. We propose a new imaging method that is a rapid, injection-, sedation-, and radiation-free alternative: the quick renal MRI. This proposal hypothesizes that the quick renal MRI has high validity compared to the DMSA scan in the detection of acute renal infections and scars. If the quick renal MRI is accurate, it could potentially replace the DMSA scan for those specific questions and ease the burden of testing for children with chronic renal disease. Findings from these studies will provide preliminary data and rationale for a multi-centered study to further test this new technology.

BACKGROUND AND SIGNIFICANCE

Pyelonephritis: a common serious infection in children.

UTI is the most common serious bacterial infection in children. It confers a significant health burden on society, affecting approximately 2.6-7.5% of febrile children and resulting in more than 1.1 million physician visits each year.[1,2] UTI can be divided into an infection of the lower tract (bladder) or upper tract (kidney). A kidney infection- also known as pyelonephritis- represents a severe illness associated with systemic symptoms and signs such as fever, rigors and costovertebral angle tenderness. Pyelonephritis may occur because the kidney is seeded from a blood borne source or, more commonly, from an infection that has ascended from the bladder. Short term complications of pyelonephritis include sepsis and acute renal failure. The treatment for pyelonephritis can usually be undertaken on an outpatient basis, but occasionally the severity of illness requires a hospital admission. In the United States, about 4.7% of children diagnosed in the emergency room with UTI will be admitted to the hospital.3 The hospital admission rate for pyelonephritis has not decreased and is possibly increasing.3, 4

Scarring: a sequelae of pyelonephritis.

Irreversible renal scarring may be a consequence of pyelonephritis and an independent risk factor for chronic kidney disease.5 After the acute inflammatory process resolves, histopathology of an area of scar will show chronic tubulointerstitial inflammation and fibrosis6. Nuclear imaging will show a defect of the renal contour which represents focal loss of renal tissue. Not every episode of pyelonephritis will lead to scarring, but one episode of pyelonephritis is sufficient to result in scarring.7 About 15% to 52% of individuals will exhibit renal scarring following pyelonephritis.8-10 Renal scarring in an individual with vesicoureteral reflux- a urinary tract defect in which an abnormal uretero-vesical junction promotes the

retrograde flow of urine from the bladder to the kidneys- can lead to reflux nephropathy. Reflux nephropathy is the third leading cause of chronic renal insufficiency and the fourth leading cause of end stage renal disease (ESRD) among children in North America.11 Significant renal scarring may also lead to hypertension in 17% to 30% of children which in turn may enhance the progression of renal insufficiency and failure.8

Certain pediatric patient groups are at high risk for developing renal scars. Children with high degrees of vesicoureteral reflux are one example and those with neurogenic bladder (NGB) are another. NGB refers to bladder dysfunction due to an underlying neurologic deficit such as spina bifida, spinal cord injury, cerebral palsy, multiple sclerosis, and Parkinson disease. It is estimated that there are 400,000 people with NGB in the United States.12 Minimizing the risk of UTIs and renal scars forms a cornerstone goal in the care and treatment of this group because sepsis and renal failure are among the leading causes of death.12-14 Adults with spina bifida develop ESRD at a younger age compared to those without spina bifida. During 1998-2011 in the United States, the rate of chronic renal insufficiency for people with spina bifida doubled from 6% to 12%.15Assessing for renal scarring is imperative and this has been highlighted recently in screening protocols for the Centers for Disease Control Spina Bifida Registry.16, 17

Current imaging standard

The 99mTechnetium-dimercaptosuccinic acid (99mTc- DMSA) renal scan is the imaging standard for pyelonephritis and renal scarring, providing qualitative and quantitative information of renal cortex injury. Following injection, DMSA is taken up by the proximal tubules and upper loop of Henle by a peritubular route or by tubular reabsorption. With the subject sitting in front of a camera, high-resolution collimator and a matrix, scanning occurs about 2 hours later.18

When pyelonephritis is induced in animal models, DMSA scans are highly sensitive and reliable for detecting and localizing the acute parenchymal inflammation using histopathology as the gold standard.6 Areas of infection will correspond to areas within the kidney of reduced uptake of DMSA with preservation of the renal outlines. Scars within the kidney are represented by areas of decreased uptake of DMSA with loss of renal contour or cortical thinning.6, 9, 18 In practice, the DMSA is a routine test to look for scarring and when the clinical picture is not clear, to diagnose acute pyelonephritis. The unattractive aspect to performing a DMSA scan is the requirement of intravenous access for injection of the radiotracer, radiation exposure (mean effective dose 2.84 mSv; a CT scan is 2-5 mSv as a reference), and an exam time of 2-3 hours.19 For these reasons, the DMSA scan is performed judiciously. In cases of suspected pyelonephritis, the approach of empiric antibiotic treatment based on the clinical picture is much more common than performing a DMSA scan to confirm diagnosis. In cases where the clinical picture of pyelonephritis is coherent (when symptoms and lab data correlate), it is common practice to initiate empiric antibiotic treatment without the use of imaging to confirm diagnosis. However, there remain many complex situations when the diagnosis of pyelonephritis is not clear and symptoms or lab results will be atypical or unreliable. The DMSA scan remains useful to confirm diagnosis pyelonephritis in these patients. If Quick MRI proves to be an accurate imaging modality for pyelonephritis, it could substitute for a DMSA scan in these cases.

Quick MRI

MRI is an imaging method that can provide both excellent morphological detail and functional information regarding the urinary tract without the necessity for ionizing radiation. These features make MRI an attractive and useful modality for pediatric practice. However, enthusiasm for its use is tempered by high cost and its sensitivity to movement artifact that can significantly impair image resolution. Young children, therefore, need to be sedated during the long scanning time of conventional MRI. The potential adverse effects of sedation include the exposure to a general anesthetic and possibility of hypoxemia, paradoxical reactions, and an inadequate study.

In the past decade however, the fields of neuroradiology and neurosurgery have improved the usefulness of MRI through the development of 'quick' MRI protocols. These are 'quick' studies, limited to a single type of pulse sequence in contrast to conventional MRIs.20 Because they are limited, they are best designed to answer specific questions.21 Quick brain MRI protocols have become widely adopted into routine neurosurgical practice, in particular to diagnose hydrocephalus secondary to shunt malfunction. 20, 21Ultrafast-spin echo T2-weighted MR images require a total imaging procedure time of 3-5 minutes and can evaluate shunt position, size and configuration of ventricles with comparable sensitivity and specificity to CT.20, 22 CT has short scanning time but requires ionizing radiation; pediatric patients with chronic conditions undergo frequent imaging and represent a population at risk for cumulative radiation risks.

Quick MRIs as a modality that is free of radiation, has a short scanning time (minutes, therefore avoiding the need for sedation), and has good validity, has largely replaced computed tomography (CT) for the diagnosis of shunt malfunction.22 Their diagnostic utility has even disseminated to the emergency room setting and in the rapid screening of other neurological diseases such as ischemic stroke, trauma, and post-operative follow-up. 23, 24 In a survey of neurosurgeons from the US and Canada, 79% of institutions use a rapid-sequence MRI protocol and 64% use it routinely. 25

MRI has proven to be valid in detecting pyelonephritis (91% sensitivity, 89% specificity compared to DMSA), but gadolinium based contrast injection is required for image enhancement.26 Gadolinium is cleared by the kidney and should be avoided in people with ESRD. Nephrogenic sclerosis is a disorder with multisystem fibrosis, myopathy, and polyneuropathy that has been described in people with renal failure who received gadolinium. 27 Only one gadolinium agent, Gadavist, is approved by the United States Food and Drug Administration for children younger than 2 years old; the other gadolinium agents are prohibited in children less than 2 due to an immature glomerular filtration rate up to that age.

Diffusion weighted imaging (DWI) is a method of non-enhanced MRI that has been primarily applied in diagnosing intracranial processes including abscesses. In areas of acute inflammation, water diffusion will be restricted due to a high concentration of inflammatory cells, bacteria, viscosity, and high protein levels. 28 DWI is not standard in the imaging of renal disease but has recently shown promise in imaging pyelonephritis. 29 Compared to the gadolinium-enhanced T1-weighted method, DW MRI has shown good agreement for the diagnosis of pyelonephritis with 95%-100% sensitivity, 93.5%-95% specificity

and excellent interobserver reproducibility.30-32 DWI may provide a gadolinium - free means of evaluation for patients suspected to have pyelonephritis but comparison to the 99mTc- DMSA standard has not yet been undertaken. We hypothesize that the quick renal MRI will have at least 80% sensitivity compared to the 99mTc- DMSA standard in the diagnosis of acute pyelonephritis.

MRI has also shown promise in the detection of renal scars. In 1999, 24 children with neurogenic bladder and a history of UTI underwent conventional MRI and 99mTc- DMSA.33 The T1 fat saturated sequence had 82% concordance with DMSA. Its images were inherently tomographic with the hyperintense renal cortex contrasting with the surrounding hypointense perinephric tissues, allowing the detection of cortical scars which relied on contour contractions. In an independent study with 34 children after their first UTI, MRI had a sensitivity of 77% and specificity of 87%.34 It was agreed that the T1 fat saturated image was the optimum method to detect renal parenchymal defects. To date, the accuracy of a quick renal MRI study compared to DMSA using a single, fat-saturated T1-W sequence for the detection of renal scarring has yet to be established. A rapid, injection- and contrast- free imaging scan would be a novel method for accurate and timely diagnosis of acute pyelonephritis and for surveillance for renal scars in high risk pediatric groups. We hypothesize that the quick renal MRI will have at least 80% sensitivity and specificity compared to the 99mTc- DMSA standard in the diagnosis of renal scars.

SPECIFIC AIMS/REGISTRY OBJECTIVES

1) To establish the feasibility of completing the quick renal MRI compared to the DMSA scan (using DMSA as the ‘gold standard’) among children with suspected urinary tract infections (UTI). Children admitted to the American Family Children's Hospital for suspected acute pyelonephritis will undergo a clinical DMSA renal scan and quick renal MRI.

2) To establish the sensitivity and specificity of the quick renal MRI compared to the DMSA scan (using DMSA as the ‘gold standard’) in the diagnosis of renal scars among children with recurrent UTI. Children with recurrent UTI will undergo a clinical DMSA renal scan and quick renal MRI. The sensitivity and specificity of the quick renal MRI to detect renal scars will be determined using DMSA as the standard.

RESEARCH DESIGN AND METHODS

Design and Methods

If study criteria are met for Aim 1, patients will be enrolled during their hospital stay and undergo both a quick renal MRI and a standard of care DMSA scan before discharge. During the patients hospital stay, they will be offered the chance to participate. The PI, a hospital, and/or Dr. Ellen Wald will be available to recruit and onboard patients. If the patient chooses to do so, they will be consented, and the DMSA and Quick MRI will be schedule to occur within one week of consent, either before or after they are discharged.

If the criteria are met for Aim 2, a DMSA scan will be recommended according to the CDC's Spina Bifida Registry protocol. Patients are also allowed to participate in Aim 2 if they've completed a DMSA scan within the past 6 months. Patients will also be invited to participate in the study by undergoing a quick renal MRI. Spina bifida patients will be identified as qualified for the study ahead of time by the research staff, and will be asked if they would like to participate at their next regularly scheduled clinic visit. If they do choose to participate, they will then be scheduled to receive the DMSA and Quick MRI within 6 months.

For aim 1 patients, there is no specific order for the scans, but both imaging tests should be performed within one week of each other. For Aim 2, there is no specific order for the scans, but they should be performed within six months of each other.

Neither group of patients would experience a delay in receiving antibiotics because it is standard of care.

Patient enrollment and the success of participants completing both studies will be evaluated every 2 months.

If the recruitment rate is less than 50% of that planned to be completed by 6 months into the study, we will be prepared to expand recruitment to pediatric patients at St. Mary's Hospital.

To enroll additional patients likely to have renal scarring we will contact families of children with spina bifida who have already had a DMSA performed in the past year and invite them to participate. We believe that the quick, non-invasive nature of the test and the accommodated scheduling will appeal to potential subjects. The hospitalist faculty staff are enthusiastic for the development of the quick MRI and are likely to be early adopters of the quick renal MRI; this will facilitate enrollment for Aim 1.

Likewise, for Aim 2, Dr. Cannon understands that many of her patients are engaged in spina bifida advocacy and will be motivated to participate in a study that promises to ease their lifelong burden of frequent invasive testing.

Quick MRI Imaging: MRI of the kidneys will be performed using a 1.5-Tesla magnet (Signa, GE Medical Systems Milwaukee, Wisconsin, USA). For pyelonephritis, axial diffusion weighted imaging sequences will be used (3 mins if respiratory triggered, 15 secs if patient can hold breath). For renal scar, coronal and axial T1-weighted fat-saturated sequences will be used (10 mins). Below are the specific sequences of the Quick MRI abdomen without contrast for all study patients. Particular sequences were selected based on prior case reports of their accuracy in diagnosing either pyelonephritis or renal scars. All 5 sequences will be done because it will be important to distinguish acute infection from scarring, as well as renal anatomy.

Sequence	Pyelonephritis	Renal scars
Coronal and axial T1 FAT		X
Axial T1 FAT		X
Axial DWI	X	
Coronal T2 SSFSE	Gives detail of renal collecting system	
Coronal T1 LAVA-Flex	Gives detail of renal vasculature	

A quick MRI scan takes about 15 mins or less. No IV or sedation will be necessary. The patient will be required to lie flat and still during the test. A parent will be allowed to be with the patient while they are in the scanner. The machine will produce loud intermittent sounds of banging or knocking so they will have to wear protective headphones. They can listen to music if you want. If they are less than 1 year old, they will be swaddled and can be "held" during the test. If a child needs to have a parent in the scanner, it is ideal if the parent can have their head near the patients' legs and arms stretched out to hold the childs' hands. If the parent needs to be by the patients' head, it can be accomplished by the parent lying head to head with the child or the parent lying on the child. Ideally they are lying head to head, or just outside of the scanner reaching in.

Subject Population

Inclusion Criteria

Our target population is a heterogeneous group of medically complex patients with atypical UTIs. Our pilot study will help to establish the feasibility of the Quick MRI protocol in these patients.

For Aim 1: All children ages 0-21 years admitted to AFCH for a febrile UTI, suspected pyelonephritis, or diagnosed pyelonephritis will be eligible. Those who undergo DMSA scan as clinically indicated will be approached for study participation.

We want to establish the sensitivity of Quick MRI in the diagnosis of pyelonephritis and as such, we have selected a group of patients with febrile UTI who have a high probability of having pyelonephritis. We have determined that patients admitted to the hospital for intravenous hydration and antibiotics fulfill this criterion. This approach includes patients who would normally receive DMSA scans, therefore, a separate trip to the hospital will be unnecessary in patients that complete the imaging tests prior to discharge. These would be potential deterrents to successful recruiting from an outpatient basis. However, due to the nature of our study and recruiting conditions, we will also allow patients to return after their inpatient stay in order to complete the imaging result, whichever may work better for the patient and family.

For Aim 2: All children ages 0-21 years seen in the AFCH Spina Bifida Multi-Disciplinary Clinic for routine-follow-up will be eligible. Patients will be screened for a history of more than 1 UTI in the past year.

All patients must be willing to undergo the Quck MRI and, depending on which aim, the DMSA scan in order to be included.

Exclusion Criteria

For Aim 1: Patients will be excluded from the study of patients with acute pyelonephritis if they do not have evidence of pyuria on their UA, if their urine culture is negative, or are not comfortable having a quick MRI completed.

For both Aims: Patients with contraindications to MRI will be excluded from eligibility (implanted devices such as pacemakers, implanted cardioverter defibrillators, or cochlear implants or if they are or are planning to become pregnant).

Data Collection, Handling, Storage

Subjects' confidentiality will be addressed in multiple ways. There will be a retrospective and prospective review of the data. Data from eligible patients' medical records will be entered into an Excel document. All study records will be kept in secure locations. All data will be maintained only on Department of Urology password- and firewall-protected computers, and on the Department of Orthopedics/Rehabilitation and Urology;s secured network server. Data will not be stored on laptops, notebooks, or other portable computers. The PI has a locked office in a security restricted building (Medical Foundation Centennial Building). Only team members will have access to the data. Data about study subjects will not be shared with anyone other than team members.

The study team will do the following things to ensure the privacy of research participants and confidentiality of data:

- use codes so that no direct subject identifiers are recorded on data collection sheets
- create codes for data that are not based on subject identifiers (i.e., avoid codes that include subject initials or are based on birth dates)
- store the links to the code and code separately from each other
- keep identifiable data in locked cabinets or drawers in rooms with restricted access and/or on password-protected computers housed in rooms with restricted access or housed on departmental servers with limited, password-protected access
- limit the number of participating site team members with access to directly identifiable information

After imaging scans are performed, only DMSA scans will be accessible to the providers via Healthlink. Data/images will be analyzed by Shannon Cannon, MD, and Kara Gill, MD and appropriate radiology staff. Results of data analysis will be passed to research coordinator in order to document findings.

Study records will be kept for a minimum of 7 years, per campus policy.

Timeline of Activities

Following IRB approval, patient enrollment and completion of imaging studies for both specific aims will occur over 18 months.

	July	August	September	October	November	December	January	February	March	April	May	June	July	August
Enrollment	→													→
Team Meeting			X			X			X			X		
Data Analysis & Manuscript													→	→

DATA AND SAFETY MONITORING PLAN

All research related activities will be approved by the institutional review board ensuring that the benefits of participating in this research will outweigh the risks. Overall, although we do not expect any

problems to occur, care will be taken to ensure complete privacy of the patient, sanitary conditions, patient safety and quality care.

The research assistant in the Department of Urology, will be responsible for the monitoring of this data, under supervision from the PI, Dr. Shannon Cannon. We plan to assess our data and do a primary study evaluation when our enrollment has reached 25% of our stated enrollment goal. Unanticipated problems, adverse events, protocol deviations and violations will be reported to the IRB within 14 days following.

If, at the point of initial evaluation (25% of targeted enrollment), any of the following circumstances occur, the study will be formally stopped for evaluation and possible discontinuation:

- A higher than expected rate of complications in either study arm
- Arm 1:
    - A lack of efficacy of the Quick MRI to accurately diagnosis acute pyelonephritis
- Arm 2:
    - A lack of efficacy of the Quick MRI to accurately image renal scarring

We will include our initial study evaluation (at 25% of targeted enrollment) in the soonest following continuing review. In the case that our evaluation shows negative results and occurs prior to a continuing review, we will contact the IRB with the information and seek to reevaluate or possible discontinue the study. All study team members have completed relevant training materials, are well versed in maintaining clinical integrity and data validity, and will be formally instructed in the proper application of this protocol. Data/images will be evaluated by the PI, Dr. Shannon Cannon, and Dr. Kara Gill, a study team member. This data will be passed to the research coordinator, whereupon it will be stored securely as outlined in the Data and Record Keeping section of our protocol. The primary data handlers, Dr. Shannon Cannon and the research coordinator, meet every two weeks and can discuss and evaluate protocol adherence, data integrity, and validity as needed during these meetings.

STATISTICAL CONSIDERATIONS

Aim 1 will determine the sensitivity of quick MRI in the diagnosis of suspected acute pyelonephritis in children with febrile UTI. With a power of at least 80%, a target significance level of 0.05, and an estimate of 90% prevalence of DMSA confirmed acute pyelonephritis among children admitted for febrile UTI, the minimum sample size required to detect a change in sensitivity from 80%-90% is 34 subjects.

Aim 2 will determine the sensitivity and specificity of quick MRI in the diagnosis of renal scars in children with spina bifida and recurrent UTIs. With a power of at least 80%, a target significance level of 0.05, and an estimate of 30% prevalence of DMSA confirmed renal scars in this patient group, the minimum sample size required to detect a change in sensitivity from 60-90% and a change in specificity from 70-90% would require a minimum sample size of 64 subjects.

The sensitivity will be calculated with TP/TP+FN. The specificity will be calculated with TN/TN+FP

This is a pilot study and we are trying to get a baseline understanding of the accuracy of Quick MRI. If the preliminary sensitivity/specificity percentages are less than 60%, we would be less enthusiastic about carrying out future research on this question, and vice versa.

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