# Importance of Methodology on $^{99m}$Technetium Dimercapto-Succinic Acid Scintigraphic Image Quality: Imaging Pilot Study for RIVUR (Randomized Intervention for Children With Vesicoureteral Reflux) Multicenter Investigation

Harvey A. Ziessman* and Massoud Majd

*From the Division of Nuclear Medicine, Russell H. Morgan Department of Radiology and Radiological Sciences, The Johns Hopkins University, Baltimore, Maryland (HAZ), and Department of Radiology, Children's National Medical Center, Washington, D. C. (MM)*

**Abbreviations and Acronyms**

$^{99m}$Tc = $^{99m}$technetium

DMSA = dimercapto-succinic acid

LPO = left posterior oblique

LT = left

POST = posterior

RIVUR = Randomized Intervention for Children With Vesicoureteral Reflux

ROI = region of interest

RPO = right posterior oblique

RT = right

SPECT = single photon emission computerized tomography

UTI = urinary tract infection

VCUG = voiding cystourethrography

VUR = vesicoureteral reflux

Submitted for publication December 3, 2008.

Study received institutional review board approval.

* Correspondence: Russell H. Morgan Department of Radiology and Radiological Sciences, Division of Nuclear Medicine, Johns Hopkins University, 601 N. Caroline Street, JHOC 3223, Baltimore, Maryland 21287 (telephone: 410-955-5152; FAX: 443-287-2933; e-mail: hziessm1@jhmi.edu).

**See Editorial on page 12.**

**Purpose:** We reviewed our experience with $^{99m}$technetium dimercapto-succinic acid scintigraphy obtained during an imaging pilot study for a multicenter investigation (Randomized Intervention for Children With Vesicoureteral Reflux) of the effectiveness of daily antimicrobial prophylaxis for preventing recurrent urinary tract infection and renal scarring. We analyzed imaging methodology and its relation to diagnostic image quality.

**Materials and Methods:** $^{99m}$Technetium dimercapto-succinic acid imaging guidelines were provided to participating sites. High-resolution planar imaging with parallel hole or pinhole collimation was required. Two core reviewers evaluated all submitted images. Analysis included appropriate views, presence or lack of patient motion, adequate magnification, sufficient counts and diagnostic image quality. Inter-reader agreement was evaluated.

**Results:** We evaluated 70, $^{99m}$technetium dimercapto-succinic acid studies from 14 institutions. Variability was noted in methodology and image quality. Correlation (r value) between dose administered and patient age was 0.780. For parallel hole collimator imaging good correlation was noted between activity administered and counts (r = 0.800). For pinhole imaging the correlation was poor (r = 0.110). A total of 10 studies (17%) were rejected for quality issues of motion, kidney overlap, inadequate magnification, inadequate counts and poor quality images. The submitting institution was informed and provided with recommendations for improving quality, and resubmission of another study was required. Only 4 studies (6%) were judged differently by the 2 reviewers, and the differences were minor.

**Conclusions:** Methodology and image quality for $^{99m}$technetium dimercapto-succinic acid scintigraphy varied more than expected between institutions. The most common reason for poor image quality was inadequate count acquisition with insufficient attention to the tradeoff between administered dose, length of image acquisition, start time of imaging and resulting image quality. Inter-observer core reader agreement was high. The pilot study ensured good diagnostic quality standardized images for the Randomized Intervention for Children With Vesicoureteral Reflux investigation.

**Key Words:** antibiotic prophylaxis, technetium Tc $^{99m}$ dimercaptosuccinic acid, urinary tract infection, vesico-ureteral reflux



0022-5347/09/1821-0272/0
THE JOURNAL OF UROLOGY®

Vol. 182, 272-279, July 2009
Printed in U.S.A.
DOI:10.1016/j.juro.2009.02.144

THE RIVUR investigation is a multicenter, randomized, double-blind, placebo controlled trial of the usefulness of antimicrobial prophylaxis in children with urinary tract infection and vesicoureteral reflux sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases. An imaging pilot study was performed before initiation of the investigative trial, with the purpose of ensuring uniform high quality diagnostic images for the subsequent clinical trial. We report our experience reviewing the $^{99m}$technetium dimercapto-succinic acid renal cortical scintigraphic images, with special attention to methodology, image quality and inter-reader agreement.

In children UTIs are considered the principal cause of renal parenchymal scarring and the sequelae of hypertension and end-stage renal disease, especially in patients with VUR. Published clinical guidelines recommend voiding cystography to assess for the presence and extent of reflux.[1,2] However, VUR is found in only 30% to 40% of children with UTI. Renal scarring is uncommon even in patients with high grades of reflux and occurs in children without VUR. Its diagnosis and treatment have not consistently resulted in decreasing end-stage renal failure.[3,4]

Studies comparing the effectiveness of combined surgical correction and antimicrobial prophylaxis vs antimicrobial prophylaxis alone have not demonstrated a difference in the frequency of renal scarring.[1,5–7] Because the currently recommended initial evaluation and followup of children with UTIs (repeat urine cultures, renal/genitourinary imaging, antimicrobial therapy, long-term prophylaxis) are costly in terms of time, money, adverse reactions and antibiotic resistance, doubts have been expressed about the efficacy of present therapeutic strategies vs prompt evaluation of urinary symptoms and early treatment of confirmed infections.[1,4–6,8]

The purpose of the RIVUR investigation is to determine, in the setting of prompt evaluation of UTI symptoms and early therapy of culture proved infection, whether daily antimicrobial prophylaxis is effective for preventing recurrent UTI and renal scarring in children with VUR. A total of 600 children are to be enrolled and randomized to antimicrobial prophylaxis and placebo treatment arms. All patients will undergo renal/bladder ultrasonography, VCUG and $^{99m}$Tc DMSA scintigraphy within 16 weeks of the initial event. The presence of acute pyelonephritis or scarring will be determined by $^{99m}$Tc DMSA scintigraphy. After randomization patients will be followed for 24 months, and VCUG and $^{99m}$Tc DMSA will be repeated. $^{99m}$Tc DMSA imaging will also be repeated at 12 months and if there is intercurrent infection. Thus, each of the 600 children will undergo at least 3, $^{99m}$Tc DMSA studies, which we will review.

To ensure uniformity in imaging methodology from all participating sites, an imaging pilot study was designed to 1) assess the ability of each site to obtain and transmit the imaging studies, 2) assess their readability and image quality, 3) demonstrate uniformity and accuracy of interpretation by the image readers, and 4) facilitate development of a standard protocol for adjudication of image interpretation between the core readers before initiation of the investigation. The pilot study has been completed and the investigational study is under way. We describe our findings during the pilot study regarding $^{99m}$Tc DMSA methodology, image quality and inter-reader agreement, and discuss how this pilot study ensures high quality imaging for the subsequent clinical investigational study.

## METHODS

For the pilot study each of 4 core sites was required to submit 10 VCUGs, ultrasonograms and $^{99m}$Tc DMSA scans, and each of 10 satellite sites was required to submit 2 sets of these evaluations. Each of the submitted studies was reviewed by 2 core image readers for each of the 3 modalities. The pilot studies had to be completed and approved by the core readers before a site could enroll and randomize patients to the main study. The $^{99m}$Tc DMSA scans were reviewed by 2 experienced nuclear medicine physicians (the authors). All participating sites received local institutional review board approval before submitting studies for the pilot study.

For the purpose of the RIVUR protocol it was decided that standardization of methodology, viewing, image quality and interpretation was important. Only planar or pinhole imaging was deemed acceptable for this investigation. There were several reasons for this decision. Few institutions in this multicenter investigation used SPECT routinely for $^{99m}$Tc DMSA scintigraphy. Similarly most imaging centers around the country do not use SPECT, but rather acquire 2-dimensional multi-view planar parallel hole or pinhole collimator images. SPECT would have posed substantial problems in standardization, quality control and review issues that are far beyond that of planar imaging. Uniformity of image acquisition, quality control, display methodology, interpretative review and analysis would be considerably more variable and complicated with SPECT. We wanted the results of this investigation to be as widely applicable as possible.

The following written guidelines were provided to each site regarding $^{99m}$Tc DMSA scintigraphic methodology. Inject 50 to 100 $\mu$Ci/kg, or 3 to 5 mCi per 1.73 m$^2$ body surface area (minimum dose 0.5 to 1 mCi, maximum 5 mCi) $^{99m}$Tc DMSA intravenously. Begin imaging 2 to 4 hours after injection. Acquire high-resolution magnified planar images using either parallel hole or pinhole collimators. Parallel hole collimator images should be magnified according to body size and have at least 300,000 counts, including posterior, LPO and RPO views (fig. 1). Pinhole collimator images should include left kidney and right kidney posterior views as well as LPO and RPO