# Is Availability of $^{99m}$Tc-DMSA Insufficient to Meet Clinical Needs in the United States? A Survey

*Ruth Lim, MD, Department of Radiology, Massachusetts General Hospital/Harvard Medical School, Boston, MA; Zvi Bar-Sever, MD, Department of Nuclear Medicine, Schneider Children's Medical Center, Petach Tikva, Tel Aviv University, Tel Aviv, Israel; and S. Ted Treves, MD, Department of Radiology, Brigham and Women's Hospital/Harvard Medical School, Boston, MA*

Imaging with $^{99m}$Tc-labeled dimercaptosuccinic acid ($^{99m}$Tc-DMSA) has proven to be of great value in the diagnosis and follow-up of pyelonephritis and other disorders of the renal cortex (Table 1), mainly in children and to a lesser extent in adults. In pyelonephritis, $^{99m}$Tc-DMSA imaging shows a very high diagnostic sensitivity (>90%) (*1–3*). Following intravenous administration, $^{99m}$Tc-DMSA localizes primarily in the proximal convoluted tubules of the renal cortex, and after uptake it does not redistribute significantly. The renal concentration of $^{99m}$Tc-DMSA closely follows regional renal blood flow (*4*).

For decades $^{99m}$Tc-DMSA was widely and routinely available in the United States. During the past few years, however, routine U.S. availability of $^{99m}$Tc-DMSA has been significantly impaired. In contrast, $^{99m}$Tc-DMSA is available and used extensively in Europe and other countries around the world. In 2014, DMSA was added to the Drug Shortages List of the U.S. Food and Drug Administration (FDA) and was commercially unavailable thereafter. With the FDA-approved drug remaining on backorder indefinitely, some providers surveyed for this article suggested unfamiliarity with how to access alternative formulations of DMSA that are available through many nuclear pharmacies, including both compounded and manufactured formulations. Some providers have access to DMSA but have been reluctant to use less stringently regulated compounded formulations and may not be aware that a manufactured option is also available. Although none of the preparations are FDA-approved generic equivalents, the FDA has maintained a temporary importation allowance for the manufactured product. In response to a 2012 fungal meningitis outbreak caused by contamination at New England Compounding Center (Framingham, MA) (*5*), the Drug Quality and Security Act (H.R. 3204) granted the FDA more authority to regulate and monitor the manufacturing of compounding drugs (*6*). In addition, multiple state boards of pharmacy responded by enforcing United States Pharmacopeia guidelines through inspections and/or new regulations for compounding pharmacies. Some compounding pharmacies were shut down (*7*).

In March 2019, one of the authors (ZB-S) of this article conducted a survey among national delegates of 26 European countries participating at the European Association of Nuclear Medicine (EANM) meeting to assess the status of DMSA in Europe. The survey showed that the radiopharmaceutical is widely available and commonly used. No shortages were reported.

The current shortage of $^{99m}$Tc-DMSA in the United States is limiting the use of this unique, highly sensitive, and well-established imaging method. This shortage has created a vicious circle in which many practitioners say that they no longer perform $^{99m}$Tc-DMSA scintigraphy, resulting in reduced demand. Other factors contributing to its reduced use include older practice guidelines (such as that from the American Academy of Pediatrics in 2011 [*8*]), lack of education of referring physicians about its value, concern about radiation exposure, and others.

### The Survey

We conducted a survey among nuclear medicine practitioners to explore and confirm the value of this imaging method and the current availability of this agent in the United States. The rationale for this survey was to confirm whether $^{99m}$Tc-DMSA imaging is indeed viewed as a valuable resource and therefore should be available to patients in this country in a safe and easily available formulation.

The survey examined practice setting, whether nuclear medicine and referring practitioners believe $^{99m}$Tc-DMSA scans to be helpful, current local usage, reasons why DMSA is unavailable, sources of DMSA, and whether their practices would perform $^{99m}$Tc-DMSA scans if DMSA were routinely available (Table 2). The Google Forms survey was sent to the SNMMI All Member Community via the SNMMI Connect Communities discussion board (https://communities.snmmi.org). Responses were tabulated.

**TABLE 1**
Indications for $^{99m}$Tc-DMSA Imaging in Children

1. Detection of acute pyelonephritis
2. Detection of renal scarring
3. Abnormal size or contour of kidney on ultrasound
4. Measurement of split renal function
5. Congenital abnormalities
   a. Antenatal or neonatal hydronephrosis
   b. Horseshoe kidney, cross-fused renal ectopia
   c. Solitary or ectopic kidney
   d. Multicystic dysplastic kidney
   e. Vesicoureteral reflux
   f. Duplicated collecting system
   g. Ectopic kidney
   h. Renal dysplasia
6. Renal infarct
7. Segmental renal artery stenosis
8. Hypertension
9. Allergy to iodinated contrast agents

**TABLE 2**
$^{99m}$Tc-DMSA Use Survey Questions/Items

1. In what ZIP code is your primary practice?
2. Describe your practice setting.
3. Do you believe that DMSA scans are helpful?
4. Do your referring physicians believe that DMSA scans are helpful?
5. Does your practice currently perform DMSA scans?
6. Indicate the reason your practice is not currently performing DMSA scans.
7. Would your practice be performing DMSA scans now if DMSA was available?
8. Who is your DMSA supplier? or Why is DMSA unavailable in your practice?
9. Has your practice ever experienced a DMSA supply interruption?
10. Any other comments?

During the 3 weeks in early 2019 when the survey was open, we received 93 responses from 33 different states. Ninety percent (90%) (84/93) of responses were from hospitals (teaching, community, mixed). Ninety percent (90%) (84/93) of responders believed $^{99m}$Tc-DMSA scans to be helpful, and 73% (68/93) stated their referring physicians felt $^{99m}$Tc-DMSA scans were helpful. However, 24% (22/93) were undecided or did not know about referring physician attitudes. Forty-five percent (42/93) currently perform $^{99m}$Tc-DMSA scans, whereas 55% (51/93) do not. The reported current sources of DMSA in this country varied from importation from other countries to a short list of both small and large U.S. suppliers.

Seventy (70) respondents answered the question "Would your practice be performing DMSA scans now if DMSA were available?" Of these, 56% (49/70) stated that they would, and 30% (21/70) stated that they might perform $^{99m}$Tc-DMSA scans if the radiopharmaceutical were available (Fig. 1).

Fifty-four (54) respondents answered the question "In the past, has your practice ever experienced a DMSA supply interruption? If yes, please describe." Of these, 63% (34/54) reported that their practices have experienced DMSA supply interruptions. Sixty-four respondents answered the question "Indicate the reason your practice is not currently performing DMSA scans." Of these, 38% (24/64) reported that DMSA is temporarily unavailable, and 20% (13/64) that DMSA is permanently unavailable. Some (14%, 9/64) have stopped offering this study.

Forty-two respondents answered the question "Please describe why DMSA is unavailable to your practice." Stated reasons included: DMSA not available, 52% (22/42); never ordered, 14% (6/42); radiologist not willing to administer non-FDA–approved agent, 10% (4/42); and lack of reimbursement, 2% (1/42). Twenty percent of respondents (20%) (19/93) shared free-text comments.

## DISCUSSION

As noted previously, $^{99m}$Tc-DMSA is used extensively in Europe and other countries around the world, and we hope that it can again become readily and reliably available in the United States. In Europe, recommended administered activities in children are listed on package inserts following the recommendation of the Pediatric Task Group of the EANM. However, the FDA does not include pediatric indications or dosages. U.S. package inserts state: "Pediatric Use: Safety and effectiveness in children have not been established." Therefore, U.S. pediatric practitioners must use $^{99m}$Tc-DMSA as an "off-label" indication (*7*) and typically refer to either the North American Consensus Guidelines (*9,10*) or the EANM Pediatric Dosage Card/Calculator to determine the appropriate pediatric dosage (*11*).

In regard to radiation dose, it may be helpful to consider that the effective dose of radiation to the patient with $^{99m}$Tc-DMSA is in the range of 0.7–0.9 mSv (*3*). In comparison, abdominal CT, which is used for numerous routine clinical indications, has an effective dose of ~5.0 mSv (*12*). If the usefulness of cortical scintigraphy to patient and physician can outweigh the potential risks of what is considered a relatively small radiation dose, then appropriately performed $^{99m}$Tc-DMSA scanning should be an available diagnostic tool. This is particularly the case when an equivalent or superior test for evaluation of functioning renal cortex is not practical. For example, MR imaging is at least equally as sensitive as $^{99m}$Tc-DMSA for detection of pyelonephritis or cortical scarring (*13*), but MR imaging requires general anesthesia or sedation in young children, must be performed at an experienced pediatric facility, is more costly, and may have lengthier wait times to schedule. As stated by the SNMMI, the aim should be to perform the right test, with "the right dose, to the right patient at the right time" (*14*).

Two approaches currently exist in the workup of patients with febrile urinary tract infection. To date, universal agreement has not been reached on which approach is most appropriate (*15*). One is known as the "top down" approach. In this case, the recommendation is that at the time of acute infection, a patient should undergo a $^{99m}$Tc-DMSA renal scan to determine the presence of acute pyelonephritis. If the $^{99m}$Tc-DMSA scan is normal, no further imaging investigation would be performed. If, on the other hand, the $^{99m}$Tc-DMSA scan is abnormal, further evaluation with voiding cystourethrography

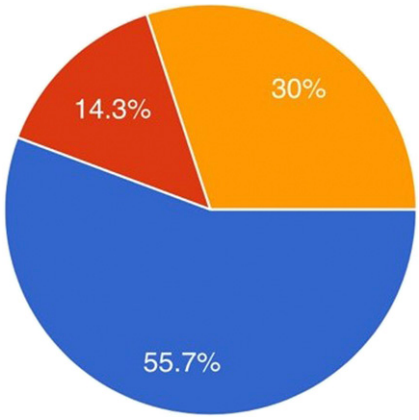


**FIGURE 1.** Responses ($n$ = 70) to the question "Would your practice be performing DMSA scans now if DMSA were available?" Blue = yes; yellow = maybe; red = no.

(VCUG) and other testing should be conducted to determine whether vesicoureteral reflux (VUR) is present. The other approach, known as "bottom up," recommends a VCUG after acute infection to determine whether the patient has VUR. If the patient has VUR, then further investigations of the kidneys, sometimes including a late (>6 months after infection) $^{99m}$Tc-DMSA scan, are conducted to determine whether permanent renal scarring has occurred (*1,2,16–24*).

A detailed discussion of the advantages and limitations of either approach is beyond the scope of this article. Suffice it to say that in either approach $^{99m}$Tc-DMSA scintigraphy provides the physician with a sensitive method to evaluate the functional integrity of the renal units.

## CONCLUSION

The $^{99m}$Tc-DMSA scan remains a highly desired, very useful, and superior sensitivity tool in the evaluation of pyelonephritis, scarring of the renal cortex, and a range of additional clinical indications (Table 1). Unfortunately, at the present time only non-FDA–approved DMSA formulations are available in the United States through a scant patchwork of local suppliers. This situation has negatively impacted practitioners' ability to evaluate renal cortical defects in children and adults. Whether regional preference is for the "top down" or "bottom up" approach in evaluation of urinary tract infection, $^{99m}$Tc-DMSA imaging is a very helpful tool for diagnosis of renal cortical abnormalities. A clear clinical need for this method has been voiced through the results of this survey. The current problem of lack of a reliable, safe, commercially available formulation of DMSA in the United States should be resolved by its stakeholders for the benefit of patients and practitioners. Perhaps an appeal to industry, the FDA, other regulatory organizations, urologists, nephrologists, pediatricians, professional societies (such as the Radiological Society of North America and SNMMI), and the broader nuclear medicine community could assist in this task.

## REFERENCES


1. Ataei N, Madani A, Habibi R, Khorasani M. Evaluation of acute pyelonephritis with DMSA scans in children presenting after the age of 5 years. *Pediatr Nephrol.* 2005;20(10):1439–1444.
2. Majd M, Nussbaum Blask AR, Markle BM, et al. Acute pyelonephritis: Comparison of diagnosis with $^{99m}$Tc-DMSA SPECT, spiral CT, MR imaging, and power Doppler US in an experimental pig model. *Radiology.* 2001;218(1):101–108.
3. Ward VL, Strauss KJ, Barnewolt CE, et al. Pediatric radiation exposure and effective dose reduction during voiding cystourethrography. *Radiology.* 2008;249(3): 1002–1009.
4. Willis KW, Martinez DA, Hedley-Whyte ET, Davis MA, Judy PF, Treves S. Renal localization of $^{99m}$Tc-stannous glucophetonate and $^{99m}$Tc-stannous dimercaptosuccinate in the rat by frozen section autoradiography. The efficiency and resolution of technetium-99m. *Radiat Res.* 1977;69:475–488.
5. Tavernise S, Pollack A. FDA details contamination at pharmacy. *New York Times*. October 27, 2012. Available at: https://www.nytimes.com/2012/10/27/health/fda-finds-unsanitary-conditions-at-new-england-compounding-center.html. Accessed on June 9, 2019.
6. U.S. Congress. Drug Quality and Security Act. Passed November 27, 2013. Available at: https://www.congress.gov/113/plaws/publ54/PLAW-113publ54.pdf. Accessed on June 10, 2019.
7. Paolino M, Treves ST. Availability of $^{99m}$Tc-DMSA. *J Nucl Med.* 2017;58(11):16N.
8. American Academy of Pediatrics. Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, Roberts KB. Urinary tract infection: Clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics.* 2011;128(3):595–610.
9. Treves ST, Gelfand MJ, Fahey FH, Parisi MT. 2016 update of the North American Consensus Guidelines for Pediatric Administered Radiopharmaceutical Activities. *J Nucl Med.* 2016;57(12):15N–18N.
10. SNMMI. Pediatric Injected Activity Tool. 2016. Available at: www.snmmi.org/ClinicalPractice/PediatricTool.aspx?ItemNumber=11216&navItemNumber=11219%22. Accessed on June 9, 2019.
11. European Association of Nuclear Medicine. Dosage card. 2016. Available at https://www.eanm.org/publications/dosage-card/. Accessed on June 9, 2019. Dosage calculator. 2016. Available at: https://www.eanm.org/publications/dosage-calculator/. Accessed on June 9, 2019.
12. Treves S, Fahey F. Pediatric nuclear medicine and radiation dose. *Semin Nucl Med.* 2014;44:202–209.
13. Cerwinka W, Grattan-Smith J, Jones R, et al. Comparison of magnetic resonance urography to dimercaptosuccinic acid scan for the identification of renal parenchyma defects in children with vesicoureteral reflux. *J Pediatr Urol.* 2014; 10(2):344–351.
14. Fahey F, Stabin M. Dose optimization in nuclear medicine. *Semin Nucl Med.* 2014;44:193–201.
15. Lim R. Vesicoureteral reflux and urinary tract infection: Evolving practices and current controversies in pediatric imaging. *AJR Am J Roentgenol.* 2009;192(5): 1197–1208.
16. Prasad MM, Cheng EY. Radiographic evaluation of children with febrile urinary tract infection: Bottom-up, top-down, or none of the above? *Adv Urol.* 2012;2012: 716739.
17. Okarska-Napierała M, Wasilewska A, Kuchar E. Urinary tract infection in children: Diagnosis, treatment, imaging—Comparison of current guidelines. *J Pediatr Urol.* 2017;13(6):567–573.
18. Bush N, Keays M, Adams C, et al. Renal damage detected by DMSA, despite normal renal ultrasound, in children with febrile UTI. *J Pediatr Urol.* 2015; 11(3):126.e1–7.
19. De Palma D, Santos A. Renal radionuclide imaging, an evergreen forty years old. *Klin Pädiatr.* 2014;226(04):225–232.
20. Herz D, Merguerian P, McQuiston L, Danielson C, Gheen M, Brenfleck L. 5-year prospective results of dimercapto-succinic acid imaging in children with febrile urinary tract infection: Proof that the top-down approach works. *J Urol.* 2010; 184(4s):1703–1709.
21. Shaikh N, Ewing AL, Bhatnagar S, Hoberman A. Risk of renal scarring in children with a first urinary tract infection: A systematic review. *Pediatrics.* 2010;126(6): 1084–1091.
22. Johnin K, Kobayashi K, Tsuru T, Yoshida T, Kageyama S, Kawauchi A. Pediatric voiding cystourethrography: An essential examination for urologists but a terrible experience for children. *Int J Urol.* 2019;26(2):160–171.
23. Narchi H, Marah M, Khan AA, Al-Amri A, Al-Shibli A. Renal tract abnormalities missed in a historical cohort of young children with UTI if the NICE and AAP imaging guidelines were applied. *J Pediatr Urol.* 2015;11(5):252.e1–7.
24. Ristola MT, Hurme T. NICE guidelines cannot be recommended for imaging studies in children younger than 3 years with urinary tract infection. *Eur J Pediatr Surg.* 2015;25(05):414–420.