CONTRAST-ENHANCED ULTRASOUND OF THE URINARY TRACT

A FREE Continuing Education Monograph

FACULTY

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Radiology
AFSUMB	Asian Federation of Societies for Ultrasound in Medicine and Biology
AIUM	American Institute of Ultrasound in Medicine
ASUM	Australasian Society for Ultrasound in Medicine
CECT	contrast-enhanced computed tomography
CEMRI	contrast-enhanced magnetic resonance imaging
CEUS	contrast-enhanced ultrasound
CT	computed tomography
EFSUMB	European Federation of Societies for Ultrasound in Medicine and Biology
FDA	U.S. Food and Drug Administration
FLAUS	Latin-American Federation of Societies for Ultrasound in Medicine and Biology
FLL	focal liver lesion
ICUS	International Contrast Ultrasound Society
MI	mechanical index
MRI	magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NPV	negative predictive value
PPV	positive predictive value
RFA	radiofrequency ablation
RNC	radionuclide cystography
SIUMB	Society for Ultrasound in Medicine and Biology
UCA	ultrasound contrast agent
VCUG	voiding cystourethrography
VUR	vesicoureteric reflux
WFUMB	World Federation for Ultrasound in Medicine and Biology

TARGET AUDIENCE

This activity is designed for pediatric radiologists, pediatric urologists, sonographers, nurses, and other healthcare providers involved with imaging of the urinary tract in pediatric patients with known or suspected vesicoureteral reflux (VUR) to help them better understand the indications, applications, and potential benefits of utilizing contrast-enhanced ultrasound (CEUS) for detecting known or suspected diseases and abnormalities of the kidneys, bladder, and urinary tract.

EDUCATIONAL OBJECTIVES

As a result of this activity, the participant should be better able to:

- Describe indications and accepted uses of CEUS of the kidneys, bladder, and urinary tract
- Summarize practice guidelines, recommendations, and clinical trials demonstrating the clinical utility of CEUS
- Review physicochemical, acoustic, and pharmacodynamics/pharmacokinetic characteristics of ultrasound contrast agents (UCAs)

STATEMENT OF NEED/PROGRAM OVERVIEW

- Urinary tract infections (UTIs) are common in young children. It has been estimated that up to 7% of girls and 2% of boys will have a UTI in the first 6 years of life. Many of these children with recurrent UTIs have VUR. Children with VUR are at risk of renal scarring. This scarring can cause serious sequelae as these children grow into adulthood, including renal hypertension, proteinuria, and end-stage renal disease. The negative health impacts of VUR can be successfully ameliorated by prompt diagnosis, allowing for early management with antibiotic prophylaxis to prevent UTIs, and surgical interventions in more severe cases
- Currently, recommendations are that children with febrile or recurrent UTIs undergo diagnostic imaging to evaluate for the presence of VUR. Three imaging modalities are currently available for VUR detection: voiding cystourethrography (VCUG), direct radionuclide cystography (DRNC), and contrast-enhanced voiding ultrasonography (CE-VUS). Many children, once diagnosed with VUR, may require serial imaging to guide treatment; therefore, the safety and cost of the imaging modality are important considerations. CE-VUS, widely used for decades primarily in Europe, was recently introduced in the United States. CE-VUS has high diagnostic accuracy in detecting reflux and does not expose children to ionizing radiation

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INTRODUCTION

Contrast-enhanced ultrasound (CEUS) is a radiation-free and highly sensitive noninvasive imaging modality that can provide continuous, real-time, high-resolution imaging.[1,2] CEUS is performed with ultrasound and the use of ultrasound contrast agents (UCAs) that can be administered intravenously or instilled into physiological (eg, urinary bladder) or nonphysiological (eg, fistulas) body cavities usually accessible via a catheter/tube.[2–8]

CEUS improves the detection and characterization of pathologies compared with conventional gray-scale and Doppler ultrasound, and demonstrates high diagnostic capabilities that in many cases are similar to that of contrast-enhanced computed tomography (CECT) and contrast-enhanced magnetic resonance imaging (CEMRI).[9] Yet CEUS has several advantages over CECT and CEMRI,[1,2] including lack of exposure to ionizing radiation, wider accessibility, and portability. Additionally, the equipment is less expensive. Particularly for pediatric patients, an additional benefit is that the patient does not need to be sedated. Furthermore, the high safety profile of UCAs and the lack of nephrotoxic effects allow for their use in patients with renal impairment and also for their repeated administration in the same session, if needed.[4,10,11]

CEUS is a well-established imaging modality for characterization of liver lesions, but an increasing number of studies has demonstrated its utility for extrahepatic applications, including the urinary tract.[4] Here we review in detail the principles of CEUS, as well as the efficacy and safety of UCAs for imaging of the urinary tract.

ULTRASOUND CONTRAST AGENTS (UCAs)

Currently, 3 second-generation UCAs are available commercially. They consist of tiny (2–5 µm in diameter) gas-filled microspheres encapsulated by a stabilizing shell of a biocompatible material composed of albumin, lipid, or phospholipid[12] (**Table 1**).[13–15]

UCAs are smaller than red blood cells (ie, <7 µm in diameter); thus, when administered intravenously, they can circulate easily through capillary beds. In addition, because of their small size, microspheres do not pass through the vascular endothelium, so the microspheres remain confined within the vascular bed and behave as purely intravascular contrast agents.[3] UCAs do not contain radioactive or iodinated material and are not excreted by the kidney; therefore, they lack nephrotoxic effects, making CEUS a good imaging option for patients with renal disease.[16] About 5 minutes after injection, the microspheres dissolve and the gas within the microspheres diffuses into the blood and is eventually exhaled through the lungs; the very small mass of shell material is then metabolized in the liver. Because UCAs act as true blood-pool agents, they provide dynamic information on contrast wash-in/wash-out kinetics and enhancement patterns that can be used to characterize various lesions.[2,6]

The 3 UCAs approved by the U.S. Food and Drug Administration (FDA) and available in the United States are Definity® (perflutren lipid microsphere), Lumason® (sulfur hexafluoride lipid-type A microspheres), and Optison™ (perflutren protein type-A microspheres).[13–15]

Table 1. Currently Available, FDA-Approved Ultrasound Contrast Agents[13–15]

Name	Manufacturer	Mean Diameter	Shell	Gas	FDA-Approved Indication(s)
Definity® (perflutren lipid microsphere)	Lantheus Medical Imaging	1.1–3.3 µm (max 20 µm; 98% <10 µm)	Lipid	Perflutren	• For use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border
Lumason® (sulfur hexafluoride lipid-type A microspheres)	Bracco Diagnostics	1.5–2.5 µm (max 20 µm; 99% ≤10 µm)	Phospholipid	Sulfur hexafluoride (SF_6)	• For use in echocardiography to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border in adult patients with suboptimal echocardiograms • For use in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients • For use in ultrasonography of the urinary tract for the evaluation of suspected or known vesicoureteral reflux in pediatric patients
Optison™ (perflutren protein-type A microspheres)	GE Healthcare	3.0–4.5 µm (max 32 µm; 95% <10 µm)	Human albumin	Perflutren	• For use in patients with suboptimal echocardiograms to opacify the left ventricle and to improve the delineation of the left ventricular endocardial borders

All 3 of the currently approved UCAs are approved for use during echocardiography. Lumason® (sulfur hexafluoride lipid-type A microspheres; called SonoVue® outside the United States) is the only UCA with FDA approval for abdominal use: in March 2016, Lumason® (sulfur hexafluoride lipid-type A microspheres) was approved for ultrasonography of the liver for characterization of focal liver lesions (FLLs) in adult and pediatric patients and, in December 2016, approval was granted for evaluation of vesicoureteral reflux (VUR) in pediatric patients.[14]

Interaction of UCAs and Ultrasound Waves

Although the type of gas and the composition of the shell may vary among the different UCAs, the physical principles of the interaction between the microspheres and the incident ultrasound waves are similar.[17] Basically, when a microsphere is exposed to an ultrasound wave, it resonates, which means the microsphere alternately compresses and expands in response to the acoustic pressures changes of the ultrasound wave, producing a strong nonlinear signal. This signal is detected by contrast-specific imaging software. A low mechanical index (MI) is essential to minimize bursting of the microspheres.[18]

When microspheres are administered intravenously, their nonlinear acoustic effects amplify signals from blood flow,[19] resulting in real-time, high-resolution images of both macrovasculature and microvasculature (ie, capillary bed).[2,20–22] The ability to detect the microvasculature is particularly beneficial, because these vessels may be too small and/or have insufficient blood-flow velocity to be visualized on color or power Doppler images. In fact, Doppler ultrasound can image blood vessels as small as 100 µm, whereas CEUS can depict vessels as small as 40 µm.[2]

GUIDELINES FOR CEUS OF THE ABDOMEN

International guidelines for CEUS of the abdomen have evolved over time.[23] The first edition of guidelines was issued in 2004 by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) and it was the first scientific endorsement of the clinical use of UCAs for evaluation of FLLs and monitoring treatment response after ablation procedures.[3] In 2008, a second edition of guidelines was published,[4] containing updates to the earlier hepatic CEUS guidelines and new recommendations for extrahepatic applications of CEUS in kidney and urinary tract (including VUR), pancreas, abdominal trauma, and cerebral circulation. In 2011 and 2012, further updates to the clinical guidelines for the hepatic and extrahepatic applications of CEUS were released.[2,5] Specifically, the 2011 guidelines on extrahepatic CEUS applications presented in detail recommendations for use of CEUS across many body organs and also introduced a grading system for the level of evidence for each recommendation.[5] The 2012 updated guidelines on hepatic CEUS applications were an international effort initiated by the WFUMB (World Federation for Ultrasound in Medicine and Biology) and EFSUMB in cooperation with representatives of AFSUMB (Asian Federation of Societies for Ultrasound in Medicine and Biology), the AIUM (American Institute of Ultrasound in Medicine), the ASUM (Australasian Society for Ultrasound in Medicine), the FLAUS (Latin-American Federation of Societies for Ultrasound in Medicine and Biology), and ICUS (International Contrast Ultrasound Society). This set of guidelines provided detailed recommendations for the use of UCAs in liver applications and interpretation of FLL enhancement patterns in various clinical scenarios (ie, cirrhotic and noncirrhotic liver).[24] The American College of Radiology (ACR) *Manual on Contrast Media* now includes a short chapter on ultrasound contrast media.[25]

CEUS OF THE KIDNEYS, BLADDER, AND URINARY TRACT

Kidneys

CEUS with intravenous administration of UCAs allows for high-resolution imaging (**Figure 1**) and provides dynamic assessment and quantification of tissue perfusion with no negative effects on renal function, an important consideration in patients with impaired renal function such as patients with a history of chronic renal disease, renal transplant, or nephrectomy, as well as in newborns and infants in whom kidneys have not reached full growth.[26,27]

CEUS is useful for the following most common renal applications[26–29]:

- Differentiating between solid tumors and renal cysts or pseudolesions;
- Further characterization of complex renal cysts with malignant potential; and
- Evaluation of other nonneoplastic lesions (ie, inflammatory, traumatic, or ischemic lesions).

Figure 1. Renal Lesions Visualized Using Various Imaging Techniques[26]
Renal cell carcinoma on **(A)** B-mode ultrasound shows a large mixed echogenicity lesion in the middle of the left kidney; **(B)** color Doppler reveals some peripheral blood flow; **(C)** CEUS shows uptake inside the lesion, but altogether different enhancement from the rest of the kidney; and **(D)** CECT confirms the mass.

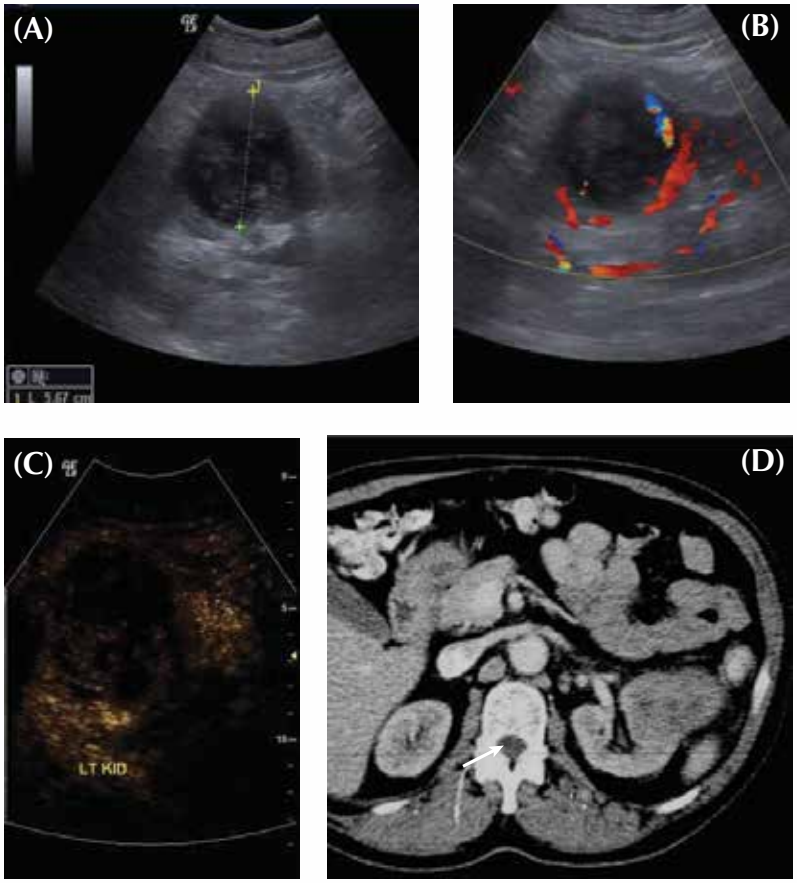

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Table 2 provides an overview of various renal pathologic entities with corresponding imaging details on baseline ultrasound and CEUS.[26]

Because of its high sensitivity to detect blood flow, CEUS is effective in distinguishing between solid tumors and simple or complicated renal cysts, ie, containing blood-breakdown products and debris. These appear on baseline gray-scale ultrasound with heterogeneous internal echogenicity that may be difficult to differentiate from intralesional solid components. However, all solid renal tumors will demonstrate a degree of enhancement during CEUS, whereas lesions without any internal enhancement are characterized as benign cysts[30] (**Figure 2**). For evaluation of cystic renal cell carcinoma and complex cystic renal masses, CEUS has demonstrated equal or superior diagnostic accuracy compared with CT, and has been shown to be useful as an alternative to CT for follow-up.[27,31–36]

Figure 2. Hemorrhagic Cyst as Visualized on B-Mode Ultrasound and CEUS[26]
(A) B-mode ultrasound shows a cystic structure with some echogenic content (arrow). **(B)** CEUS, which shows no enhancement, is suggestive of a hemorrhagic cyst rather than a solid lesion.

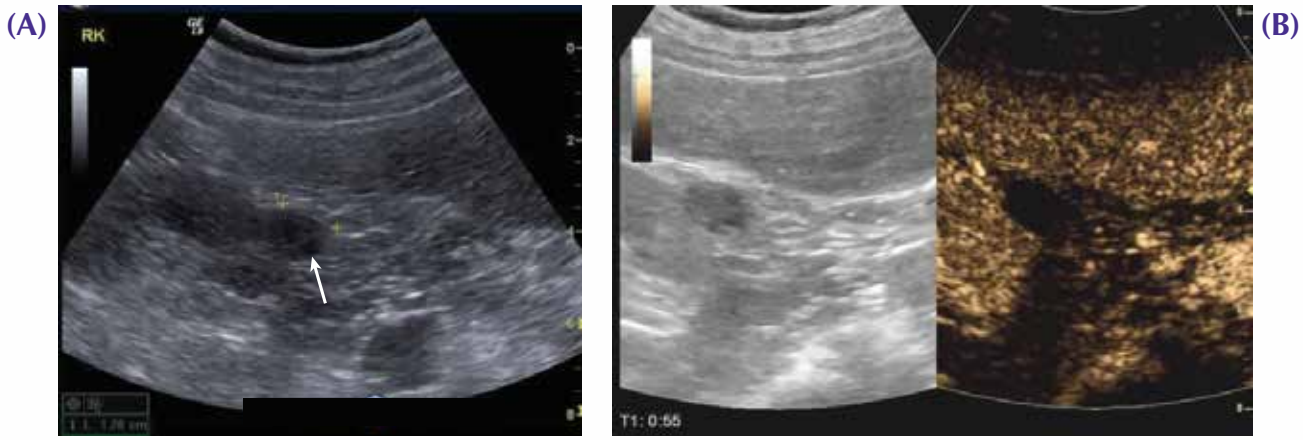

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Table 2. Overview of Various Renal Pathologic Entities with Corresponding Imaging Details on Baseline Ultrasound and CEUS[26]

Pathologic Entity	Baseline Unenhanced Ultrasound Findings	CEUS Findings
Solid renal masses vs simple or complex renal cyst vs pseudotumors	• Not always possible to differentiate true neoplasms from benign cysts or normal variants • Color Doppler has limitations in imaging small or slow flow blood vessels	• Tumor vascularity different from normal parenchyma, at least in one vascular phase • Pseudotumors enhance parallel to the kidney parenchyma in all phases • Solid tumors do not show specific perfusion patterns to differentiate between benign and malignant lesions • Malignant renal vein thrombus enhances, while bland thrombus does not • Enhancing material in the collecting system is characterized as neoplastic tissue, contrary to nonenhancing infectious material
Cystic vs solid lesions	• Color Doppler has limitations in imaging perfusion in echogenic content of cysts	• Solid hypovascular tumors enhance, even minimally, while debris does not • CEUS is at least equal or superior to multiphase CECT and CEMRI for diagnosing cystic renal cell carcinoma
Characterization of complex cystic renal masses	• Color Doppler has limitations in imaging perfusion in septa and nodules of cysts	• CEUS shows enhancement in solid irregular septa and nodules, with equal or superior diagnostic accuracy compared to CT for cyst classification using the Bosniak system • CEUS is an alternative to CT for complex cyst follow-up
Renal ischemia	• Color Doppler has limitations in imaging perfusion in small blood vessels with slow flow	• CEUS is comparable to CECT for detecting parenchymal ischemia. Infarcts appear as triangular or wedge-shaped areas with no contrast uptake • CEUS differentiates infarcts from parenchymal areas with diminished perfusion
Renal infections	• B-mode ultrasound needed to rule out presence of calculi and urinary tract obstruction	• Focal pyelonephritis shows areas of reduced enhancement. An abscess appears as a nonenhancing area with peripheral uptake • Pus in the collecting system or bladder shows no uptake
Renal trauma	• Baseline ultrasound is adequate for fluid detection, but has low sensitivity for imaging traumatic lesions, which may be isoechoic and can be missed	• CEUS reveals injuries not visible on baseline ultrasound as nonenhancing areas • CEUS can accurately grade the lesions based on their location and extent with respect to the organ capsule • Patients initially imaged with CT can be followed with CEUS
Renal artery stenosis	• Doppler examination of renal arteries is first imaging examination to be performed for assessing stenosis	• Routine use of CEUS offers no significant advantage for renal artery stenosis evaluation
Percutaneous ablation therapy assessment	• Baseline ultrasound does not offer significant information	• CEUS confirms treatment results, imaging remaining tumor vascularity. Areas still enhancing after ablation are considered as residual tumor

CEUS=contrast-enhanced ultrasound; CT=computed tomography; MR=magnetic resonance imaging.
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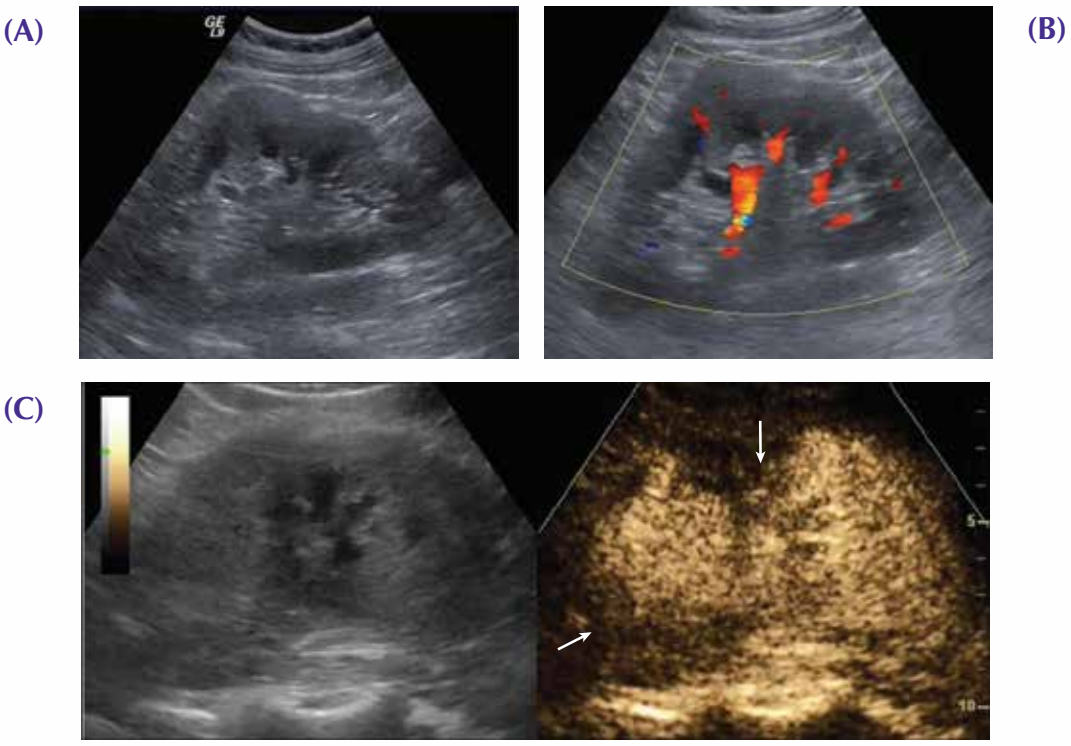
CEUS is commonly used to further improve characterization of complex cystic renal lesions and identification of morphological features with malignant potential, such as irregular or nodular wall thickening, intralesional septa, or solid components that can result in upgrading the Bosniak score as typically classified by multiphase CECT.[31,36] Park et al. compared CT and CEUS in 31 patients with confirmed cystic renal masses, and found CEUS visualized septa number, wall thickness, and solid component better than CT, resulting in an upgrade in Bosniak classification in 8 lesions.[31] In a similar study comparing CT and CEUS in 32 patients with atypical or complex cystic renal masses, CEUS depicted more thin septa or upgraded wall thickness, resulting in an upgraded Bosniak score in 5 lesions.[32] Barr, in a series of 1018 indeterminate renal masses followed for up to 10 years, found CEUS had a sensitivity of 100% (126 of 126; 95% confidence interval [CI], 97.1-100), specificity of 95.0% (132 of 139; 95% CI, 89.9-98.0), positive predictive value (PPV) of 94.7% (126 of 133), and negative predictive value (NPV) of 100% (132 of 132).[27] The 5 false-positive masses included 3 oncocytomas and 2 Bosniak category III cystic lesions. Of the 290 lesions that had at least 36 months of follow-up, none demonstrated changes that necessitated lesion reclassification. If these lesions were included, assuming lesions classified as malignant were indeed malignant, then of the 596 lesions, sensitivity was 100% (161 of 161), specificity was 96.6% (420 of 435), PPV was 91.5% (161 of 176), and NPV was 100% (420 of 420).

Another useful application of CEUS is the accurate characterization of mass-like lesions also known as pseudolesions, thus eliminating the need for additional cross-sectional imaging with CECT or CEMRI.[28] These pseudolesions refer to areas of renal parenchyma that may mimic a neoplastic process on imaging studies, such anatomic or developmental variants including prominent column of Bertin, dromedary or splenic hump, and persistent fetal lobulations. In these cases, the enhancing characteristics are identical to the adjacent renal parenchyma in all phases.

CEUS can also be used for evaluation of renal ischemia and infection.[5,37,38] For detection of parenchymal ischemia, CEUS has been shown to be superior to color Doppler ultrasound and comparable to CECT.[26] As they do in other organs, infarcts in the kidney appear as triangular or wedge-shaped areas with no contrast uptake, while the parenchyma enhances normally[37] (**Figure 3**). For uncomplicated pyelonephritis, further imaging is usually not required, but for focal pyelonephritis complicated with renal abscess, CEUS can be used to detect areas of parenchymal hypoperfusion and confirm the presence of nonenhancing abscess cavities with thickened and irregular outer walls.[39]

Figure 3. Kidney Infarct as Visualized on B-Mode Ultrasound, Color Doppler Ultrasound, and CEUS[26] **(A)** B-mode ultrasound and **(B)** color Doppler ultrasound detect no abnormality in the left kidney, whereas on **(C)** CEUS, a triangular peripheral enhancement defect is evident (arrow).



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In patients with blunt abdominal trauma who are hemodynamically stable, conventional unenhanced ultrasound is typically used for initial evaluation, followed by CECT, particularly in the case of multitrauma. However, CECT is overused for this application and has disadvantages, including radiation exposure (an important consideration in younger patients with trauma), higher cost, and use of iodinated contrast agents with the potential adverse effects on renal function or anaphylactic reactions. Therefore, in the appropriate clinical setting of low- to moderate-impact trauma, CEUS can be used in place of CECT in the initial evaluation and follow-up of traumatic lacerations and hematomas that are treated conservatively. These injuries appear on CEUS as nonenhancing areas.[40,41] However, because UCAs are not excreted in the collecting system, CEUS cannot rule out pelvicaliceal and ureter injuries.

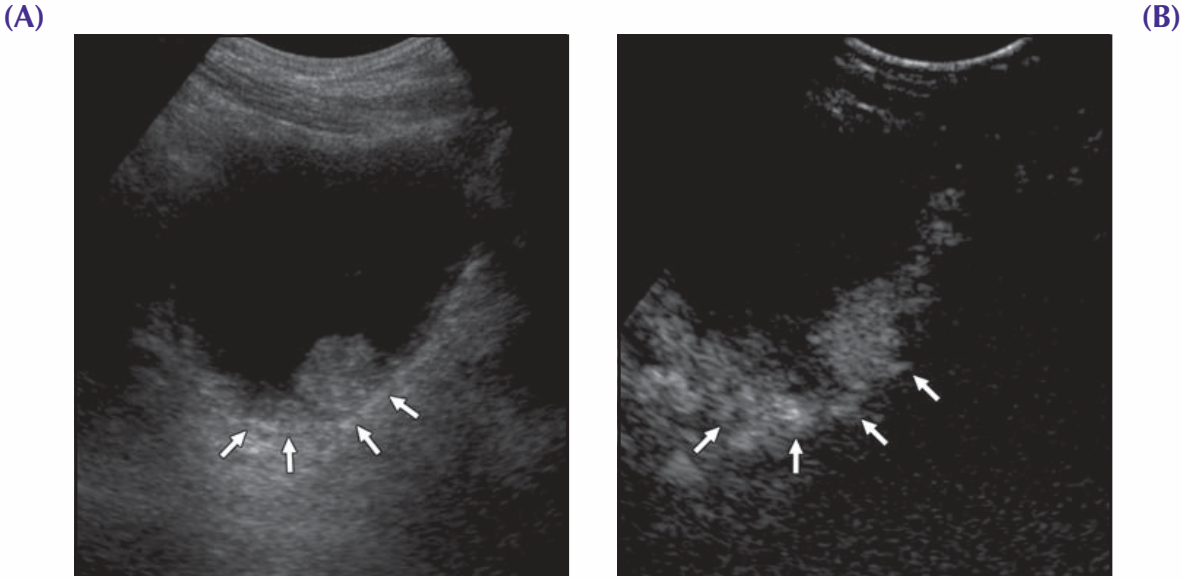
CEUS is a useful tool in monitoring the status of the transplanted kidney, particularly vascular complications after renal transplant and focal renal lesions due to allograft dysfunction or prolonged immunosuppression. CEUS can help visualize new solid or complex cystic lesions or post-transplant lymphoproliferative disorder.[29]

Finally, CEUS is useful for assessment of radiofrequency ablation (RFA) therapy in the kidney, both for confirmation of treatment results and for evaluation of residual tumor vascularity.[42–45] CEUS allows for multiple injections during the procedure to evaluate if residual tumor is present and then to reposition RFA needles into the residual tumor, allowing for more complete ablation in a single treatment. Concordance between low-MI CEUS and CECT or CEMRI for detection of local tumor progression after percutaneous RFA of renal tumors was shown to be 100% in 27/28 (96.4%) hypervascular renal tumors,[44] with a sensitivity and specificity for detection of residual tumor, respectively, of 64% and 98% on 24-h CEUS, and 79% and 100% on 6-week CEUS.[43]

Bladder

Tumors of the bladder are relatively common, accounting for 6% of all malignancies in men and 2% in women.[46] CEUS is considered useful for differentiating between superficial and muscle-infiltrating urinary bladder tumors and thus improving bladder cancer detection and staging, even though CEUS cannot replace cystoscopy and histopathology staging.[46,47] Specifically, UCAs can be used to define the degree of infiltration of a lesion, and to differentiate the various layers of the bladder wall[47] (**Figure 4**). Bladder tumors are characterized by rapid contrast uptake, which persists in later phases. CEUS has been shown to have better accuracy relative to baseline unenhanced ultrasound for diagnosis of bladder malignancies.[46,47]

Figure 4. Visualization of Infiltrating Bladder Wall Tumor[46]
A 58-year-old man with infiltrating bladder wall tumor **(A)** understaged with gray-scale ultrasound (image shows intact hyperechoic bladder wall [arrows] at base of tumor), and **(B)** correctly staged with CEUS (image shows intact hyperechoic bladder wall [arrows] at base of tumor).



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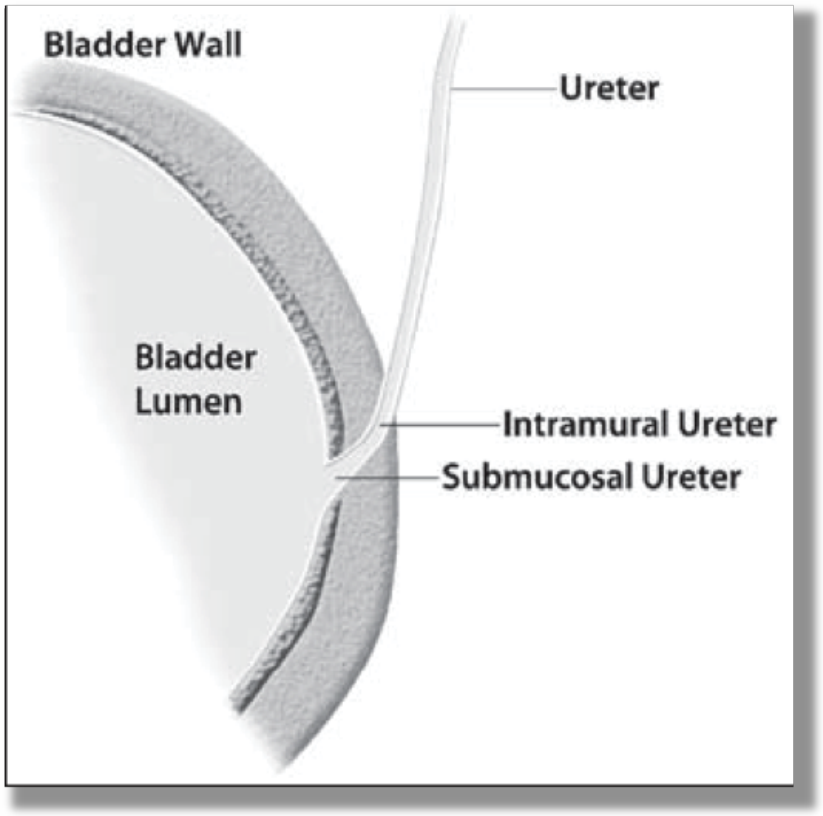
VUR in Children

VUR is a pathologic condition of the urinary tract characterized by the abnormal retrograde flow of urine from the bladder through the ureters into the kidneys (**Figure 5**).[48] The phenomenon occurs as a result of functional or structural incompetence of the vesicoureteral junction.[49–52] This retrograde urine flow provides a conduit for bacteria, resulting in increased risk of urinary tract infections, with potentially serious long-term complications if left untreated, such as renal scarring, hypertension, and even end-stage renal damage.

Figure 5. Pathophysiology of VUR[48]
Shorter intramural–submucosal course of distal ureter increases likelihood of VUR.



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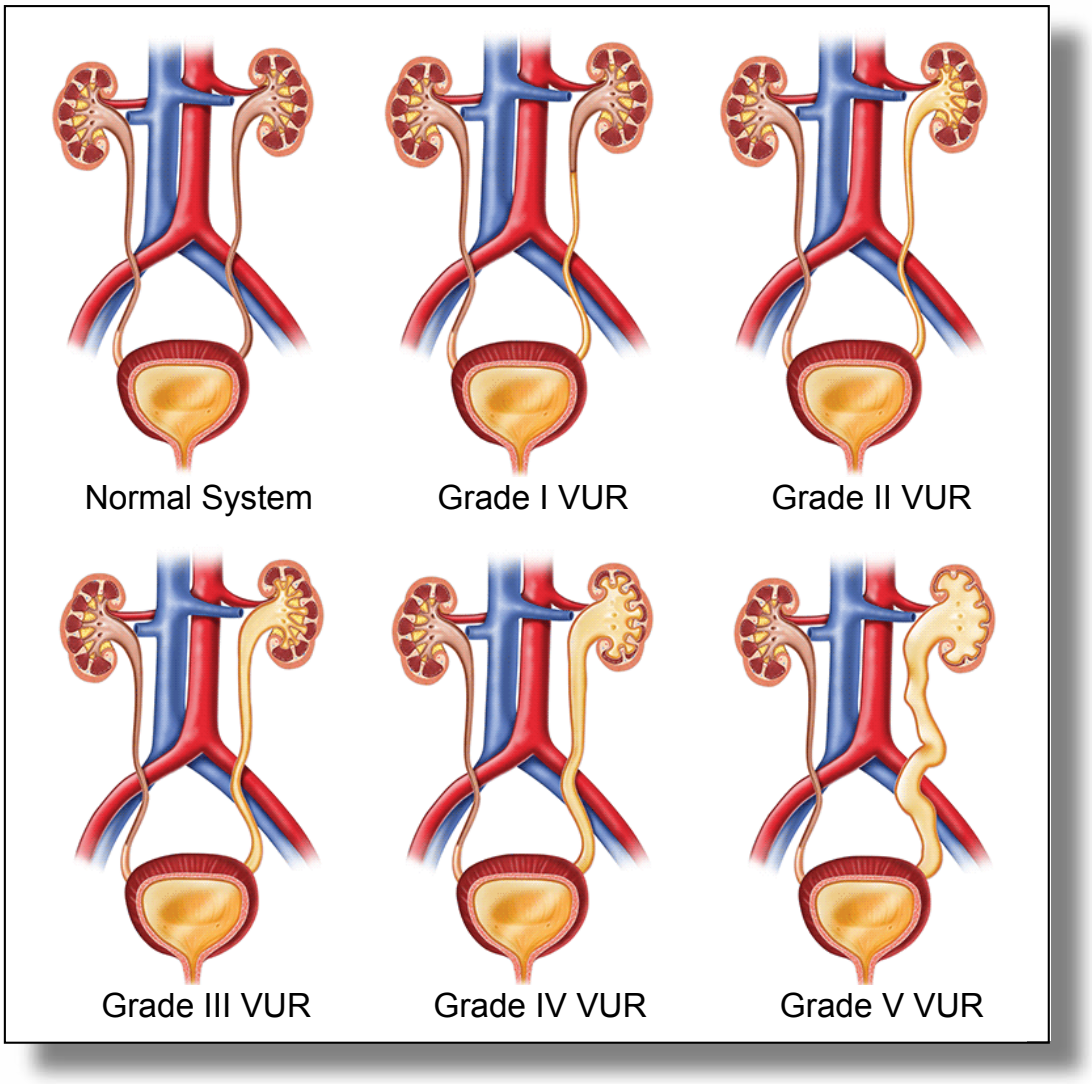
VUR is relatively common in children, occurring in 1% to 2% of the general pediatric population, and may be as high as 25% to 40% in children with recurrent UTIs.[48,53,54]

In most children, VUR will resolve spontaneously over time, and therefore in mild cases no treatment is necessary. Moderate to severe cases may be treated with antibiotic prophylaxis to prevent infection. When children have infections along with VUR, endoscopic management or surgical repair may be needed.[55]

Imaging plays an important role in the diagnosis and subsequent treatment of reflux and is possible with a variety of imaging modalities.[48,56–58] The current gold standard for VUR diagnosis is fluoroscopic voiding cystourethrography (VCUG). However, this technique uses ionizing radiation that in addition to the overall somatic exposure of young patients, also involves direct irradiation of the gonads, particularly in girls. Moreover, due to the intermittent nature of the reflux phenomenon, prolonged examination times may be required, further increasing overall radiation exposure. Radionuclide cystography (RNC) is another technique used to image VUR; RNC uses technetium-99m, exposing children to a lower dose of ionizing radiation than VCUG. In the last few decades, contrast-enhanced voiding ultrasonography (CE-VUS) has been used increasingly, particularly in Europe, as a highly sensitive and radiation-free alternative imaging modality for the detection and grading of VUR.[56,59,60] CE-VUS involves intravesical administration of UCAs under continuous ultrasound imaging of the bladder, retrovesical region, and kidneys, during bladder filling and voiding.

Performing CE-VUS involves 5 basic steps: (1) baseline ultrasound scan of the urinary tract before contrast administration; (2) bladder catheterization; (3) intravesical administration of UCA; (4) scanning of the urinary tract after administration of contrast, during bladder filling and voiding; and (5) transperineal or transabdominal scan of the urethra during voiding.[14,57] During the procedure, if VUR is present, the observer can assess continuously and in real time the retrograde flow of the contrast microspheres into the ureters and the kidneys, forming the basis for grading VUR via CE-VUS (**Figure 6**).[61]

Figure 6. VUR Grading Based on CE-VUS[61]
Grade I=microspheres only in the ureter; grade II=microspheres up to the nondilated pelvicalyceal system; grade III=microspheres up to the mildly dilated pelvicalyceal system; grade IV=microspheres up to the moderately dilated pelvicalyceal system, with preserved papillary impressions; grade V=microspheres up to the severely dilated pelvicalyceal, with loss of papillary impressions and tortuous ureter.



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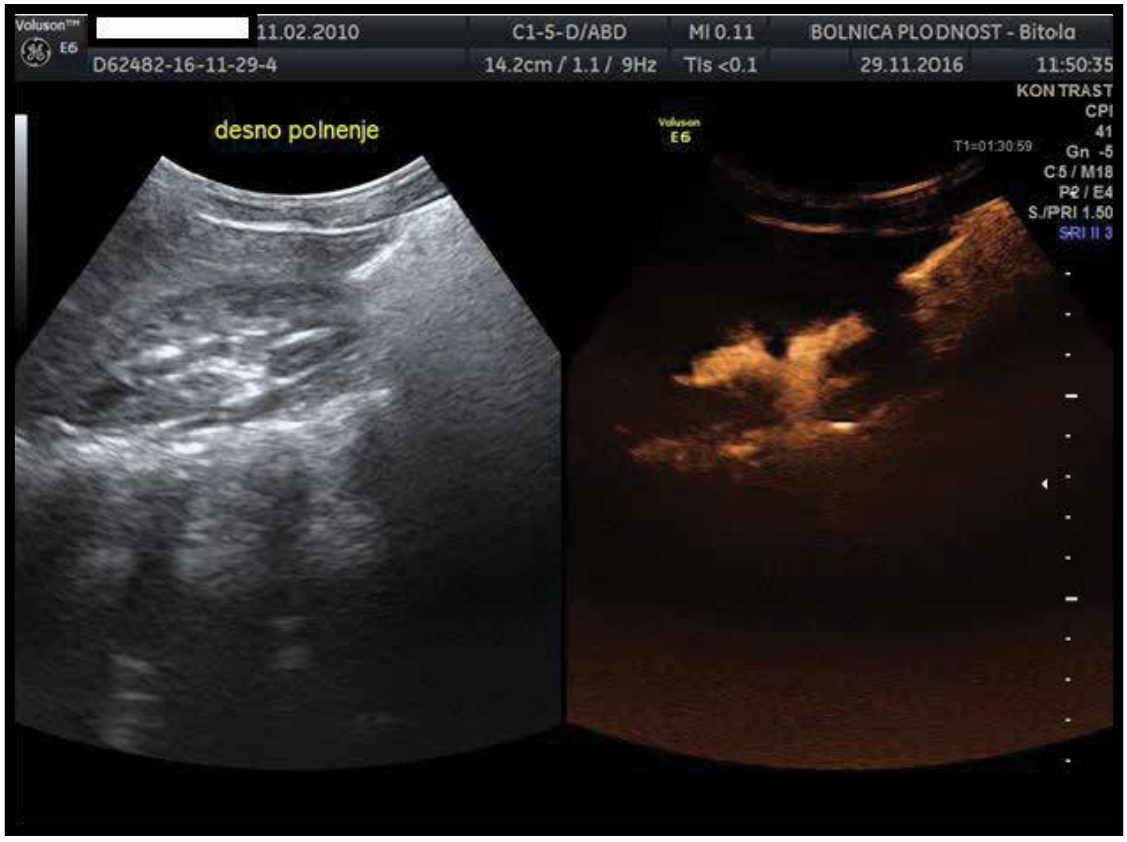
Several studies have shown that CE-VUS has a sensitivity comparable to or even higher than that of VCUG for initial diagnosis and follow- up of VUR in children (**Figure 7**).[14,56,57,62]

Figure 7. Ultrasound Contrast Agent in the Collecting System of the Right Kidney Using **(A)** B-mode "Gray-Scale" and **(B)** B-mode + Contrast-Specific Software[62]



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In 2 open-label studies, a total of 411 pediatric patients with suspected VUR were evaluated using Lumason® for CE-VUS.[14] The first study evaluated 183 patients (94 boys, 89 girls; age 2 days–44 months) with a total of 366 kidney-ureter units. Of 103 reference standard-positive images, CE-VUS with Lumason® was positive in 89 units and falsely negative in 14 units. In 263 units with negative reference standard, CE-VUS with Lumason® was negative in 226 and falsely positive in 37.[14] The second study evaluated 228 patients (123 boys, 105 girls; age 6 days–13 years) with a total of 463 kidney-ureter units (some patients had >2 units). Of 71 reference standard-positive images, CE-VUS with Lumason® was positive in 57 and falsely negative in 14. In 392 units with negative reference standard, CE-VUS with Lumason® was negative in 302 and falsely positive in 90.[14]

PHARMACOECONOMICS OF CEUS

In general, ultrasound is more accessible and less costly than CT or MRI. Several studies have demonstrated cost savings when CEUS was compared with CECT or CEMRI in general,[63–67] and for abdominal imaging, specifically.[68,69] In addition, the NICE (National Institute for Health and Care Excellence) diagnostic guidance publication on sulfur hexafluoride microspheres (SonoVue®) for CEUS of the liver found that the lower cost combined with slightly better performance meant that CEUS was more cost effective than either CECT or CEMRI.[70]

For renal masses, particularly in the case of pseudolesions or Bosniak category II cystic lesions, CEUS can be used to reach a final diagnosis quickly, eliminating the need for more invasive and expensive methods.[71]

CEUS SAFETY

UCAs are considered safe, with a low incidence of adverse events[2]; adverse event rates reported with intravenous UCAs are lower than those for CT contrast agents and comparable to those for MRI contrast agents.[72] Because UCAs are not excreted by the kidneys, no nephrotoxic effects occur, and no laboratory tests are needed to assess liver or kidney function prior to their administration.[1] In addition, UCAs contain no iodine, so they are not associated with any thyroid effects.[1] Life-threatening anaphylactoid reactions are rare in abdominal intravenous CEUS applications (0.001%–0.002%), with no deaths reported in a series of more than 23,000 patients.[73,74] Nevertheless, healthcare providers administering UCAs should receive training in resuscitation and have appropriate facilities available in the event of a severe adverse event.

Older FDA labeling contained a contraindication for all UCAs in patients with severe cardiopulmonary disease and imposed electrocardiogram monitoring for 30 minutes after injection; however, in 2008, the contraindications were downgraded to warnings and, in 2011, the requirement to observe patients for 30 minutes after injection was removed.[2]

Data from small animal models suggest that microvascular disruption can occur when microspheres are insonated.[75] Therefore, low-MI techniques are recommended for CEUS of the liver; presumably the same risks apply for imaging of kidney, pancreas, etc. When high-MI sequences are deemed necessary, the risks should be considered in light of the potential benefits.[2] Data are limited on the use of UCA during pregnancy or breastfeeding.[2,76]

Regarding the safety of intravesical administration of UCAs during CE-VUS, a large volume of safety data has been published on the use of SonoVue® (sulfur hexafluoride microspheres), the version of sulfur hexafluoride microspheres (Lumason®) approved for use outside of the United States.[77,78] In the largest study including 1010 children, only minor, self-limited adverse events were reported in 37 (3.66%) children, with the most common being dysuria (n=26, 2.6%), urinary retention (n=2, 0.2%), and abdominal pain (n=2, 0.2%). The type and the incidence of these adverse events were similar to those encountered with VCUG or RNC and were most likely related to the inevitable minimally invasive process of bladder catheterization rather than the contrast agent itself.[78]

SUMMARY AND CONCLUSIONS

CEUS has advantages over other imaging modalities, including lack of radiation, lack of nephrotoxic contrast, increased access and patient comfort, and lower costs, particularly when performed in a specialized setting. The use of second-generation UCAs together with contrast-specific ultrasound modes permits detection and characterization of a wide variety of urinary tract pathologies in adults and children. In addition, CEUS has demonstrated utility for evaluation of VUR in children—a patient population in whom minimizing exposure to ionizing radiation is important—and sulfur hexafluoride microspheres (Lumason®) is now approved by the FDA for this clinical application.

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