

# ANSWERING REVIEWERS

**Manuscript NO: 27712**

Off-label-use of sulfur hexafluoride in voiding urosonography for diagnosis of vesicoureteral reflux in children: A survey on adverse events

**Reviewer 00503255:**

1. As suggested by the reviewer a short running title was provided: "Adverse events in off-label SH-VUS".
2. The main object of this study was to evaluate the risk profile of SH in VUS. On the reviewer's recommendation we provided a brief review about detection rates of VUR using VUR versus X-ray based voiding cysturethrography. The corresponding paragraph integrated into the *Discussion* section reads as follows: "Recent studies have demonstrated an equal or higher sensitivity of VUS when compared to VCUG, especially in cases of high grade VUR<sup>[3, 8, 9]</sup>. In a metaanalysis Darge *et al.* <sup>[9]</sup> described a sensitivity of 57-100%, a specificity of 85-100%, positive/negative predictive values of 58-100%/87-100%, respectively, and a diagnostic accuracy of 78-96%. Moreover Kis *et al.* <sup>[13]</sup> examined a total of 183 children using VCUG and VUS in parallel. They detected VUR with VUS in 34.4% and with VCUG in 28.1%. Reflux was detected by both methods in 24.3%. VCUG missed cases of high-grade reflux whereas VUS missed only low-grade reflux. They suggest - based on their study results - that contrast-enhanced harmonic VUS using SH is superior to VCUG in the detection and grading of VUR".
3. We adapted the references according to the journal's guidelines.

**Reviewer 00646241:**

1. As suggested by the reviewer we added additional information about the number of participating study hospitals. The study took place in 2 two hospitals: one tertiary and one secondary care hospital. The corresponding paragraph adapted into the *Methods* section reads as follows: "Within a four-year period, 531 children with suspected or proven VUR (f/m = 478/53; mean age 4.9 years; range 1 month - 25.2 years) underwent VUS in one of the two participating study hospitals (n=487 in tertiary care hospital and n=44 in secondary care hospital), which perform VUS in daily routine for several years." Moreover as suggested by the reviewer we added information about the number of performing individuals. The corresponding paragraph adapted into the *Methods* section reads as follows: "All examinations were digitally recorded and performed/supervised by one specialized pediatric radiologist (in the tertiary care university hospital) and one trained pediatrician (in the secondary care hospital)".
2. The reviewer asks whether the contrast medium is prepared and applied in a sterile manner. Concerning this question we added a corresponding paragraph into the *Methods* section which reads as follows: "SH was always prepared according to the manufacturer's recommendation and was applied in a sterile manner".
3. The reviewer asks how often catheter-induced discomfort is reported in children receiving conventional X-ray based urography? Concerning this question we added a corresponding paragraph into the *Discussion* section which reads as follows: "Zerin *et al.* described postprocedural symptoms in 35.1% of the children (n=228) undergoing VCUG, radionuclide cystography (RNC) or diuretic renal scintigraphy (DRS). The frequency of postprocedural symptoms was nearly identical in the VCUG group and the two other groups. Dysuria was the most common symptom (32.9%). Symptoms disappeared within

24 hours in 40%. They concluded that most postprocedural symptoms could be attributed to the discomforting, minimally invasive procedure of bladder catheterization itself as well as its psychological impact on the children, rather than the contrast agent. Wesse *et al.* report 2 cases (0.3%) of anaphylactoid reactions during VCUG or retrograde pyelography in a retrospective review of 783 patients“.

4. The main object of this study was to evaluate the risk profile of SH in VUS. On the reviewer’s recommendation we provided additional information about the discrimination of the different reflux stages as well as detection rates of VUR in VUS and VCUG. Moreover we added additional VUS-images of a six-year-old girl with proven, bilateral vesicoureteral reflux (grade I left and grade III right) for illustrating the different VUR grades in VUS (Figure 2). The corresponding paragraph integrated into the *Discussion* section reads as follows: “Recent studies have demonstrated an equal or higher sensitivity of VUS when compared to VCUG, especially in cases of high grade VUR<sup>[3, 8, 9]</sup>. In a metaanalysis Darge *et al.* <sup>[9]</sup> described a sensitivity of 57-100%, a specificity of 85-100%, positive/negative predictive values of 58-100% / 87-100%, respectively, and a diagnostic accuracy of 78-96%. Moreover Kis *et al.* <sup>[13]</sup> examined a total of 183 children using VCUG and VUS in parallel. They detected VUR with VUS in 34.4% and with VCUG in 28.1%. Reflux was detected by both methods in 24.3%. VCUG missed cases of high-grade reflux whereas VUS missed only low-grade reflux. They suggest - based on their study results - that contrast-enhanced harmonic VUS using SH is superior to VCUG in the detection and grading of VUR“.

**Reviewer 00069139:**

1. As suggested by the reviewer we added the percentage of detected reflux in the performed VUS series. The corresponding paragraph integrated into the *Results* section reads as follows: “In the present study cohort in 224/531 (42.2%) children a VUR was detected. In those cases with described adverse events in 8/22 (36.4%) children a VUR was observed. In those children with potential allergic reaction a VUR was detected in 2/5 (40%)“.
2. As suggested by the reviewer we reedited the manuscript according to the attached file.