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Streamlining risk stratification in infants and young children with spinal dysraphism: Vesicoureteral reflux and/or bladder trabeculations outperforms other urodynamic findings for predicting adverse outcomes

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Summary

Background
Baseline and interval dimercaptosuccinic acid (DMSA) scans and urodynamic (UD) studies are often obtained in infants and young children with spinal dysraphism (SD).

Objective
To identify practical UD parameters which accurately stratify urologic risk young children with SD.

Study design
130 expectantly managed infants/young children with SD and initial DMSA and UD before age 2 were reviewed. End fill pressure (EFP), bladder trabeculations, vesicoureteral reflux (VUR), initial volume (IV) drained at UD catheter placement, and detrusor pressure at initial volume (DPIV) were evaluated for association with subsequent febrile urinary tract infection (UTI), DMSA abnormalities, and early clean intermittent catheterization (CIC). A combination of factors to accurately stratify risk was sought. Groups were compared by log-rank test. The association of CIC and febrile UTI incidence was evaluated.

Results
31/130 patients developed DMSA abnormalities, 52/130 started early CIC, and 61/130 developed a febrile UTI with median follow-up of 3.8 years. Trabeculations, VUR, EFP $\geq$40 cm H_2O, IV $\geq$50% estimated bladder capacity (EBC), and DPIV $>$10 cm H_2O were associated with subsequent abnormal DMSA scan ($p < 0.001$). The best predictor was combination of trabeculation and/or VUR ($p < 0.001$) (Figure). Among patients who maintained a non-trabeculated bladder without VUR during follow-up, 0/51 developed DMSA abnormalities compared with 31/79 who developed one or both ($p < 0.001$). Patients with trabeculations and/or VUR were more likely to start early CIC (8/51 vs. 44/79; $p < 0.001$) and have febrile UTI (11/51 vs. 50/79; $p < 0.001$). In those with trabeculations, CIC was associated with decreased incidence of febrile UTI (incidence rate ratio (IRR) 0.5, 95% CI 0.3–0.9); in those without trabeculations, CIC was associated with increased incidence of febrile UTI (IRR 1.8, 95% CI 1.1–3.1).

Conclusions
VUR, bladder trabeculations, EFP $\geq$40 cm H_2O, IV $\geq$50% of EBC, and DPIV $>$10 cm H_2O were associated with subsequent DMSA abnormalities in young children with SD managed expectantly. Many of these parameters were associated with febrile UTI and early CIC. The combination of trabeculations and/or VUR outperformed other UD parameters in identifying those high and low-risk for adverse urologic outcomes. Routine DMSA scan may have limited utility in patients with a non-trabeculated bladder without VUR, as none developed an abnormal DMSA. Most (71%) abnormal DMSAs were in patients with trabeculations and/or VUR following a febrile UTI. Given these findings and that incidence of febrile UTI may be lower in those with trabeculations while on CIC, patients with trabeculations and/or VUR should be managed aggressively to protect kidneys.

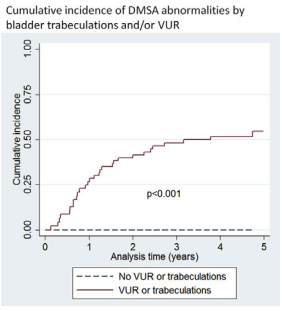

Figure Cumulative incidence of DMSA abnormalities for patients with trabeculations and/or VUR compared with those with neither finding.

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Introduction

The urologic care of infants and children with spinal dysraphism (SD) is a complex challenge involving monitoring of renal health, estimation of upper tract risk, and thoughtful intervention with clean intermittent catheterization (CIC), medications, and/or surgery to prevent or limit upper tract damage. In 2016, a Centers for Disease Control (CDC) working group issued a protocol aiming to standardize newborn management and allow outcomes analysis [1]. The protocol calls for baseline and interval technetium 99m dimercaptosuccinic acid (DMSA) scan in all patients, as well as routine urodynamic (UD) evaluations in early life [1].

Several studies describe the predictive utility of early UD findings in this population [2—6]. However, it is difficult to compare results of these studies and apply them in practice because of the variety of outcome measures and multitude of UD parameters used [7]. A recent study questioned the inter-rater reliability of UD interpretation among pediatric urologists—particularly with respect to electromyographic (EMG) synergy, detrusor overactivity (DO), bladder compliance, and end fill pressure (EFP) [8].

Our purpose was to identify simple video UD parameters which accurately stratify urologic risk in young children with SD. We hypothesized that elevated EFP, bladder trabeculations, vesicoureteral reflux (VUR), high initial volume (IV) drained at UD catheter placement, and elevated detrusor pressure at initial volume (DPIV) may be associated with subsequent febrile urinary tract infection (UTI), DMSA scan abnormalities, and starting early CIC. We sought a UD parameter or combination of parameters to accurately identify (i) low-risk patients who may not benefit from routine DMSA scans and (ii) high-risk patients who may warrant more aggressive evaluation and management.

Materials and methods

Following institutional review board approval, we identified SD patients referred to our center between January 2009 and October 2016. We retrospectively reviewed the medical record. We included patients with initial UD evaluation and DMSA scan before age 2. Patients were managed without CIC from birth within a previously described program [9]. We extracted data from the electronic health record into REDCap (research electronic data capture system) [10] to create a longitudinal dataset. The presence of VUR and bladder trabeculations was based on review of images during video UD evaluation or voiding cystourethrogram (VCUG). Bladder trabeculations were defined as irregularity in the contour of the bladder dome and/or walls. Bladder appearance was categorized as non-trabeculated, mild trabeculations, or moderate/severe trabeculations (Fig. 1). IV was defined as the volume of urine drained at time of UD catheterization. DPIV was defined as the detrusor pressure at a volume equal to IV on the cystometric curve. EFP was defined as the maximum end fill detrusor pressure measured in cm H_2O—excluding any detrusor contractions—measured during filling cystometry. If an organized detrusor contraction with leakage occurred, EFP was the pressure prior to contraction. If no organized detrusor contraction or leakage occurred, EFP was the pressure at estimated bladder capacity (EBC) for age or volume causing patient discomfort.

Early CIC was defined as CIC prior to attempts to achieve urinary continence. Indications for early CIC included VUR, febrile UTIs, concerning urodynamic findings such as high EFP, and abnormal DMSA scan but were not standardized. Febrile UTI was defined as a febrile illness (>38.5° Celsius) with positive urine culture (>50,000 colony forming units of

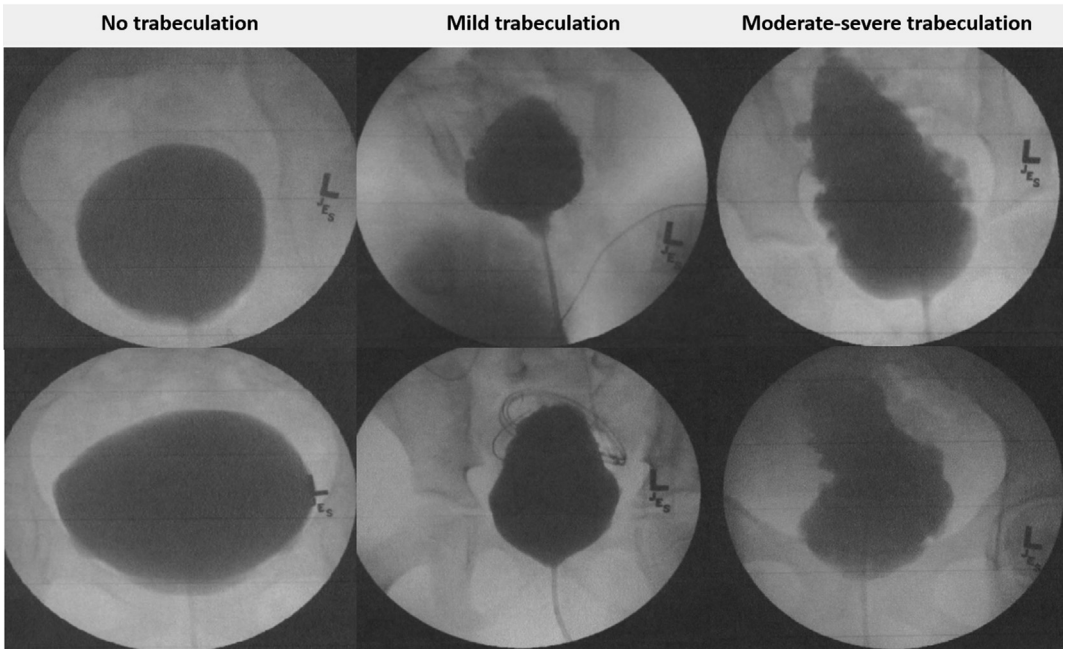

Figure 1 Fluoroscopic appearance of bladders with no trabeculation, mild trabeculation, and moderate to severe trabeculation, respectively.

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Table 1 Cohort characteristics ($N = 130$).

Female	69 (53%)
Diagnosis	
Spina bifida	118 (91%)
Caudal regression	7 (5%)
Lipomeningocele	5 (4%)
Neurologic lesion level[a]	
Thoracic	8 (7%)
High lumbar (L1–L2)	7 (6%)
Low lumbar (L3–L5)	48 (41%)
Lumbar (unknown)	38 (32%)
Sacral	17 (14%)
VP shunt[a]	97/118 (82%)
Median follow-up time in years (IQR)	3.8 (2.1–5.5)

[a] Among 118 patients with spina bifida.

pathogenic bacteria) from a catheterized specimen. DMSA abnormality was defined as a focal cortical defect or differential renal function less than 40%, identified on an initial study or upon follow-up DMSA evaluation. Focal defects were identified by a radiologist as areas of decreased uptake with volume loss and/or concavity. To account for transient DMSA abnormalities caused by pyelonephritis, studies were delayed for at least 3 months following a febrile UTI. Bladder trabeculations, VUR, EFP, IV, and DPIV were evaluated for association with subsequent febrile UTI, DMSA abnormality, and starting early CIC by longitudinal analysis. We sought a combination of factors to accurately stratify risk for clinically meaningful decision making. Outcomes between groups were compared by survival curve analysis with log-rank test. More attention was given to DMSA abnormalities as this is a permanent end organ effect. The association of being on CIC and incidence of febrile UTI was also studied by reporting incidence rate ratios (IRR).

Results

One-hundred and thirty patients were included (Table 1). Initial DMSA was obtained at a median age of 4.6 months (interquartile range [IQR] 3.3–8.2 mo) and patients had a median of two DMSA scans (IQR 1–3). Initial UD test was performed at a median age of 3.9 months (IQR 3.0–7.1) and patients had a median of 3 UD tests (IQR 2–4). A summary of outcomes of interest including cumulative incidence at 1, 3, and 5 years is shown in Table 2. Of the 130 patients, 31 (24%) developed DMSA abnormalities, 52/130 (40%) started early CIC, and 61/130 (47%) developed a febrile UTI over a median follow up of 3.8 years (IQR 2.1–5.5 years).

DMSA abnormalities

Among the 31 identified DMSA abnormalities; 11 were found on initial scan, 15 on the second, and five on a third or subsequent scan. Six of 11 patients with abnormal initial scan had VUR at a young age without a preceding recognized febrile UTI.

Bladder trabeculations, VUR, EFP $\geq$40 cm H_2O, IV $\geq$50% of EBC, and DPIV $>$10 cm H_2O were all associated with subsequent abnormal DMSA scan by log-rank test (Fig. 2). The best predictor of DMSA abnormalities in terms of clinical utility of identifying a low-risk group was the combination of bladder trabeculations and/or VUR ($p < 0.001$) (Fig. 3). None of the 51 patients who maintained a non-trabeculated bladder without VUR during follow-up developed DMSA abnormalities, compared with 31/79 (39%) who developed one or both findings ($p < 0.001$).

Of the 51 patients with bladder trabeculations, nine developed moderate/severe trabeculations with eight having prior mild trabeculations. There were only two patients with moderate/severe trabeculations who developed an abnormal DMSA scan only after developing moderate/severe trabeculations. Therefore, bladder trabeculations was treated as a dichotomous variable.

The grade of VUR was associated with subsequent risk of abnormal DMSA scan. Of those with initial low-grade VUR (grade 1–2), 4/21 (19%) had abnormal DMSA scan compared with 21/31 (68%) with high-grade VUR (grade 3–5) ($p < 0.001$).

Among the 79 patients who developed trabeculations and/or VUR, we evaluated whether other UD parameters could stratify risk of abnormal DMSA scan further. In this high-risk group, maintaining a DPIV $\leq$10 was associated with lower risk of subsequent DMSA abnormalities (Fig. 4). However, as the incidence of DMSA abnormalities was not insignificant even in the group with DPIV $\leq$10, this may not have clinical utility (Fig. 4). Febrile UTI was associated with abnormal DMSA scan in the high-risk group with trabeculation and/or VUR. Among the 79 high-risk patients; 50/79 (63%) had a febrile UTI. Among the 50 with febrile UTI, 27/50 (54%) had an abnormal DMSA scan compared with 4/29 (14%) who did not have a febrile UTI ($p < 0.001$ log-rank test) (Fig. 4). Of the nine patients who developed an abnormal DMSA scan before a febrile UTI, the abnormal DMSA scan was the first DMSA scan performed before 1 year of age in 6/9 with VUR in five of these patients suggesting congenital renal dysplasia. In three patients the abnormal DMSA scan was after a normal DMSA scan, with two developing VUR which may suggest unrecorded UTIs. Twenty-two of 31 (71%) patients with abnormal DMSA were in those with trabeculations and/or VUR who had a prior febrile UTI.

Table 2 Total proportion and estimated cumulative incidence of outcomes of interest.

	Proportion	1-Year cumulative incidence (95% CI)	3-Year cumulative incidence (95% CI)	5-Year cumulative incidence (95% CI)
Febrile UTI	61/130 (47%)	21% (15–30%)	42% (34–52%)	57% (46–67%)
DMSA abnormality	31/130 (24%)	10% (6–17%)	22% (16–32%)	28% (20–39%)
Early CIC	52/130 (40%)	15% (10–22%)	31% (24–40%)	43% (34–53%)

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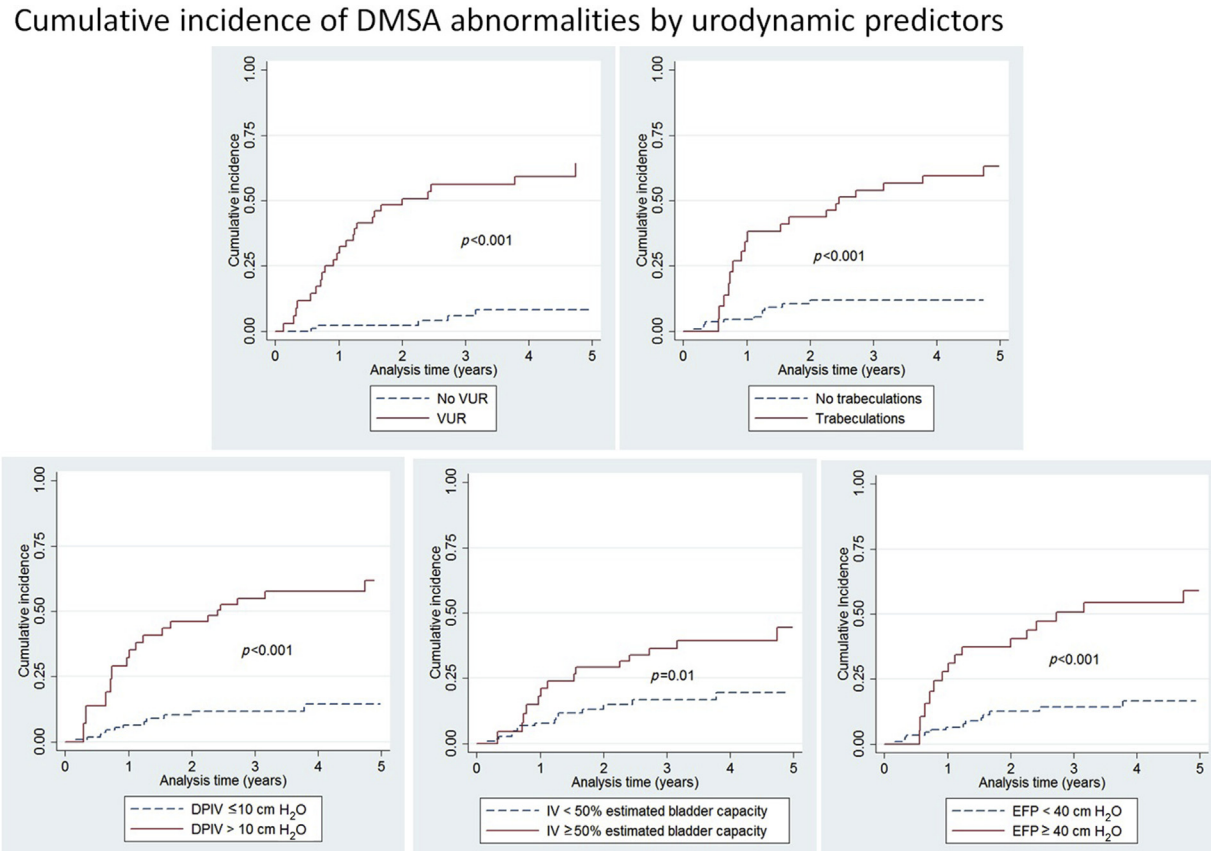

Figure 2 Cumulative incidence of subsequent DMSA abnormality for the five UD parameters examined. Each parameter was significantly associated with development of DMSA abnormalities by log-rank test.

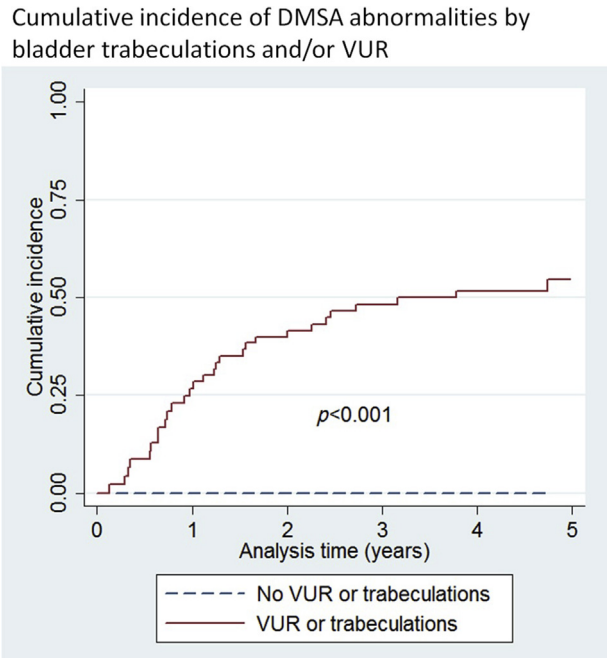

Figure 3 Cumulative incidence of DMSA abnormalities for patients with trabeculations and/or VUR compared with those with neither finding.

Febrile UTI

During follow-up, 61/130 (47%) developed a febrile UTI. Trabeculations ($p < 0.001$), DPIV >10 cm H_2O ($p = 0.007$), and VUR ($p = 0.008$) were associated with febrile UTI by log-rank test. Patients with EFP ≥40 cm H_2O and those with IV ≥50% of estimated capacity had higher incidence of febrile UTIs, but this was not statistically significant ($p = 0.2$, $p = 0.1$). Eleven of 51 (22%) who never developed trabeculations or VUR had a febrile UTI, compared with 50/79 (63%) with one or both ($p < 0.001$, chi-square and log-rank test). No combination of predictors identified a group with zero risk of febrile UTI.

Association of CIC and incidence of febrile UTI

For the entire cohort, being on CIC for any reason was not associated with incidence of febrile UTI (IRR 1.1, 95% CI 0.8–1.6). In those without trabeculations, CIC was associated with increased incidence of febrile UTI (IRR 1.8, 95% CI 1.1–3.1). In those with trabeculations, CIC was associated with decreased incidence of febrile UTI (IRR 0.5, 95% CI 0.3–0.9). In those without VUR, CIC was associated with increased incidence of febrile UTI but was not statistically significant (IRR 1.3, 95% CI 0.7–2.2). In those with VUR, CIC

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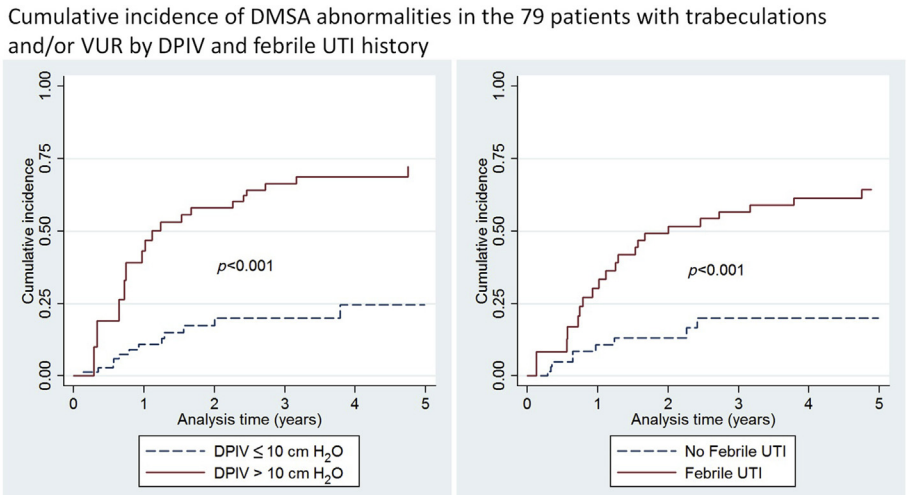

Figure 4 Among 79 patients with trabeculations or VUR, DPIV $\leq$10 cm H_2O and absence of febrile UTI was associated with lower risk of subsequent DMSA abnormality.

was not associated with incidence of febrile UTI (IRR 0.9, 95% CI 0.5–1.5). In those without trabeculations or VUR, CIC was associated with increased incidence of febrile UTI but this was not statistically significant (IRR 2.0, 95% CI 0.9–4.5). In those who developed bladder trabeculation and/or VUR, CIC was associated with decreased incidence of febrile UTI but this was not statistically significant (IRR 0.7, 95% CI 0.5–1.1).

Early CIC

Fifty-two of 130 (40%) started early CIC. Bladder trabeculations, EFP $\geq$40 cm H_2O, and DPIV $>$10 cm H_2O were associated with early CIC by log-rank test ($p < 0.001$). An IV $\geq$50% of EBC was associated with early CIC ($p < 0.03$). Patients with VUR did have a higher incidence of early CIC, but this was not statistically significant ($p = 0.08$). As with DMSA abnormalities, the best predictor of early CIC was bladder trabeculations and/or VUR. Eight of 51 (16%) without trabeculations or VUR started early CIC, compared with 44/79 (56%) with one or both findings ($p < 0.001$, chi-square and log-rank). No combination of predictors identified a group with zero risk of early CIC.

Discussion

This study aimed to describe practical video UD parameters that accurately stratify urologic risk in infants with SD managed from birth without CIC. Bladder trabeculations, VUR, EFP $\geq$40 cm H_2O, IV $\geq$50% of EBC, and DPIV $>$10 cm H_2O identified on UD evaluation were found to be significantly associated with subsequent DMSA abnormalities. In addition, several of these predictors were also associated with starting early CIC and subsequent febrile UTI. Of particular clinical utility, no patients who maintained a non-trabeculated bladder without VUR (around 40% of cohort) developed DMSA abnormalities during follow-up. In contrast, those with bladder trabeculations and/or VUR and at least one febrile UTI (38% of cohort) were the highest risk with 54% developing an abnormal DMSA scan. Based on IRR calculations, the incidence of febrile UTI may be increased in those without trabeculations while on CIC, but decreased in those with bladder trabeculations while on CIC.

While elevated storage pressures and low bladder compliance have been reported to be associated with upper tract risk in young patients with SD [2,11], other authors have not found this association [7,12,13]. While we did find EFP $\geq$40 cm H_20 to be significantly associated with subsequent DMSA abnormality, we would suggest that outlet physiology—which may be altered by the presence of a UD catheter—should be considered as well. Among infants who are not on CIC, a patient who tends *not* to leak easily—carrying a high volume in a noncompliant reservoir—are at higher risk for upper tract injury. Conversely, a leakier patient—even if terminal bladder compliance is low on CMG—may not typically reach volumes where the bladder pressure becomes dangerous. Although not a perfect measure, IV drained at UD catheter placement in patients who are not on CIC may represent the bladder volume most of the time, and DPIV in patients who are not on CIC may represent bladder pressure most of the time. However, this was not validated by our study and merits further study. We did find that IV $\geq$50% of EBC and DPIV $>$10 cm H_2O were significantly associated with subsequent DMSA abnormalities, febrile UTIs, and starting early CIC in infants with SD. We acknowledge that IV and DPIV are imperfect measurements. Nonetheless, we consider these measurements to be imperfect-yet-practical indicators of urologic risk in children not on CIC, which should be considered within a child's overall clinical picture.

While recent data from the Vanderbilt group [8] suggest discordance among urologists with interpretation of DO, compliance, EFP and EMG synergy, interrater reliability for interpretation of fluoroscopic variables such as bladder shape appears to be good [8]. Additionally, agreement among pediatric urologists on grading of VUR has been shown to be very high [14]. In our study, fluoroscopic parameters—presence or absence of VUR and/or trabeculations—outperformed all other UD parameters for identifying young children with SD at high and low-risk for

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subsequent adverse urologic outcomes. These results are congruent with previous studies describing the significant association between VUR [5,12,13,15] and trabeculation [16] on upper tract deterioration. Febrile UTI further increases the risk of upper tract injury, as 71% of all abnormal DMSA scans in our cohort were seen in patients with bladder trabeculations and/or VUR and a history of febrile UTI.

We did not analyze detrusor sphincter dyssynergia (DSD) in this study. While the presence of DSD has been shown to predict upper tract deterioration and renal scarring in children with SD [2,5], accurate assessment of DSD can be difficult because of the artifact that occurs when crying infants undergo EMG monitoring. Interpretive reliability for DSD has been shown to be low [8]. We did not analyze detrusor leak point pressure (DLPP) as not all patients leaked during UD and interpretation of DLPP during a detrusor contraction can be unreliable. We chose EFP as this is measurable in patients who do not leak, is often equal to the DLPP in patients who leak, and is measurable in patients who leak during a detrusor contraction.

Streamlining evaluation

Evaluation and management of young children with SD in our clinic continues to evolve. Our results indicate that VUR and/or bladder trabeculation may be useful variables to help determine when additional testing such as DMSA should be obtained and when more aggressive bladder management is indicated, such as CIC. Of 79 patients who developed bladder trabeculations and/or VUR, 31 (39%) developed a subsequent abnormal DMSA scan with 22/31 (71%) found in patients with prior febrile UTI. Conversely, none of 51 patients who maintained a non-trabeculated, non-refluxing bladder developed DMSA abnormalities. While these results support utility of DMSA in patients with trabeculations and/or VUR, they question routine DMSA in patients with neither finding. This is important given increased sensitivity of children to carcinogenic effects of ionizing radiation [17]. Therefore, we no longer obtain routine DMSA in patients who maintain a non-trabeculated bladder without VUR. Conversely, if a patient develops trabeculations and/or VUR, we are more likely to recommend CIC $\pm$ anticholinergics, consider vesicostomy or botulinum toxin, and perform DMSA scan—especially if there is a history of febrile UTI.

The CDC newborn protocol recommends serial video UD evaluation or VCUG + CMG during infancy and early childhood [1]. Based on our results, the absence of trabeculation and/or VUR on cystogram, especially in patients without febrile UTI, may be sufficient for low-risk stratification. Moving forward, an approach to risk stratification in young SD patients might include more VCUGs and less UD studies to monitor more frequently for VUR or trabeculations. VCUG results could be used to determine who might benefit from UD evaluation. Based on our results, one could hypothesize that in infants with SD managed expectantly, VCUG appearance, renal ultrasound findings, and UTI history could be used to guide management if UD testing is not available. We continue to obtain routine video UD around 3 months, 1 year, and clinically indicated thereafter.

Limitations

This study is limited by its retrospective nature. While discrete cut-offs for variables such as EFP were used, risk exists on a continuum and our analysis may have failed to identify high-risk patients whose values fell below cut-offs. The UD parameters we studied are correlated; a patient with a high EFP is more likely to have a high DPIV, bladder trabeculations, and VUR. Therefore, it is not surprising that all parameters were associated with DMSA abnormalities. For outcome of early CIC, the parameters studied were used to decide when to start early CIC and therefore would be expected to be associated. However, despite this limitation we include this outcome for counseling expectations. Abnormal DMSA may have been congenital dysplasia in 11 patients who had an abnormal first DMSA as 6/11 had VUR as infants with initial abnormal DMSA prior to febrile UTI. Febrile UTI was recorded as a binary variable within the longitudinal dataset. Therefore, if multiple febrile UTIs occurred between follow-up visits, only a single event was captured for analysis (potentially underestimating incidence). In addition, some febrile UTIs may have been missed by retrospective review. As our patients were managed expectantly, these results may not apply to patients managed with CIC from birth. Indications for CIC were not rigorously defined and varied by provider. Prophylactic antibiotics were not used in a standardized fashion and this may affect results. We used surface patch EMG electrodes and do not include analysis of EMG findings for reasons stated above.

Conclusions

VUR, bladder trabeculations, EFP $\geq$40 cm H_20, IV $\geq$50% of EBC, or DPIV $>$10 cm H_2O were associated with increased risk for subsequent DMSA abnormalities in young children with SD managed expectantly. Many of these parameters were also associated with febrile UTI and early CIC. The combination of trabeculations and/or VUR outperformed other UD parameters in identifying those at high and low-risk for subsequent adverse urologic outcomes. Routine DMSA scan may have limited utility in patients who maintain a non-trabeculated bladder without VUR, as none of these patients developed an abnormal DMSA. Most (71%) of the abnormal DMSA scans were seen in patients with trabeculations and/or VUR following a febrile UTI. Given these findings and that the incidence of febrile UTI may be lower in those with trabeculations while on CIC, patients with trabeculations and/or VUR should be managed aggressively to protect upper tracts.

Conflicts of interest

None.

Funding

None.

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