Published in final edited form as:

J Urol. 2009 September ; 182(3): 1152–1157. doi:10.1016/j.juro.2009.05.049.

Is the availability of endoscopic treatment changing the initial management of vesicoureteral reflux?

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Abstract

Introduction and Objective—The optimal management of vesicoureteral reflux (VUR) continues to be controversial. Since the approval of Dextranomer/Hyaluronic Acid copolymer implants (Dx/HA; Deflux) for endoscopic anti-reflux surgery (EARS) in 2001, the perception that EARS is less morbid than open anti-reflux surgery (OARS), combined with concerns over potential adverse effects of prophylactic antibiotics, have led some to advocate EARS as initial therapy for VUR. We sought to examine whether the availability of EARS has changed management of VUR.

Methods—The Innovus i3 database contains longitudinal claims data on over 39 million individual patients over a 5 year period. Pediatric patients with diagnosis of VUR were identified (ICD9 code 593.7, plus claim for radiographic or nuclear cystogram within 90 days), and those with at least 1 year of follow-up data were analyzed. Patient characteristics were assessed, and diagnostic and therapeutic interventions analyzed. Surgical trends were evaluated including the changing utilization of EARS vs. OARS.

Results—Among 9496 children with VUR with follow-up of 1 year or more, 1998 (21%) underwent anti-reflux surgery during the study period (2002–2006). Median follow-up was 894 days in the surgical group. Of those that underwent surgery, 1046 (52.4%) underwent OARS while 952 (47.6%) underwent EARS. Females were more likely to undergo EARS (52% of females vs. 33% of males ($p<.0001$)), as were older children (53% of those >5 years vs. 45% of those ≤ 5 years, $p=.0002$). 1234 (62%) of those who had ARS underwent surgery within 12 months of diagnosis. During the study period, the proportion of newly diagnosed VUR patients who underwent early ARS (during the first 12 months after diagnosis) increased from 12.0% to 17.3% (M-H chi-square $p<0.0001$). This increase was primarily due to a doubling of the proportion of patients undergoing early EARS during this time, from 4.2% in 2002 to 9.7% in 2006 ($p<0.0001$); the proportion of newly diagnosed patients undergoing early OARS did not change significantly ($p=0.3446$).

Conclusions—During a five-year period after the introduction of Dx/HA for endoscopic therapy, the number of children newly diagnosed with VUR who undergo early ARS has increased. This increase is primarily due to increased utilization of endoscopic ARS. This finding suggests that, despite the lack of evidence of benefit, EARS is increasingly viewed as first-line therapy for VUR.

Keywords

vesicoureteral reflux; antireflux surgery; socioeconomic

The optimal management of vesicoureteral reflux (VUR) continues to be controversial. Since the approval of dextranomer/hyaluronic acid copolymer (Deflux®; Dx/HA) for endoscopic anti-reflux surgery (EARS) in 2001, the perception that EARS is less morbid than open anti-reflux surgery (OARS), combined with concerns over potential adverse effects of prophylactic antibiotics, have led some to advocate EARS as initial therapy for VUR. While many physicians who manage children with VUR have now incorporated EARS into their armamentarium of treatments, there is little evidence regarding the impact of this new therapy on VUR management and decision-making.

We hypothesized that physician perceptions regarding the efficacy of EARS have led to its increased use as primary therapy for VUR compared with traditional antibiotic prophylaxis. The purpose of this study was to utilize a large database to investigate patterns of care for VUR, with specific focus on trends in utilization of open versus endoscopic surgical treatment of VUR, during the time period when endoscopic treatment was becoming widely available.

Methods

This study is based on analysis of the medical insurance claims data found in the Innovus i3 database. i3 is a business unit of Ingenix, a wholly-owned subsidiary of UnitedHealth Group. The database contains medical claims data for over 39 million lives, derived from the UnitedHealthcare family of health insurance plans and products. UnitedHealth Group operates in all 50 states, although we do not have information regarding the specific geographic distribution of the patients in the database. Although de-identified, the database allows longitudinal follow-up of individual patients during the data period. Information accessible via the database includes diagnoses (via ICD-9 codes), procedures and diagnostic studies including radiology and laboratory tests (via CPT codes), and pharmacy prescribing information, including agent(s), dose, duration, and refills ordered and fulfilled. We had access to data from 2002 through the first quarter of 2007. The data were housed at UCLA and analyzed at RAND.

Included subjects

Patients were included as subjects in this study if they met the following criteria: 1) age 18 years or younger at time of diagnosis, and 2) presence of ICD-9 diagnosis codes for VUR (593.7, 593.70, 593.71, 593.72, 593.73), and 3) presence of CPT codes for radiologic diagnostic studies (voiding cystourethrogram -74455, nuclear cystogram - 78740), and 4) at least 1 year of follow-up after VUR diagnosis. To limit the study set to patients with primary VUR, we excluded patients with codes for ureterocele and ureteral obstruction (753.2), neurogenic bladder and spina bifida (596.5, 741), posterior urethral valves (753.6), bladder exstrophy (753.5), renal transplant (V42), and prune belly (756.71). The “initial” diagnosis of VUR was defined as the initial claim for a VUR diagnostic code, combined with a procedure code for cystogram. Date of the initial diagnosis, as indicated by the initial claim, was used to determine time to events, such as ARS. Follow-up time was defined as the time between the initial diagnosis and the final clinical encounter recorded in the study period.

Other variables collected regarding the study sample included diagnosis of UTI (ICD-9 codes 590.0, 590.1, 590.2, 590.3, 590.8, 590.9, 595.0, 595.2, 595.9, 599.0, 771.82) and additional imaging performed (nuclear renal scan - CPT 78700, 78701, 78707, 78708, 78709, 78710; abdominal ultrasound - CPT 76700, 76705, 76770, 76775; intravenous urography - CPT 74400, 74410, 74415; CT scan abdomen/pelvis -CPT 74150, 74160, 74170, 72191, 72192, 72193, 72194).

Surgical Treatment of VUR

Rate of surgical intervention was based on presence of CPT codes for OARS (CPT 50780, 50782, 50783, 50785, 50947, 50948) and/or EARS (CPT 52327). Only initial surgical procedures were included; repeat ARS were not counted. (We will seek to analyze the incidence of repeat surgical intervention, and specifically the rate of repeat injection and/or reimplantation, in subsequent analyses). Timing with respect to the initial diagnosis of VUR was assessed. In particular, we focused on early ARS. The number undergoing early ARS was calculated as the proportion of subjects diagnosed with VUR during the study period who underwent ARS within 12 months of VUR diagnosis. This proportion was calculated for the overall sample, as well as for each year of the study period, to determine if the proportion changed during the study period. Surgery within one year of was selected as the cut-off because it is common during medical management of VUR to perform follow-up cystography on an annual basis. Therefore it was reasonable to classify children undergoing surgery within 1 year as children who did not go through a full attempt at observation with expectation of spontaneous resolution of VUR while on medical management, but instead proceeded directly to surgery. Cost data related to ARS was derived from the associated billing data for these claims.

Statistical analysis

Data were analyzed with SAS statistical software (SAS Institute, Cary NC). Continuous variable were compared with t-tests. Categorical variables were compared using chi-square tests. For categorical variables along an ordinal scale (e.g. year of study), significance of trends were assessed with Mantel-Haenszel chi-square. Significance level of 0.05 was applied for hypothesis testing.

RESULTS

Initial analysis of the claims data revealed 26,155 patients with a diagnosis code for VUR, of whom 22,862 (87.4%) were pediatric patients. After excluding patients without cystographic imaging (n=6989), follow-up of less than 1 year after diagnosis (n=6355), and exclusion of subjects with secondary VUR (n=22), the dataset included 9496 pediatric patients available for analysis. Only patients diagnosed during the first quarter of 2006 were included, due to the time limits of the available data and our 1-year follow-up requirement. Therefore, the number of subjects from 2006 is lower than the other study years.

The characteristics of the included patients are shown in Table 1. As expected, most patients were young (< 5 years old), most were female, and most had been diagnosed with a urinary tract infection. Radiographic voiding cystourethrogram (VCUG) is far more commonly used as the initial diagnostic test compared to nuclear cystogram. Most patients do undergo upper tract imaging of some kind within 90 days of diagnosis, with sonography being the most common modality (76.7%). Less than 5% had nuclear renal scans within 90 days, and very small numbers had CT scan or IVP. Median follow-up was 894 days in the surgical group, and 794 days in the non-surgical group.

Overall, 1998 patients (21%) underwent ARS during the study period. Of these, 1037 (51.9%) underwent OARS, while 961 (48.1%) underwent EARS. Differences between the EARS and OARS groups are presented in Table 2. Females undergoing ARS were significantly more likely to undergo EARS ($p<.0001$), as were older children ($p<0.0001$). The mean time from diagnosis to ARS was 40 days longer in the EARS group than the OARS group ($p=0.0035$). Patients with history of UTI were less likely to undergo ARS than those without history of UTI (18.5% vs. 27.7%, $p<0.0001$).

Of those undergoing ARS, 1234 (61.7%) underwent early ARS (surgery within 12 months of VUR diagnosis). Among the early ARS groups, the mean time from diagnosis to surgery was 128 days (median: 101) for OARS and 129 days (median: 107) for EARS. Taking the surgical cohort as a whole, the OARS group was slightly more likely to undergo early surgery than the EARS group (64% vs. 59%, $p=0.03$).

However, when we examined the number of newly diagnosed VUR patients who underwent early ARS as a function of the year of diagnosis, we found that the number undergoing early ARS increased during the course of the study period (Table 3). The overall proportion of newly diagnosed VUR patients who underwent early ARS increased from 12.0% in 2002 to 17.3% in 2006 (M-H chi-square $p<0.0001$). The changes in utilization of early ARS were not equal between EARS and OARS, however; the increase was primarily due to a doubling of the proportion of patients undergoing early EARS during this time, from 4.2% in 2002 to 9.7% in 2006 ($p<0.0001$) (Figure 1). In contrast, the proportion of newly diagnosed patients undergoing early OARS did not change significantly during the study period ($p=0.3446$).

Discussion

Urologists have long sought a less invasive way to correct VUR. In 1981, the first injection technique was reported by Matouschek¹. Using polytetrafluoroethylene (PTFE; Teflon) paste as a bulking agent, he elongated the intramural tunnel - and created a more substantial backing for the ureter - by injecting PTFE into the submucosa below the refluxing ureteral orifice. The technique was widely adopted after reports that success rates of 75% could be achieved with injection techniques^{2,3}. Although concern over migration of PTFE particles to distant body sites⁴ limited the use of this bulking agent in the U.S., the proof of principle led to efforts to identify other bulking agents that could be used safely. Investigated substances have included collagen, polydimethylsiloxane, autologous chondrocytes, blood and other agents⁵.

In 1995, a Swedish group reported development of a copolymer of cross-linked dextranomer microspheres suspended in a carrier gel of stabilized hyaluronic acid (Dx/HA), marketed as Deflux®. The FDA approved Deflux for correction of VUR in 2001, and since then its use has increased significantly in many parts of the U.S.⁶ Reported success rates after DX/HA injection have ranged from 53–100%^{7–11}. Comparison of outcomes has been complicated by the tendency of some groups, particularly in Europe, to report “success” even when Grade I VUR persists after treatment. In other series, it can be difficult to determine how many injection procedures were required. It is also clear that recurrence of VUR after initial success with DX/HA injection occurs in a significant minority of patients⁸.

Because of the perception that morbidity with endoscopic therapy is extremely low, suggestions have begun to appear in the literature and at national meetings that endoscopic treatment should be utilized as initial therapy for patients diagnosed with VUR. Advocates argue that immediate endoscopic therapy is preferable to antimicrobial prophylaxis in children just diagnosed with VUR¹². Along these lines, studies have been published claiming that incidence of UTI is lower after EARS with DX/HA, both in comparison to UTI incidence before ARS¹³, as well as in comparison to UTI incidence after OARS¹⁴. Although these studies have design flaws that limit their generalizability, such reports may be impacting practice patterns among urologists who care for children with VUR.

Indeed, our findings suggest that the trend of early surgery as initial therapy for newly diagnosed VUR may be **increasing**. Our data span the time frame immediately following the approval of Dx/HA for VUR management and supporters of EARS have aggressively promoted this therapeutic option through the literature. Current standards of care do not yet embrace such early treatment: the current Campbell-Walsh textbook states that “the indications for correction

of reflux should remain unchanged regardless of whether reflux is corrected by open surgery, endoscopy, or laparoscopy”¹⁵. Our data, however, suggest that practice trends may already be leaving the textbooks behind.

This study is one of the first to document trends in management of VUR in the community. Most of the urological literature consists of case series from tertiary pediatric care centers, where treatment trends again may not reflect actual community standards and practices. One exception was Lendvay et al. who used the Pediatric Health Information System (PHIS) database to analyze trends in VUR surgery⁶, but this dataset is limited to highly subspecialized children’s hospitals, and may not reflect broader care in the community, or even at all children’s hospitals. Our findings, while qualitatively similar to Lendvay et al’s, expand upon their findings using a much larger database with a broader subject population. Thus, the current findings reinforce and strengthen Lendvay’s observations, giving credence to the observation that a shift in practice patterns is underway.

As a general rule, the effects of new technology and therapies on practice patterns and on quality of care have been poorly understood. There have been efforts to document the impact of novel therapies in areas such as cardiology (effects of drug-eluting stents on management of coronary artery disease¹⁶), vascular medicine (effects of endovascular procedures on management of abdominal aortic aneurysm¹⁷), and even urology (role of robotic-assisted laparoscopy training in surgical practice¹⁸). However, the majority of such studies are limited to single centers or regions, and very few seek to create the kind of comprehensive picture of national practice patterns, or utilize longitudinal patient data, as we have done in this study. No such data exist regarding UTI/VUR management trends.

Our finding that 21% of VUR patients underwent surgery during the study period (and 13% of newly diagnosed VUR patients underwent surgery in the first 12 months after diagnosis) is consistent with some previous findings, but not all. Among International Reflux Study patients (IRS), 24 of 72 North American patients randomized to medical therapy (33%), but only 8/155 European patients (5%), crossed over to ARS^{19,20}. Arant reported a longitudinal cohort of 113 patients with primarily grade I, II, and III VUR, of whom only 3 (2.6%) underwent ARS during the study²¹. Thus, it appears that contemporary surgical treatment rates for VUR patients may be higher than those seen historically. The availability of endoscopic ARS as a widely-accepted modality may be pushing surgical intervention to the forefront earlier and more aggressively than before. Another factor may be increasing concern over the efficacy (or lack thereof) of prophylactic antibiotics. Another factor, difficult to quantify, is the aggressive marketing of endoscopic therapy for VUR both to clinicians and to the lay public. Marketing may influence physician decision making²², as well as that of families²³, who may arrive at the physician’s office requesting endoscopic therapy.

Certain limitations inherent in studies of this type need to be considered. First, there are the limitations of using large administrative databases. This database is comprised of insurance claims data. Treatment for which no claim was made will not be captured by the database. Conversely, we cannot be certain that the appearance of a new claim for a particular diagnostic code reflects the actual timing of the clinical diagnosis. Thus, it is possible that some of our “newly” diagnosed patients actually were late in the course of their disease. However, we investigated this by assessing how many of our “newly” diagnosed VUR patients had claims data available for more than 6 months prior to the “initial” diagnosis. Over two-thirds of the patients had 6 or more months of data (without any VUR-related claims); this suggests that a substantial majority of our subjects’ VUR diagnoses were verifiably “new” diagnoses. For the minority without 6 months of prior data, there will remain some uncertainty about timing. Second, our diagnosis and procedure classifications rely on the ICD-9 and CPT coding systems, and represent secondary data extracted from the original medical record. It is therefore subject

to potentially inaccurate data transfer or inaccurate coding. Furthermore, these coding systems do not provide us with VUR grade, or with indications for surgery, which are potentially important covariates. A further limitation is that, in utilizing a database of private insurance claims, this study is, by definition, limited to those children with private insurance coverage. As such, these patients may differ systematically from those patients without insurance or with public insurance (e.g. Medicaid). Thus, the generalizability of these findings is limited. Finally, follow-up is limited in this context. Although we restricted the analysis to those with a minimum of one-year follow-up, it is possible that this group differs systematically from those who dropped out of the database before 1 year of follow-up.

From a practical standpoint, these limitations mean that caution should be exercised in generalizing our findings to broader populations. Most specifically, these data may not be applicable to uninsured pediatric populations, or to those with public insurance such as Medicaid. In these groups, VUR management trends may differ due to financial and other pressures affecting both families and clinicians. Further work with data that include these populations is needed to extend these results to the broader pediatric population.

Conclusions

During a five-year period after the introduction of DX/HA for endoscopic therapy, the number of children newly diagnosed with VUR who undergo early ARS has increased. This increase is primarily due to increased utilization of endoscopic ARS. This finding suggests that, despite the lack of evidence of benefit, EARS is increasingly viewed as first-line therapy for VUR.

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Figure 1.

Graph showing relative increase in proportion of newly diagnosed patients with VUR who undergo early anti-reflux surgery (ARS). Early ARS is defined as ARS within 12 months of VUR diagnosis. The increase in the number of patients undergoing early ARS is significant (Mantel-Haenszel Chi-Square p-value < 0.0001). The increase is due primarily to the increase in early endoscopic ARS (EARS); there was no significant change over time in the proportion of patients undergoing early open ARS (OARS) (p=0.3446).

Table 1

Characteristics of children diagnosed with VUR (2002–2006), having claims for cystographic imaging, and followed for at least 1 year (n=9496)

Variable	N (%)
Age (years)	
<1 year	1366 (14.4)
1–2 years	2926 (30.8)
3–5 years	2748 (28.9)
6–10 years	1944 (20.5)
11–18 years	512 (5.4)
Gender	
male	2032 (21.4)
female	7549 (78.6)
History of UTI	
UTI history	6889 (72.55)
No UTI history	2607 (27.45)
Diagnostic Test	
VCUG	6988 (73.6)
RNC	1337 (14.1)
Both	1171 (12.3)
Additional imaging within 90 days of VUR diagnosis	
Ultrasound	7279 (76.7)
Renal scan	457 (4.8)
CT	193 (2.0)
IVP	40 (0.4)
Anti-Reflux Surgery	
Yes	1998 (21.0)
No	7498 (79.0)

Table 2

Characteristics of vesicoureteral reflux (VUR) patients undergoing anti-reflux surgery (ARS), with comparison between open ARS (OARS) versus endoscopic ARS (EARS)

Variable	OARS	EARS	P-value
	N=1037	N=961	
Age (years)			
<1 year	137 (64.6%)	75 (35.4%)	<0.0001
1–2 years	282 (59.9%)	189 (40.1%)	
3–5 years	296 (47.5%)	327 (52.5%)	
6–10 years	264 (47.2%)	295 (52.8%)	
11–18 years	58 (43.6%)	75 (56.4%)	
Gender			
male	281 (66.6%)	141 (33.4%)	<0.0001
female	756 (52.0%)	820 (48.0%)	
Time from VUR diagnosis to ARS (days, mean $\pm$ SD)	315 $\pm$ 309	356 $\pm$ 344	0.0053
Cost of ARS based on claims (\$, mean $\pm$ SD)	22944 $\pm$ 10549	11110 $\pm$ 6088	<0.0001
Length of Stay (days, mean $\pm$ SD)	2.0 $\pm$ 1.2	*	
Early ARS [‡]	664/1037 (64.0%)	570/961 (59.3%)	0.0305

* 97% of EARS were performed on outpatient basis

[‡] ARS performed within 12 months of initial diagnosis of VUR

Changes in utilization of early anti-reflux surgery (ARS), defined as ARS within 12 months of VUR diagnosis. Increase in early ARS between 2002 and 2006 is a statistically significant trend (M-H chi-square <0.0001). Figures in parentheses are column percents.

Table 3

	2002	2003	2004	2005	2006	Total
Early ARS	326 (12.0)	259 (11.5)	258 (12.8)	271 (14.9)	120 (17.3)	1234
Early EARS	115 (4.2)	109 (4.9)	130 (6.5)	149 (8.2)	67 (9.7)	570
Early OARS	211 (7.8)	150 (6.7)	128 (6.4)	122 (6.7)	53 (7.7)	664
No Early ARS	2396 (88.0)	1990 (88.5)	1756 (87.2)	1547 (85.1)	573 (82.7)	8262
Total	2722	2249	2014	1818	693	9496