Impact of Clinical Guidelines on Voiding Cystourethrogram Use and Vesicoureteral Reflux Incidence

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Purpose: To prevent over diagnosis and overtreatment of vesicoureteral reflux the 2007 NICE (National Institute for Health and Care Excellence) and 2011 AAP (American Academy of Pediatrics) guidelines recommended against routine voiding cystourethrograms in children presenting with first febrile urinary tract infections. The impact of these guidelines on clinical practice is unknown.

Materials and Methods: Using an administrative claims database (Clinformatics™ Data Mart) children who underwent voiding cystourethrogram studies or had a diagnosis of vesicoureteral reflux between 2001 and 2015 were identified. The cohort was divided into children age 0 to 2 and 3 to 10 years. Single and multiple group interrupted time series analyses (difference-in-difference) were performed with the guidelines as intervention points. The incidence of vesicoureteral reflux was compared across each period.

Results: Of the 51,649 children who underwent voiding cystourethrograms 19,422 (38%) were diagnosed with vesicoureteral reflux. In children 0 to 2 years old voiding cystourethrogram use did not decrease after the 2007 NICE guidelines were announced (−0.37, 95% CI −1.50 to 0.77, p = 0.52) but did decrease significantly after the 2011 AAP guidelines were announced (−2.00, 95% CI −3.35 to −0.65, p = 0.004). Among children 3 to 10 years old voiding cystourethrogram use decreased during the entire study period. There was a decrease in the incidence of vesicoureteral reflux in both groups that mirrored patterns of voiding cystourethrogram use.

Conclusions: The 2011 AAP guidelines led to a concurrent decrease in voiding cystourethrogram use and incidence of vesicoureteral reflux among children 0 to 2 years old. Further studies are needed to assess the risks and benefits of reducing the diagnosis of vesicoureteral reflux in young children.

Key Words: vesico-ureteral reflux, diagnostic imaging, pediatrics, urinary tract infections, practice guidelines as topic

Abbreviations and Acronyms

AAP = American Academy of Pediatrics

NICE = National Institute for Health and Care Excellence

VCUG = voiding cystourethrogram

VUR = vesicoureteral reflux

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Overall 25% to 40% of young children presenting with a febrile urinary tract infection have an underlying diagnosis of vesicoureteral reflux.[1] Since the majority of vesicoureteral reflux resolves with time and growth, there is controversy over the ideal time to obtain screening studies.[2,3] The 2007 British National Institute for Health and Care Excellence and the 2011 American Academy of Pediatrics guidelines on pediatric urinary tract infection recommended against the routine use of voiding cystourethrogram studies in children presenting with a febrile urinary tract infection, and instead recommended only a routine renal ultrasound and

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reserving the voiding cystourethrogram for specific circumstances.[4,5] Supporters believed that these changes would mitigate the over diagnosis and overtreatment of vesicoureteral reflux, while others were concerned that the diagnosis of vesicoureteral reflux would be delayed or missed in some patients, resulting in recurrent urinary tract infections, pyelonephritis and renal scarring episodes that would have been preventable.[6,7]

The effect of these guidelines on rates of voiding cystourethrogram use and incidence of vesicoureteral reflux remains undefined. Previous investigators have studied the impact of these guidelines on voiding cystourethrogram use and vesicoureteral reflux detection rates at an institutional level.[8,9] We built on this work by examining the impact of major guidelines at a national level by using a large administrative claims database. We hypothesized that the 2007 NICE and 2011 AAP guidelines decreased voiding cystourethrogram use and vesicoureteral reflux incidence in the United States following their publication.

MATERIALS AND METHODS

Data and Study Population

The data were obtained using an administrative claims database composed of members of a national managed care company affiliated with Clinformatics Data Mart (OptumInsight, Eden Prairie, Minnesota). The Clinformatics Data Mart database includes de-identified enrollment information of more than 111 million unique members across the United States dating back to 1993. The database is capable of following subjects longitudinally, providing access to all inpatient and outpatient claims data from community and tertiary referral centers. The geographic diversity of the database allowed us to assess trends across the nation. This study was deemed exempt from review by our university institutional research board.

We included all children less than 10 years old who underwent VCUG with a principal diagnosis of urinary tract infections and/or pyelonephritis as defined by claims based ICD-9 definitions (supplementary Appendix 1, http://jurology.com/). Among these patients we identified those with a principal diagnosis of vesicoureteral reflux. We excluded from the study those children with coexisting diagnoses that involve voiding cystourethrogram as part of standard evaluation or diagnoses that may predispose them to urinary tract infections (supplementary Appendix 2, http://jurology.com/).

Outcomes

Our outcomes of interest were the quarterly rate of voiding cystourethrogram use per 100,000 and the incidence of vesicoureteral reflux per 100,000 children per year before and after the release of the 2007 NICE and 2011 AAP guidelines. The 2011 AAP guidelines were intended to affect children from age 2 months to 24 months. Therefore, our cohort was divided into children 0 to 2 years old and children 3 to 10 years old. We included the 2007 NICE and 2011 AAP guidelines as intervention points of our analysis. Time periods were defined as before NICE (2001 to 2007 Q2), before AAP (2007 Q3 to 2011 Q2) and after AAP (2011 Q3 to 2015 Q2).

Statistical Analysis

A single group interrupted time series analysis was performed to assess voiding cystourethrogram use trends in each age group from January 2001 to June 2015.[10] Since the intended target group of the 2011 AAP guidelines was children less than 2 years old, we expected that any decrease due to the guidelines would be more pronounced in the age 0 to 2 years group. Therefore, we used a multiple group interrupted time series analysis (difference-in-difference) to examine the impact of the guidelines on rates of voiding cystourethrogram use for children 0 to 2 years old vs 3 to 10 years old.[11] Only the first voiding cystourethrogram ordered for a child was included for interrupted time series models.

In addition to the previously mentioned analysis the incidence of vesicoureteral reflux was captured for each period. We calculated the incidence of VUR by quantifying children with a diagnosis of VUR and all unique children included in the claims database in each period. For children 0 to 2 years old and those 3 to 10 years old the t-test was performed between each period to assess significant change in vesicoureteral reflux incidence.

Baseline demographic characteristics by age groups across each period were compared using the t-test for continuous variables and the chi-square test for categorical variables. Statistical analyses were performed using statistical software (STATA 13/SE®) with $p < 0.05$ considered statistically significant.

RESULTS

There were 51,649 unique children who had at least 1 voiding cystourethrogram from January 2001 through June 2015. Mean age at VCUG was 3.2 years. Overall 25,706 tests were obtained in children 0 to 2 years old and 25,943 were obtained in children 3 to 10 years old. Of the tests 82% were performed on female children. Among all children in whom voiding cystourethrogram was performed 19,422 (38%) were diagnosed with vesicoureteral reflux. Demographics, including age, race, geographic location and gender, are detailed in the table.

The single group interrupted time series analysis among children 0 to 2 years old revealed a decreased quarterly rate of 2.82 voiding cystourethrogram studies per 100,000 children during the post-AAP period (−2.82, 95% CI −4.17 to −1.47, $p < 0.0001$). There was no decrease in quarterly rates of voiding cystourethrogram during the pre-NICE or pre-AAP periods (0.51, 95% CI −0.56 to 1.59, $p = 0.34$ and −1.06, 95% CI −2.19 to 0.06, $p = 0.06$, respectively). The single group interrupted time series analysis

Demographic characteristics

	Pre-NICE		Pre-AAP		Post-AAP		Overall	
No. pts	30,790		14,775		6,084		51,649	
Age:								
Mean (SD)	3.3	(2.7)	3.0	(2.7)	3.2	(2.7)	3.2	(2.8)
Median (range)	3.0 (0.0—10.0)		2.0 (0.0—10.0)		2.0 (0.0—10.0)		3.0 (0.0—10.0)	
No. gender (%):								
Female	25,597	(83.1)	12,090	(81.8)	4,716	(77.5)	42,403	(82.2)
Male	5,184	(16.8)	2,681	(18.1)	1,336	(22.5)	9,201	(17.8)
Unknown	9	(0.0)	4	(0.0)	2	(0.0)	15	(0.0)
No. race (%):								
White	20,900	(76.0)	10,306	(70.0)	4,341	(71.8)	35,547	(73.6)
Hispanic	2,758	(10.0)	1,921	(13.1)	706	(11.7)	5,385	(11.2)
Black	1,295	(4.7)	932	(6.3)	345	(5.7)	2,572	(5.3)
Asian	1,016	(3.7)	900	(6.1)	399	(6.6)	2,315	(4.8)
Unknown	1,541	(5.6)	661	(4.5)	253	(4.2)	2,455	(5.1)
Missing	3,280	(10.6)	55	(0.37)	40	(0.66)	3,375	(6.5)
No. census level division (%):								
East North Central	5,412	(17.6)	2,047	(13.9)	904	(14.9)	8,363	(16.2)
East South Central	1,635	(5.3)	562	(3.8)	217	(3.6)	2,414	(4.7)
Middle Atlantic	1,745	(5.7)	906	(6.1)	365	(6.0)	3,016	(5.8)
Mountain	2,899	(9.4)	1,626	(11.0)	785	(12.9)	5,310	(10.3)
New England	890	(2.9)	430	(2.9)	192	(3.2)	1,512	(3.0)
Pacific	1,268	(4.1)	992	(6.7)	381	(6.3)	2,641	(5.1)
South Atlantic	7,174	(23.3)	3,872	(26.2)	1,349	(22.2)	12,395	(24.0)
West North Central	4,768	(15.5)	1,656	(11.2)	800	(13.1)	7,224	(14.0)
West South Central	4,993	(16.2)	2,681	(18.1)	1,083	(17.8)	8,757	(16.9)
Unknown	6	(0.0)	3	(0.0)	8	(0.1)	17	(0.0)

All values $p < 0.0001$ (t-test).

among children 3 to 10 years old revealed significantly decreased quarterly rates in all 3 periods (pre-NICE, pre-AAP and post-AAP: −0.49, 95% CI −0.73 to −0.26, $p < 0.0001$; −0.70, 95% CI −0.91 to −0.49, $p < 0.0001$ and −0.82, 95% CI −1.01 to −0.62, $p < 0.0001$, respectively). Trends of voiding cystourethrogram use among children 0 to 2 and 3 to 10 years old are shown in figure 1.

The multiple group time series analysis revealed a greater decrease in quarterly voiding cystourethrogram use rates among children 0 to 2 years old compared to those of children 3 to 10 years old only after the release of the 2011 AAP guidelines (−2.00, 95% CI −3.35 to −0.65, $p = 0.0019$). There was no difference in trend after the release of the 2007 NICE guidelines (−0.37, 95% CI −1.50 to 0.77,

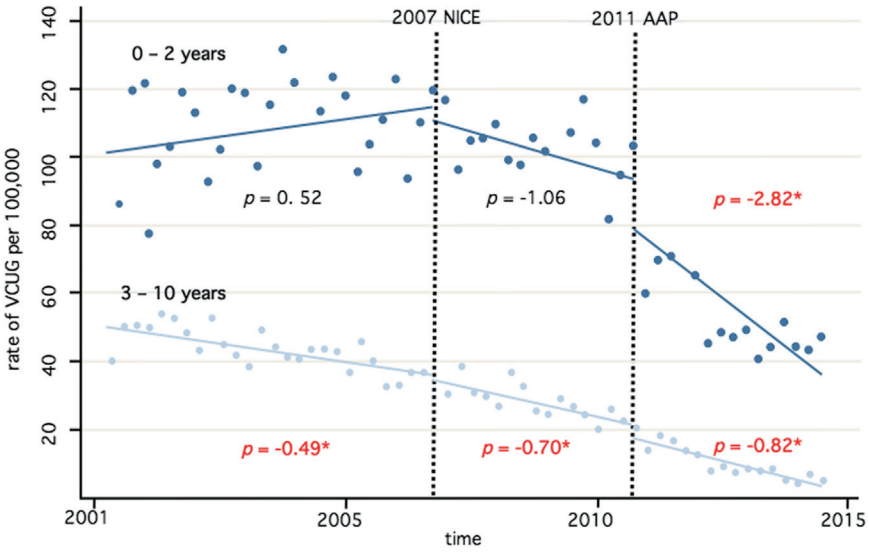

Figure 1. Trends in VCUG use rates among children 0 to 2 and 3 to 10 years old. Asterisk indicates statistically significant $p < 0.05$ on single group interrupted time series analysis.

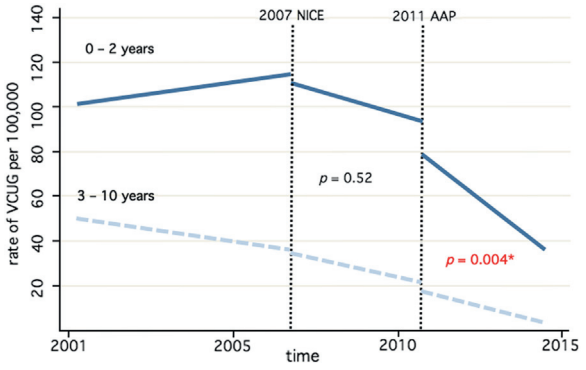

Figure 2. Difference in rate of change after major guidelines. Asterisk indicates statistically significant p <0.05 on multiple group interrupted time series analysis.

p = 0.52). The difference-in-difference analysis is shown in figure 2.

During the pre-NICE guideline, pre-AAP guideline and post-AAP guideline periods the incidence of VUR among children 0 to 2 years old was 41.32, 37.98 and 25.30 per 100,000 children, respectively. The incidence of VUR among children 3 to 10 years old was 15.88, 10.31 and 6.02 per 100,000 children, respectively. Among children 0 to 2 years old there was a significant decrease in vesicoureteral reflux incidence between the post-AAP and pre-AAP periods (p <0.0001). Among children 3 to 10 years old the vesicoureteral reflux incidence decreased between the pre-NICE and pre-AAP periods (p <0.0001), and between the pre-AAP and post-AAP periods (p <0.0001). The incidence of vesicoureteral reflux in children 0 to 2 and 3 to 10 years old is shown in figure 3.

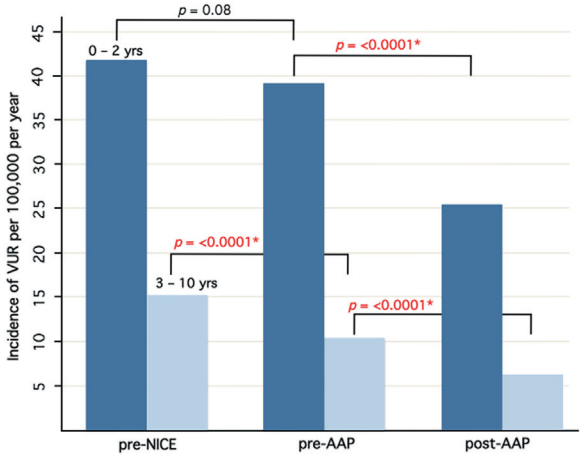

Figure 3. VUR incidence. Asterisk indicates statistically significant p <0.05 on t-test.

DISCUSSION

After the release of the 2011 AAP guidelines there was a significant decrease in voiding cystourethrogram use among children 0 to 2 years old. Likewise, there was a significant decrease in vesicoureteral reflux incidence for this same population only after the release of the 2011 AAP guidelines. Among children 3 to 10 years old voiding cystourethrogram use and vesicoureteral reflux incidence were declining before the release of the 2011 AAP guidelines. Collectively, although there was a preexisting reluctance to diagnose vesicoureteral reflux in older children, these findings suggest that the 2011 AAP guidelines effectively decreased vesicoureteral reflux diagnosis in young children less than 2 years old.

Previous investigators reported fewer voiding cystourethrogram studies performed at a local level during the last decade. Vereen et al reported a decreasing trend in voiding cystourethrogram use at a tertiary care center from 2005 to 2013 among children less than 18 years old.[9] Lee et al reported a steady decrease in the number of voiding cystourethrogram studies performed at another large tertiary care center from 2008 to 2015 among all patients.[8] The time series regression analysis with the 2011 AAP guidelines as the intervention time point did not reveal a significant decrease in trend after the publication of the guidelines. Our current study reveals that voiding cystourethrogram use rates among older children were trending down before the release of the 2011 AAP guidelines, while voiding cystourethrogram use rates among children 0 to 2 years old significantly decreased following the 2011 AAP guidelines.

In terms of vesicoureteral reflux Vereen et al reported that the ratio of patients seen with vesicoureteral reflux did not change from 2006 to 2013.[9] Lee et al reported that there was no significant difference in vesicoureteral reflux detection rates between 2009 and 2014 but there was a threefold increase in the detection of high grade reflux in 2014 (2.6% vs 8.4%, p = 0.03).[8] The current study demonstrates that among older children vesicoureteral reflux detection rates have been on the decline since 2001. Among children less than 2 years old vesicoureteral reflux detection rates significantly decreased only after the release of the 2011 AAP guidelines.

Our study does have several limitations. It is limited to privately insured children, excluding children with lower socioeconomic backgrounds who may have higher barriers to health care access. In addition, although patients are followed longitudinally, not all patients were included in the database since birth. There may be patients who were already diagnosed with vesicoureteral reflux before

inclusion in the database. However, the considerable size and diversity of the Clinformatics Data Mart database may help account for the relatively small group of subjects not reflected in our database and, therefore, unlikely to affect our findings. Although the 2011 AAP guidelines were intended to impact children age 2 to 24 months, we divided the groups based on age in years because the database provides only the year of birth for each patient. Considering this limitation, we believed that the 2 groups of 0 to 2 years and 3 to 10 years old were most accurate and appropriate. We also could not differentiate between high grade and low grade reflux. However, based on recent findings of the RIVUR (Randomized Intervention for Children with Vesicoureteral Reflux) trial, it may be argued that children with high grade as well as those with low grade reflux may benefit from intervention.[12]

These limitations notwithstanding, our findings help us understand the implications of the 2011 AAP guidelines on voiding cystourethrogram use and vesicoureteral reflux incidence. Relevant to policymakers our results suggest that the 2011 AAP guidelines achieved the intended effects of decreasing routine voiding cystourethrogram use in young children less than 2 years old presenting with a first-time febrile urinary tract infection. This, in turn, decreased diagnosis of VUR in many children who would have been diagnosed with vesicoureteral reflux before the release of the guidelines. Some may welcome this paradigm shift in vesicoureteral reflux. Children presenting with a febrile urinary tract infection without a diagnosis of vesicoureteral reflux are spared a morbid test that involves urethral catheterization and radiation exposure. Those with underlying vesicoureteral reflux that self-resolves without a repeat episode of febrile urinary tract infection or pyelonephritis are spared long-term prophylactic antibiotics, additional voiding cystourethrogram studies and potential procedures such as ureteral reimplantation and/or injection therapies. Conversely, patients with underlying vesicoureteral reflux may experience repeat urinary tract infections or pyelonephritis episodes that may have been prevented with earlier diagnosis. The missed opportunity for management with prophylactic antibiotics or prompt intervention with surgical or endoscopic procedures may result in renal scarring that may have been prevented.

From a health care expenditure perspective, at first glance the guidelines may appear to cut cost and conserve resources by decreasing the number of voiding cystourethrogram studies performed and modalities used for management of vesicoureteral reflux. However, episodes of recurrent urinary tract infections, pyelonephritis and renal scarring may represent considerable long-term health care costs.

Our collective findings suggest that while there was a preexisting reluctance to diagnose vesicoureteral reflux among older children, the 2011 AAP guidelines effectively decreased voiding cystourethrogram use and vesicoureteral reflux diagnosis among young children less than 2 years old. Moving forward, research in this area should focus on understanding changing management patterns and overall cost in managing vesicoureteral reflux. In addition, it is imperative to examine the rates of recurrent urinary tract infections, pyelonephritis and renal scarring among patients whose diagnosis was delayed as a result of this paradigm shift in vesicoureteral reflux. In the end we must achieve the optimal balance to limit the over diagnosis and overtreatment of vesicoureteral reflux while minimizing the number of children who may suffer as a result.

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EDITORIAL COMMENTS

The authors hypothesized that the 2007 NICE and 2011 AAP guidelines for imaging after urinary tract infection corresponded to decreased use of VCUG in children, and indeed this is what they observed, particularly after 2011. These findings add to the growing literature documenting the overall decrease in VCUG use during the last decade (reference 8 in article).[1]

The question, of course, is whether this decrease is a good thing. Certainly there are many who believe that universal VCUG in children after urinary tract infection is misguided, resulting in over diagnosis of "indolent" VUR. Others have argued strongly that skipping the VCUG will eventually result in delayed presentations of children with significant renal damage that could have been prevented had they been diagnosed earlier.

The debate reflects a broader ongoing discussion in medicine reflecting the tension between more aggressive testing and screening (with a goal of minimizing missed diagnoses) vs a more noninterventionist approach (with a goal of avoiding diagnosis of indolent disease and unnecessary overtreatment). For example, for prostate cancer the U.S. Preventive Services Task Force initially recommended against prostate specific antigen screening, but after significant concerns were raised about the potential for increased morbidity and mortality, the recommendations were revised to advocate "individualized decision making."[2] In contrast, the AAP recently doubled down on its 2011 recommendation to defer VCUG, despite new data released since 2011, most notably the RIVUR study (reference 6 in article). Time will tell if the consequences of this paradigm change regarding evaluation after urinary tract infection will represent a net positive or negative. The law of unintended consequences has a way of surprising us.

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By analyzing a large insurance claims database the authors demonstrated that the 2011 AAP guideline not to perform a VCUG after a first urinary tract infection in all infants up to 24 months old has resulted in fewer studies obtained (reference 5 in article). Interestingly, it appears that fewer VCUGs were also performed in older children despite the fact that the guidelines did not make any recommendations for the older cohort. It should not be surprising that primary care physicians and specialists ignored the age cutoff, which may be one of the hazards of making rigid pronouncements, since such recommendations can somehow migrate beyond the intended subpopulation. It also is not surprising that the United Kingdom based 2007 NICE recommendations did not appear to have any impact, since it is probable that physicians in the United States were either unaware of their existence or they generally dismiss suggestions from abroad (reference 4 in article). The most important question, and not answered by this analysis, is how many children, if any, were adversely affected. To answer this question the perusal of large databases will not be sufficient, since the data are not sufficiently granular. Hard work will be needed to tabulate the detailed clinical histories of children seen in outpatient settings, emergency rooms and departments of pediatric nephrology to determine how many not evaluated after a first urinary tract infection experienced VUR related morbidity that could have been avoided.

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