Timing of Follow-up Voiding Cystourethrogram in Children With Primary Vesicoureteral Reflux: Development and Application of a Clinical Algorithm

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ABSTRACT. *Background and Objectives.* Of children diagnosed with urinary tract infection, 30% to 40% have primary vesicoureteral reflux (VUR). For the majority of these children, treatment involves long-term prophylactic antibiotics (ABX) and a periodic voiding cystourethrogram (VCUG) until resolution of VUR as detected by VCUG. Radiation exposure and considerable discomfort have been associated with VCUG. To date, no clear guidelines exist regarding the timing of follow-up VCUGs. The objective of this study was to develop a clinically applicable algorithm for the optimal timing of repeat VCUGs and validate this algorithm in a retrospective cohort of children with VUR.

Methods. Based on previously published data regarding the probability of resolution of VUR over time, a decision-tree model (DTM) was developed. The DTM compared the differential impact of 3 timing schedules of VCUGs (yearly, every 2 years, and every 3 years) on the average numbers of VCUGs performed, years of ABX exposure, and overall costs. Based on the DTM, an algorithm optimizing the timing of VCUG was developed. The algorithm then was validated in a retrospective cohort of patients at an urban pediatric referral center. Data were extracted from the medical records regarding number of VCUGs, time of ABX prophylaxis, and complications associated with either. VUR in patients in the cohort was grouped into mild VUR (grades I and II and unilateral grade III for those ≤2 years old), and moderate/severe VUR (other grade III and grade IV). Kaplan-Meier survival curves were created from the cohort data. From the survival curves, the median times to resolution of VUR were determined for the cohort, and these times were compared with the median times to VUR resolution of the data used for the DTM. The numbers of VCUGs performed, time of ABX exposure, and costs in the cohort were compared with those that would have occurred if the algorithm had been applied to both mild and moderate/severe VUR groups.

Results. Using an algorithm that results in a recommendation of VCUGs every 2 years in mild VUR would reduce the average number of VCUGs by 42% and costs by 33%, with an increase in ABX exposure of 16%, compared with a schedule of yearly VCUGs. For moderate/severe VUR, a VCUG performed every 3 years would reduce the average number of VCUGs by 63% and costs by 51%, with an increase in ABX exposure of 10%. Applying this algorithm to the retrospective cohort consisting of 76 patients (between 1 month and 10 years old) with primary VUR would have reduced overall VCUGs by 19% and costs by 6%, with an increase in ABX exposure of 26%. The patterns of VUR resolution, age distribution, and prevalence of severity of VUR were comparable between previously published results and the retrospective cohort.

Conclusions. Delaying the schedule of VCUG from yearly to every 2 years in children with mild VUR and every 3 years in children with moderate/severe VUR yields substantial reductions in the average numbers of VCUGs and costs, with a modest subsequent increase in ABX exposure. *Pediatrics* 2005;115:426–434; *vesicoureteral reflux, voiding cystourethrography, antibiotic prophylaxis, vesicoureteral reflux resolution.*

ABBREVIATIONS. UTI, urinary tract infection; VUR, vesicoureteral reflux; VCUG, voiding cystourethrogram; ABX, antibiotics; CA, clinically applicable algorithm; DTM, decision-tree model.

O f children diagnosed with urinary tract infection (UTI), 30% to 40% have primary vesicoureteral reflux (VUR).[1] VUR has been graded from I to V depending on severity. VUR is currently best detected by a voiding cystourethrogram (VCUG), which (whether fluoroscopic or nuclear) is regarded as the "gold standard" and is the most commonly used modality.[2,3] The majority of children will have resolution of their VUR over time.[4–12] The probability of reflux resolution with continuous antibiotics (ABX) prophylaxis has been documented in a large study combining prospective data from 893 patients with VUR grades I to IV.[13–15] This study stratified variables into predictors of persistence of VUR on patients followed between the years 1976 and 1990, presented in Fig 1 in the form of a survival nomogram.[16] The medical management of VUR, namely long-term ABX prophylaxis, has been shown to be as effective as surgical management in reducing the risks associated with VUR grades I to IV.[7–9,17–22] Guidelines regarding the management of primary VUR in children recommend that, for most children with VUR, initial treatment is comprised of continuous ABX prophylaxis until indication for surgery or spontaneous resolution of VUR.[16,23–25] However, no specific guidelines are given with regards to
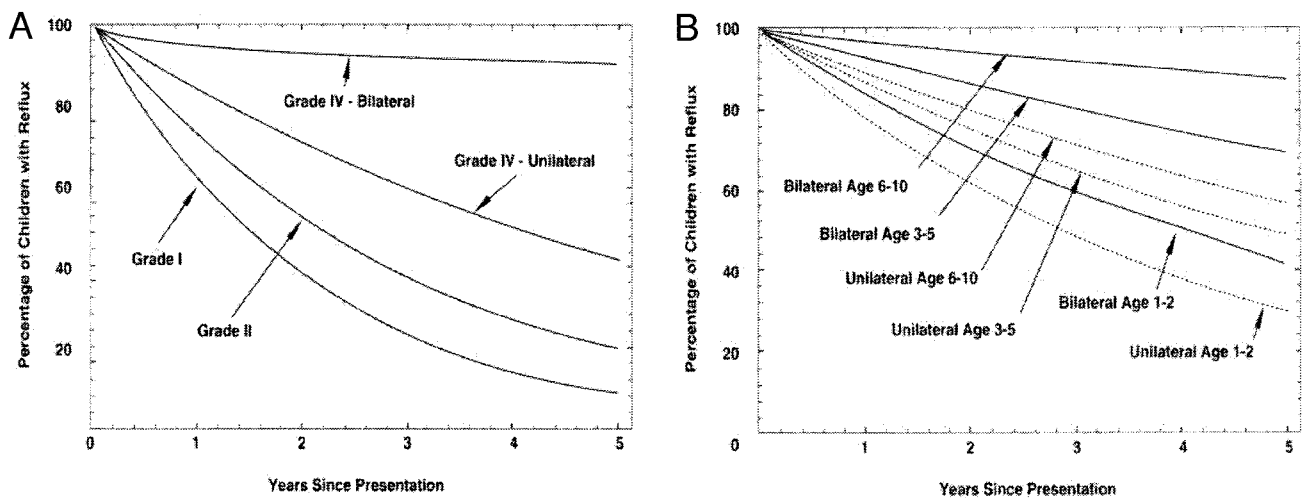
Fig 1. Probability of resolution of reflux over time: A, grades I, II, and IV; B, grade III. (Reproduced with permission from *J Urol.* 1997;157:1846-1851.)

the timing of follow-up VCUGs to detect VUR resolution.

Currently, wide variation exists regarding the frequency of obtaining VCUGs after diagnosis of VUR. Some authors recommend VCUGs at intervals of 6 to 18 months.[26–28] A VCUG is an invasive procedure that is a source of significant patient discomfort resulting from instrumentation of the urinary tract for the purpose of instilling contrast material through a bladder catheter.[29–32] Furthermore, as much as 25% of exposure to ionizing radiation during childhood may be the result of imaging of the urinary tract.[2] On rare occasions the procedure may be followed by an infection.[33] Additionally, there are cost considerations regarding the surveillance of VUR. Beyond the expense of the imaging study, there are the costs of work missed by caregivers, travel expenses, etc.[1,34–37] However, early detection of VUR resolution by a VCUG may minimize the use of prophylactic antimicrobials, which would result in a reduction in the cost of unnecessary prophylactic treatment and reduce the risk of potential side effects associated with ABX exposure and the possible emergence of bacteria resistant to common antimicrobials.[38–42]

The ideal medical management of children with primary VUR would require only the minimal number of invasive imaging studies while concomitantly minimizing any unnecessary exposure to antimicrobial prophylaxis. The timing of follow-up VCUGs should be based on a rational approach guided by the best available data.[43] The primary goal of the present study was to develop a clinically applicable algorithm (CA) for the timing of follow-up VCUGs in children with VUR. A secondary objective was to validate this CA by applying it to a retrospective cohort of children with VUR at an urban pediatric referral institution.

METHODS

This study was considered exempt by the University of Missouri (Kansas City) Pediatric Institutional Review Board, according to criteria 45 CFR 46.101 (b)[4] because it involved the collection of existing data, with information recorded by the investigator in

such a manner that subjects could not be identified directly or through identifiers linked to the subjects.

Decision-Tree Model Analysis

Structure of Decision-Tree Model Analysis

To develop a CA for the optimal timing of follow-up VCUG in children ≤10 years old with primary VUR, decision-tree model (DTM) analysis was used. Three different strategies were modeled for the timing of VCUG: (1) VCUG conducted once yearly; (2) VCUG conducted every 2 years; and (3) VCUG conducted every 3 years. Grades of VUR were grouped into stratification groups identified by Elder et al[16] to be significant predictors of VUR resolution. These stratification groups were based on VUR grade, age in the case of grade III, and laterality in the case of grades III and IV VUR. Mild VUR included grades I and II and unilateral grade III in a child ≤2 years old, and moderate/severe VUR included all other grades III and IV. Each stratification group was evaluated by using the 3 timing strategies. Figure 2 demonstrates the DTM.

Assumptions

Assumptions made for the analysis were: all VCUGs occur at yearly intervals; ABX are discontinued at yearly intervals; no patient drop-out occurs due to death, kidney transplant, etc; and any additional costs (ie, costs of risks associated with ABX and complications from VCUGs) are negligible and were not included in the analysis. The cost estimates were assumed to be $475 per study for a VCUG and $100 per year for ABX. This was based on the billed charges for a VCUG and the average generic cost of a prophylaxis dose of trimethoprim/sulfamethoxazole at our institution in 2002. Costs were considered from the societal perspective, not taking into account work missed, travel expenses, etc.

Probabilities

Data regarding the probability of the resolution of VUR was based on nomograms published by Elder et al[16] (Fig 1).

Outcomes

The following outcomes were estimated: average number of VCUGs per patient; average time receiving ABX prophylactic therapy; and total costs of VCUG and ABX per patient.

The relative change in average number of VCUGs, time of ABX exposure, and costs were analyzed for each different timing strategy. A CA was developed based on this analysis.

Validation Using a Retrospective Cohort

Medical records of a retrospective cohort of patients with VUR at an urban pediatric referral center were reviewed for the secondary objective of validating the CA developed from the DTM.
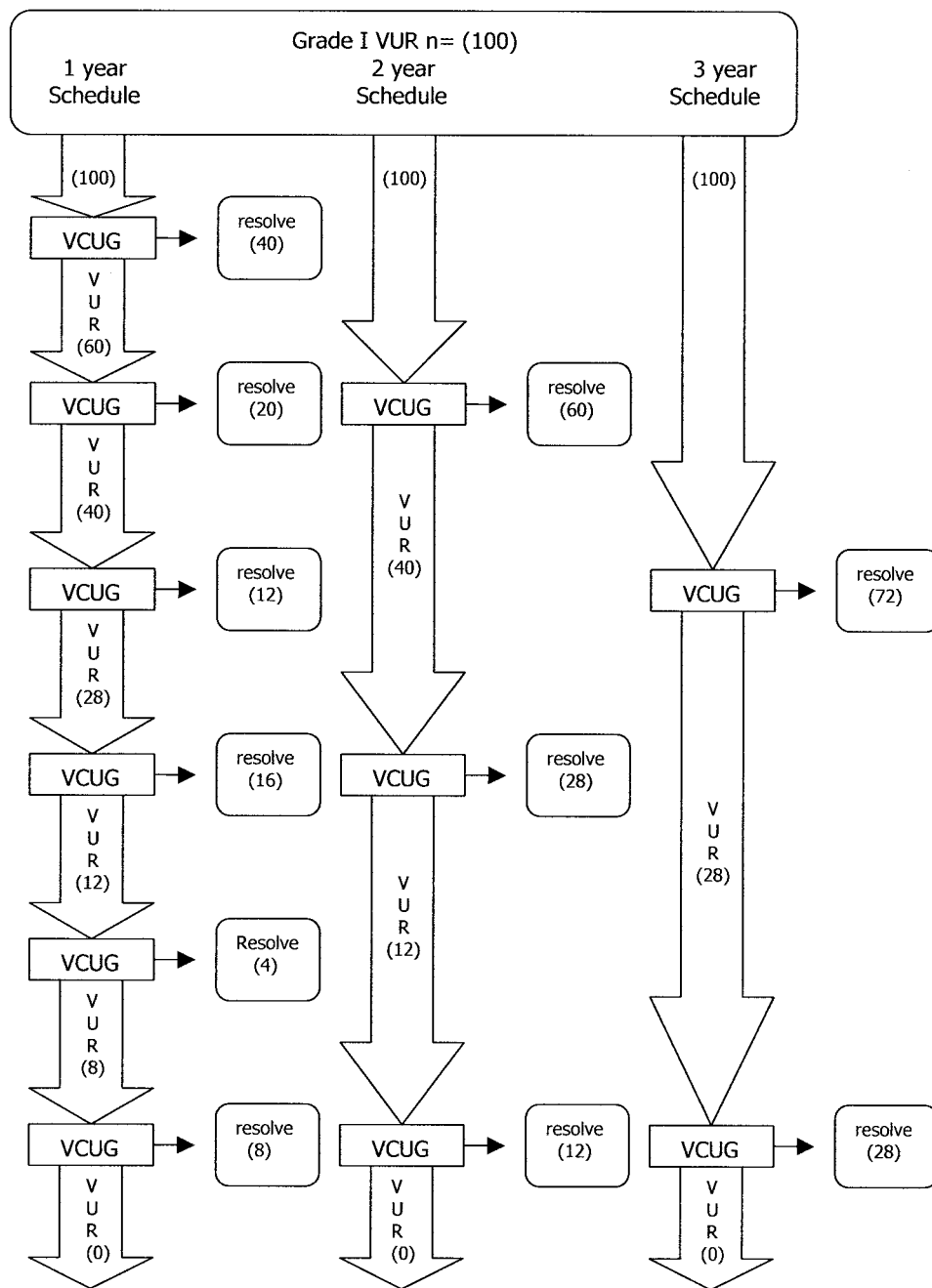
Fig 2. Example of a decision-tree analysis of 100 hypothetical patients with grade I VUR evaluated by follow-up VCUG under 3 different timing regimens. Probability of resolution is 40% at 1 year, 60% at year 2, 78% at year 3, 88% at year 4, 92% at year 5, and 100% at year 6. With an every-1-year schedule, over the course of the analysis (which needs to be 6 years to allow for VCUG intervals of 1 year, 2 years, and 3 years) 40 patients had 1 VCUG, 20 patients had 2 VCUGs, 12 patients had 3 VCUGs, 16 patients had 4 VCUGs, 4 patients had 5 VCUGs, and 8 patients had 6 VCUGs. Calculations to determine average number of VCUGs:

$$\text{total VCUGs: } (40 \times 1) + (20 \times 2) + (12 \times 3) + (16 \times 4) + (4 \times 5) + (8 \times 6) = 464$$
$$\text{average VCUGs per patient: } 248 \text{ VCUGs}/100 \text{ patients} = 2.48$$

Patients were included if they were diagnosed with VUR after an episode of UTI during the years 1995 and 1998 and were <10 years old at diagnosis. Patients were excluded if they had secondary causes for VUR (ie, spina bifida, voiding dysfunction, neurogenic bladder, etc). Excluded also were those diagnosed with VUR as a result of evaluation for prenatal hydronephrosis or due to a sibling screening. Medical records were reviewed, and data were extracted regarding the age, laterality, VUR grade at diagnosis and at follow-up imaging, and the duration of ABX prophylaxis. Cohort data were analyzed in the mild and moderate/severe stratification groups. Kaplan-Meier survival curves were computed by using SPSS 12.0 software (SPSS Inc, Chicago, IL). Data were censored in cases of loss of follow-up or surgical intervention. From the survival curves the median time to resolution was determined for the cohort and compared with median time to resolution of the Elder et al data.[16] The actual average number of VCUGs and average duration of prophylactic ABX were then established for the cohort. Next, based on the cohort's actual rates of resolution, we determined the average numbers of VCUGs and time of ABX exposure that would have occurred if the CA had been applied to the cohort. Finally, the average numbers of VCUGs, ABX exposure, and estimated costs were compared between the actual cohort values and the CA values.

RESULTS

DTM

Average numbers of VCUGs, years of ABX exposure, and cost are shown in Table 1 and Fig 3.

Mild VUR (Grades I and II and Unilateral Grade III for Those ≤2 Years Old)

The change from once-yearly VCUG to an every-2-year schedule of imaging results in a dramatic decrease (42%) in average VCUGs, with minimal change (16%) in ABX exposure. By further delaying to an every-3-year schedule, compared with a yearly schedule, the decrease in average VCUGs (55%) continues but is less substantial compared with the commensurate increase (35%) in ABX exposure. By delaying follow-up VCUG by 2 and 3 years, overall costs would be reduced by 33% and 39%, respectively.

Moderate/Severe VUR (All Other Grades III and IV)

The change from once-yearly VCUG to an every-2-year schedule of imaging results in a dramatic decrease in average VCUGs (48%) with minimal change (7%) in ABX exposure. By further delaying to an every-3-year schedule, compared with a yearly schedule, there is a further decrease in average VCUGs (63%), with a minimal increase (10%) in ABX exposure. By delaying follow-up VCUG by 2 and 3 years, overall costs would be reduced by 38% and 51%, respectively.

For the CA, a schedule of a VCUG every 2 years in mild VUR and every 3 years for moderate/severe VUR was therefore considered optimal (Fig 4).

Retrospective Cohort Chart Review

The medical charts of 92 patients with primary VUR were reviewed. Sixteen patients were excluded based on diagnosis after evaluation for prenatal hydronephrosis ($n = 9$), evaluation without a history of UTI ($n = 4$), and grade V VUR ($n = 3$). A total of 76 patients was included in the analysis. The mean age of the cohort was 1.9 years, and the median age 1.0 year; 10% were male. At the time of diagnosis, 6 patients had VUR grade I (8%), 26 had grade II (34%), 37 had grade III (49%), and 7 had grade IV (9%).

Kaplan-Meier survival curves were created for grades I to III VUR (Figs 5–7). Because of the small sample size, we pooled all grade III patients together. VUR did not resolve in any of the children with grade IV, and therefore a survival curve was not produced (Fig 8). Based on the 3 VUR survival curves, estimates of median months to resolution were calculated. These results demonstrate compa-
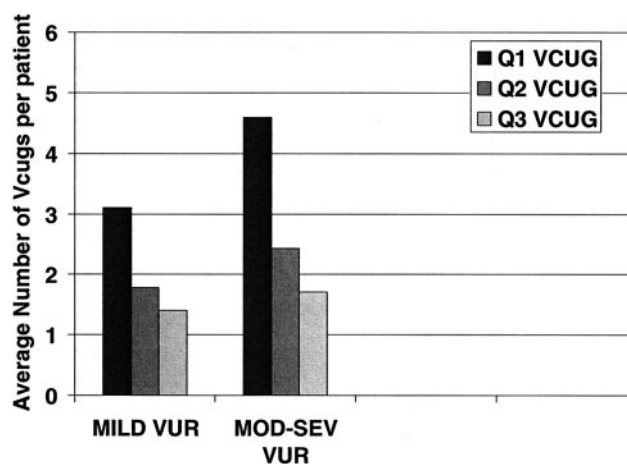

Fig 3. Weighted average VCUG per patient following a yearly schedule (Q1), every-2-year schedule (Q2), or every-3-year schedule, as calculated from data published by Elder et al.[16]

rable or somewhat prolonged median time to resolution compared with median times to resolution calculated from survival curves presented by Elder et al[16] (Fig 8). Additionally, the pattern of VUR resolution, distribution of age, and prevalence of VUR follows that of the largest database ($n = 468$) used by Elder et al for the development of the nomograms.[15] In their cohort, 62% of children with grades I to IV were <2 years old, compared with 60% in our cohort. Also, they had a similar distribution of prevalence of VUR, with 82% of their patients having VUR grades II and III, compared with 83% in our cohort.[15]

The actual average number of VCUGs in the cohort was 2.0 with 2.9 years on ABX and a cost of $1250. Applying the CA to the cohort would have reduced the predicted numbers of average VCUGs by 19% ($P = .001$) and the costs by 6% ($P = .17$) and increased ABX exposure by 26% ($P = .001$), as shown in Figs 9–11.

DISCUSSION

In 1997, Elder et al,[16] serving as an ad hoc committee of expert pediatric urologists and nephrologists, thoroughly reviewed the world literature to establish guidelines for the medical and surgical management of VUR in children. Among these guidelines, they included important nomograms (Fig 1) that illustrated the natural course of VUR resolution in children. However, numerous publications, including the most recent editions of *Nelson's Textbook of Pediatrics*[27] and *Pediatric Nephrology*,[28] recommend repeat VCUG anywhere between 6 and 18 months.[26] These recommendations are inconsistent

TABLE 1. DTM: Effect of 3 Time Schedules of Follow-up VCUG on Average Numbers of VCUGs, Use of ABX, and Cost Per Patient in Children With Mild and Moderate/Severe VUR

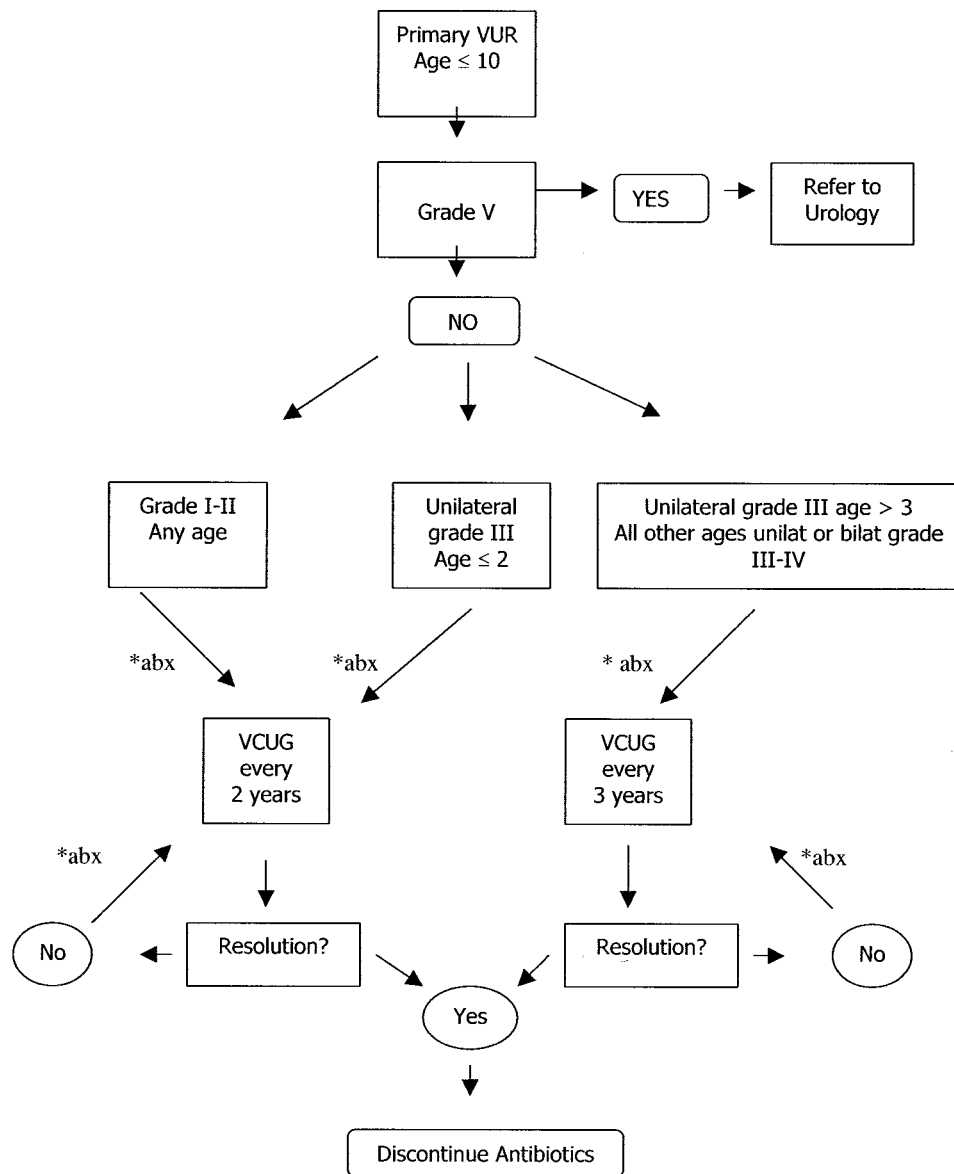| Averages by Interval of Surveillance	VCUGs		ABX		Cost, $	
	Mild VUR	Moderate/Severe VUR	Mild VUR	Moderate/Severe VUR	Mild VUR	Moderate/Severe VUR
1 y	3.1	4.6	3.1	4.6	1790	2650
2 y	1.8	2.4	3.6	4.9	1200	1650
3 y	1.4	1.7	4.2	5.1	1100	1300

Fig 4. Clinical algorithm for surveillance of primary VUR in children ≤10 years old.

with the above-mentioned nomograms and indicate the need for a more rational approach to surveillance of VUR based on the probability of its spontaneous resolution. By using the data presented by Elder et al, we have identified an approach to the timing of repeat VCUG, which moves 1 step closer to the goal of balancing the number of VCUGs, prophylactic ABX exposure, and total costs. Additionally, our analysis of a cohort of patients with VUR strengthens the validity and applicability of the proposed algorithm, because the pattern of VUR resolution, distribution of age, and prevalence of VUR follows that of the largest database used by Elder et al.[15]

The DTM analysis suggests that, when balancing exposure to VCUGs, exposure to ABX prophylaxis, and costs, the optimal timing of follow-up VCUG is every 2 years for children with mild VUR (grades I and II as well as those ≤2 years old with unilateral grade III). The placement of younger children with unilateral grade III VUR in the mild group is consis-

tent with the findings of Elder et al (Fig 1) and other recent recommendations.[27] For those with moderate/severe VUR (all other grade III-IV), the DTM analysis found 3-year intervals to be optimal, based on which we made our recommendations as presented in the form of an algorithm (Fig 4). Our recommendations are consistent with the opinion expressed by Arant[12] in an editorial in which he suggested that VCUG only needs to be performed every 2 to 3 years unless the clinical course is complicated.

Retrospective review of a cohort at our institution suggests that we perform follow-up VCUGs on average every 18 months. As a result of this trend toward delaying VCUG, applying the CA to our own cohort yielded less substantial change in average VCUGs, ABX exposure, and costs than would have been predicted by the DTM schedule of yearly VCUG (Figs 9–11). Although the decrease in VCUGs was statistically significant ($P = .001$), so was the
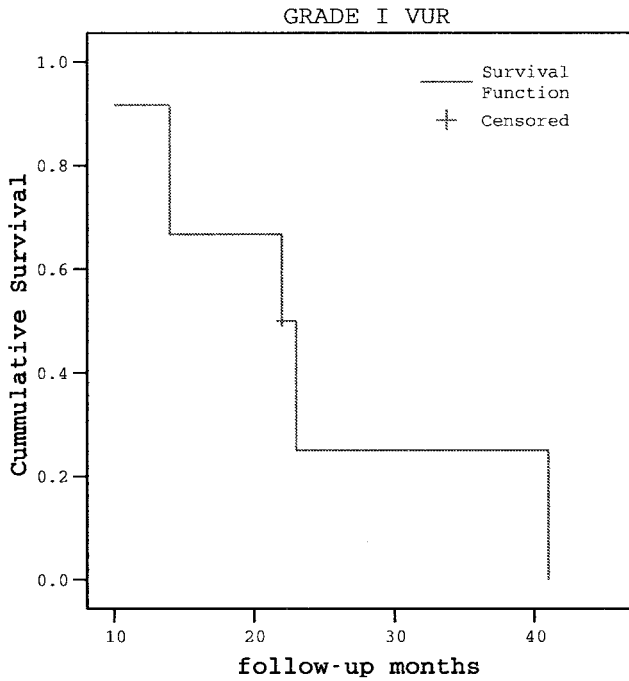
Survival Function

GRADE I VUR

Fig 5. Kaplan-Meier survival curve of patients in the cohort with grade I VUR.

Survival Function

GRADE II VUR

Fig 6. Kaplan-Meier survival curve of patients in the retrospective cohort with grade II VUR
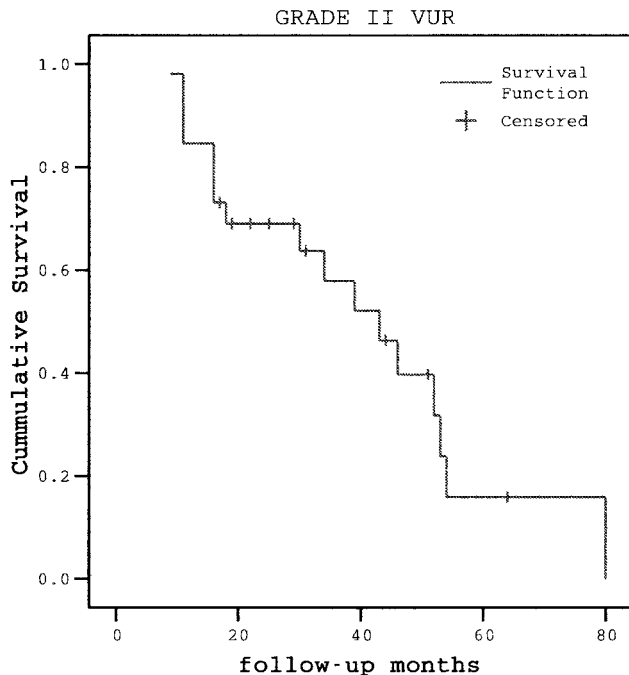
Survival Function
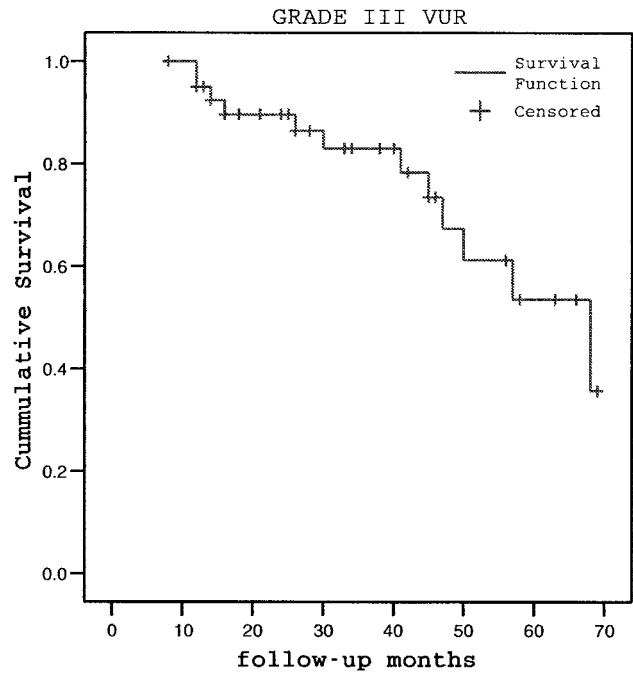
GRADE III VUR

Fig 7. Kaplan-Meier survival curve of patients in the retrospective cohort with grade III VUR

though it is a widely accepted method for VUR follow-up that reduces radiation exposure, it is no less invasive and is more costly than standard fluoroscopic VCUG ($650).

This study does not apply to children with secondary VUR. The management of secondary VUR requires additional considerations including anticholinergics, bladder training, and numerous other specific issues. In regards to primary VUR, we acknowledge that there are many variables that play a role in the decision of when to order a follow-up VCUG. Among these factors are parental anxiety surrounding the invasiveness of the procedure, length of antimicrobial treatment, breakthrough infections, voiding dysfunction, and cost. Additionally, our analysis only included children diagnosed with VUR after a UTI. However, it seems pathophysiologically reasonable to assume that a similar course of resolution of VUR could be expected in children of similar age and severity diagnosed with VUR without a history of UTI (eg, as a result of a work-up of prenatal hydronephrosis or during evaluation of siblings of an index case with VUR). Nonetheless, additional research might be required on these specific groups. Therefore, the local application of this algorithm should reflect individual physician experiences, patient preferences, and other factors not measured in this study.

Another important question that should be raised is whether follow-up VCUG should be performed at all in the context of mild VUR. Several recent studies have found that the majority of children with mild VUR do not have recurrence of UTI while off prophylaxis,[39,40,44] further indicating the need for additional studies to clarify the best approach to the surveillance and management of VUR in children.

increase in ABX exposure ($P = .001$), whereas the cost reduction was not statistically significant ($P = .17$). These findings possibly reflect a local recognition that less frequent VCUGs may strike a better balance between invasive imaging procedures and ABX exposure. We did not include nuclear cystogram as a surveillance modality in our study; al-

Fig 8. Median months to resolution of VUR in the retrospective cohort compared with Elder et al[16] data (dark bars indicate 95% confidence interval).
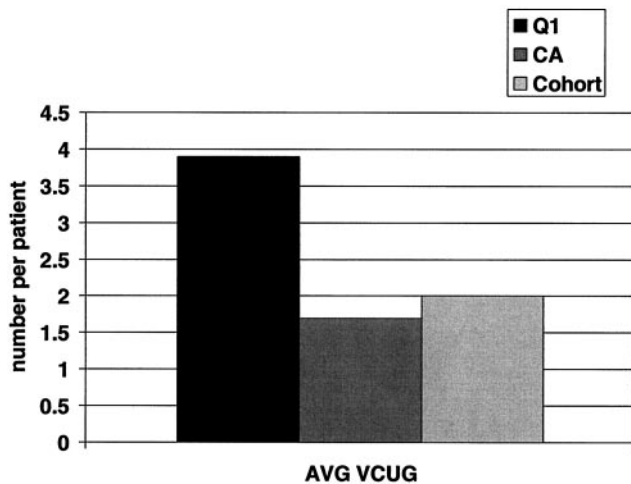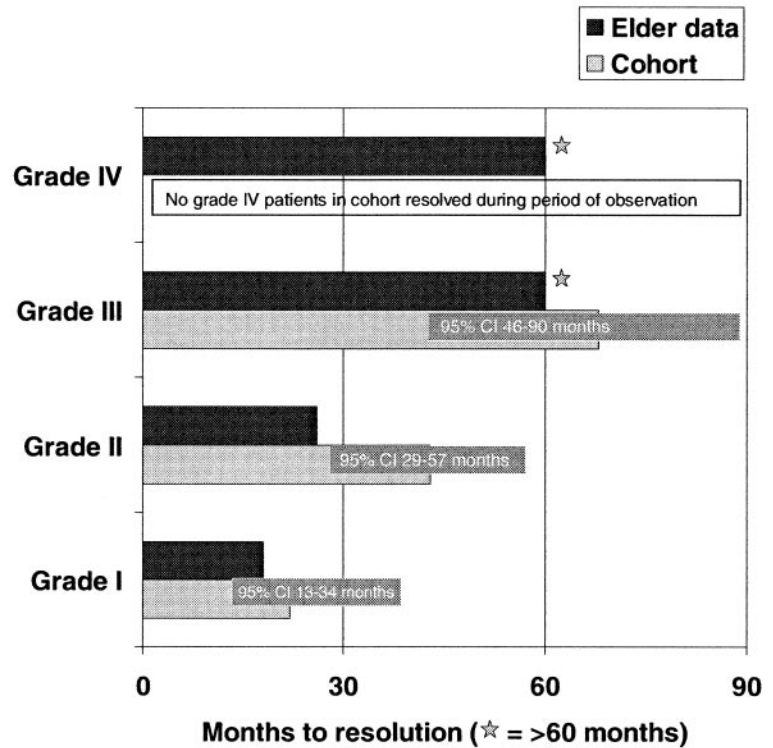

Fig 9. Comparison of overall average VCUGs (total number) between a yearly schedule of VCUG (Q1), a schedule following the CA, and actual retrospective cohort data (Cohort).
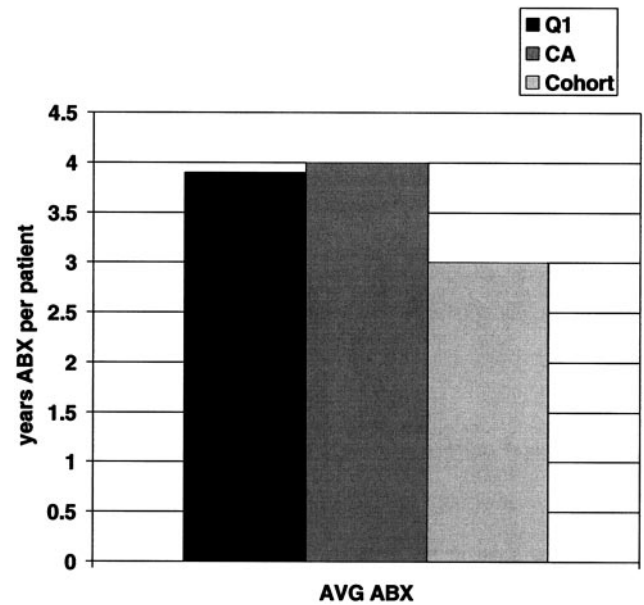

Fig 10. Comparison of overall average ABX use (years) between a yearly schedule of VCUG (Q1), a schedule following the CA, and actual retrospective cohort data (Cohort).

Recently, a meta-analysis by Wheeler et al[45] questioned the justification of the need to detect VUR at all and questioned the indication for long-term antimicrobial prophylaxis. Hellerstein and Nickell[39] recently reported findings to suggest that children with VUR less than grade 3 and without voiding dysfunction are not at significant risk for recurrent UTI and may not need ABX prophylaxis at all. Also, with the advent of new techniques that are proving effective in eliminating VUR in children, such as subureteral injection of dextranomer/hyaluronic acid copolymer, there may be a shift in the entire approach to VUR in children.[46,47] The issue of the timing of VCUG will remain pertinent as long as children with VUR are managed along the current management

guidelines for VUR, which call for surveillance imaging to stage rate of resolution of VUR.[1,16,27,28]

Limitations of our study include its retrospective and observational design. There were no interventions done and no randomization of the algorithm; only a randomized, controlled trial, assigning patients to the different timing strategies, can provide definite evidence of the relative benefits of the different timing procedures. Calculated costs were based on US costs, possibly limiting the international applicability of the cost analysis. Limitations not
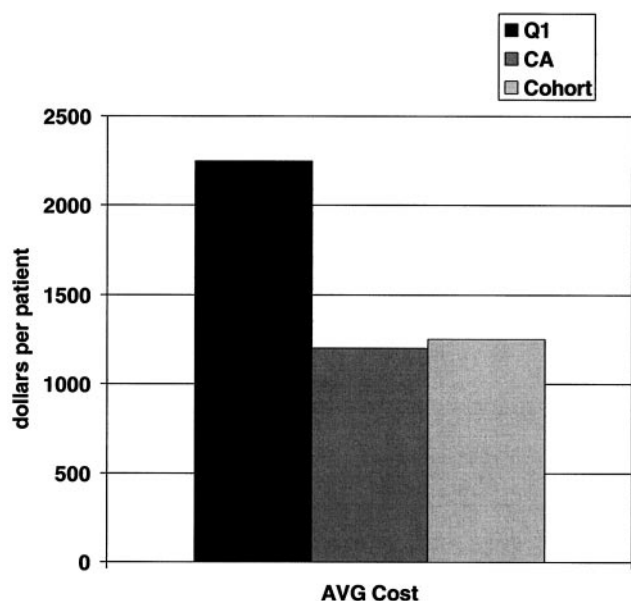
Fig 11. Comparison of overall average costs (dollars) between a yearly schedule of VCUG (Q1), a schedule following the CA, and actual retrospective cohort data (Cohort).

withstanding, this study provides data that help to lay a foundation for a less arbitrary and more scientific approach to the optimal timing of follow-up VCUG in children with VUR.

CONCLUSIONS

Whether for the purpose of reducing unnecessary radiologic imaging or reducing overall costs of management of primary VUR in children, a schedule of surveillance of every 2 or 3 years is preferred to a yearly schedule in children maintained on prophylactic ABX until resolution of VUR. In particular, we found the optimal timing of follow-up VCUG in children with primary VUR to be every 2 years for children with grades I and II VUR and for those ≤2 years old with unilateral grade III VUR. For all others with grade III and those with grade IV VUR, the optimal timing of VCUG is every 3 years.

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"SORRY" SEEN AS A MAGIC WORD TO AVOID SUITS

"It's a lesson children learn even before their ABCs—say you're sorry when you hurt someone. But it's now being taught in the grown-up world of medicine as a surprisingly powerful way to soothe patients and head off malpractice lawsuits. . . . The hospitals in the University of Michigan Health System have been encouraging doctors since 2002 to apologize for mistakes. 'The system's annual attorney fees have since dropped from $3 million to $1 million, and malpractice lawsuits and notices of intent to sue have fallen from 262 filed in 2001 to about 130 per year,' said Rick Boothman, a former trial attorney who launched the practice there."

Associated Press. November 15, 2004

Submitted by Roger Soll, MD

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