Pediatric Urology

Targeted Workup after Initial Febrile Urinary Tract Infection: Using a Novel Machine Learning Model to Identify Children Most Likely to Benefit from Voiding Cystourethrogram

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Purpose: Significant debate persists regarding the appropriate workup in children with an initial urinary tract infection. Greatly preferable to all or none approaches in the current guideline would be a model to identify children at highest risk for a recurrent urinary tract infection plus vesicoureteral reflux to allow for targeted voiding cystourethrogram while children at low risk could be observed. We sought to develop a model to predict the probability of recurrent urinary tract infection associated vesicoureteral reflux in children after an initial urinary tract infection.

Materials and Methods: We included subjects from the RIVUR (Randomized Intervention for Children with Vesico-Ureteral Reflux) and CUTIE (Careful Urinary Tract Infection Evaluation) trials in our study, excluding the prophylaxis treatment arm of the RIVUR. The main outcome was defined as recurrent urinary tract infection associated vesicoureteral reflux. Missing data were imputed using optimal tree imputation. Data were split into training, validation and testing sets. Machine learning algorithm hyperparameters were tuned by the validation set with fivefold cross-validation.

Results: A total of 500 subjects, including 305 from the RIVUR and 195 from the CUTIE trials, were included in study. Of the subjects 90% were female and mean ± SD age was 21 ± 19 months. A recurrent urinary tract infection developed in 72 patients, of whom 53 also had vesicoureteral reflux (10.6% of the total). The final model included age, sex, race, weight, the systolic blood pressure percentile, dysuria, the urine albumin-to-creatinine ratio, prior antibiotic exposure and current medication. The model predicted recurrent urinary tract infection associated vesicoureteral reflux with an AUC of 0.761 (95% CI 0.714-0.808) in the testing set.

Conclusions: Our predictive model using a novel machine learning algorithm provided promising performance to facilitate individualized treatment of children with an initial urinary tract infection and identify those most likely to benefit from voiding cystourethrogram after the initial urinary tract infection.

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Abbreviations and Acronyms

AAP = American Academy of Pediatrics
Abx = antibiotics
ACR = urine albumin-to-creatinine ratio
BBD = bladder and bowel dysfunction
CUTIE = Careful Urinary Tract Infection Evaluation
fUTI = febrile UTI
OCT = optimal classification tree
RIVUR = Randomized Intervention for Children with Vesico-Ureteral Reflux
rUTI = recurrent UTI
UTI = urinary tract infection
VCUG = voiding cystourethrogram
VUR = vesicoureteral reflux
Urinary tract infection affects up to 1.8% of boys and 8.4% of girls within the first 6 years of life. Children with a fUTI are at increased risk for anatomical anomalies, including VUR in 25% to 40%, which is associated with recurrent pyelonephritis and renal scarring. Historically this elevated risk has prompted genitourinary imaging to identify VUR and other anomalies, leading to interventions. However, reports of high resolution rates in patients with lower grade VUR, successful conservative treatment in select patients and the association between BBD and fUTI suggests that VUR is heterogeneous and individualized management is warranted but difficult to achieve.

VCUG is at the center of uncertainty in the treatment of children after an initial UTI. Given its invasive nature, infection risks and radiation, there is a desire for judicious use. In 2011 the AAP modified its guidelines for fUTI management in children 2 to 24 months old. Unlike the previous version, which recommended VCUG following the first fUTI, the 2011 guidelines recommended deferring VCUG until after the second UTI unless abnormalities were noted on renal ultrasound. However, the correlation between VUR and renal ultrasound abnormalities is poor. Therefore, the guidelines are controversial and groups have expressed concern regarding the potential consequences of a delayed diagnosis of VUR even while acknowledging concern for over diagnosis with universal testing. This controversy suggests that our current clinical tools are inadequate to guide management in targeted fashion.

In such circumstances modern machine learning techniques may be useful to improve clinical decision making. Unlike traditional methods which rely heavily on statistical assumptions, machine learning algorithms can identify highly complex patterns from data, enabling robust predictions. If the risk of recurrent fUTI and VUR in children who present with a first fUTI could be predicted accurately, informed decisions would be possible regarding diagnostic imaging and management. Such a model would require highly performing algorithms and a robust data source. The RIVUR trial and the ancillary CUTIE trial provide a unique opportunity. They represent one of the largest groups of children who presented with a first UTI and were followed meticulously for 2 years.

We sought to use machine learning techniques to predict the risk of rUTI and the presence of VUR (rUTI associated VUR) in children who presented with an initial UTI. By identifying such children we could determine those most likely to benefit from early VCUG while also identifying children unlikely to have rUTI or VUR in whom VCUG can be reasonably deferred. We hypothesized that using this model we could characterize the probability of rUTI associated VUR, given a limited set of patient baseline characteristics.

**MATERIALS AND METHODS**

**Data Source and Cohort Selection**

The randomized, double-blind, placebo controlled RIVUR trial, which was performed at 19 centers across the United States, was designed to determine whether daily antimicrobial prophylaxis would be effective to prevent rUTIs in children with VUR. The trial cohort and rationale were reported previously. Briefly, study eligibility included 1) age at randomization between 2 months and 6 years, 2) a diagnosed first or second febrile or symptomatic index UTI within 112 days to randomization and 3) the presence of VUR based on VCUG. Patients were followed for 2 years with rUTI as the primary outcome.

In addition to patients with VUR groups at 3 centers collaborated to develop a parallel cohort of children in the CUTIE trial who were otherwise eligible for RIVUR without VUR. Participants were also followed for 2 years with the same protocol.

Together the RIVUR placebo group and the CUTIE group represented a unique cohort of children in whom UTI recurrence and VUR status were known and who were followed for a 2-year period without treatment (fig. 1, A). The study received Institutional Review Board approval (IRB No. P00026562).

**Covariate Selection and Outcome Definition**

The goal of model development was to identify patients with rUTI associated VUR using data available after the index UTI but prior to VCUG. These data included basic demographic factors, physical examination, history, BBD, urine specimen data and ultrasound. Additionally, interaction terms were made a priori. Supplementary Appendix 1 (https://www.jurology.com) shows a complete list of predictor candidates.

In the RIVUR and CUTIE studies stringent UTI criteria were applied. For an index UTI or rUTIs the event must have met all of certain criteria, including pyuria on urinalysis, culture proven infection with single organism (50,000 cfu/mm³ or greater for a catheterized or suprapubic aspirated specimen and 100,000 cfu/mm³ or greater for a clean voided specimen), fever (38°C or
greater) or UTI symptoms within 24 hours of urine collection (suprapubic, abdominal, flank pain/tenderness, urgency, frequency, hesitancy, dysuria, foul smelling urine or failure to thrive or dehydration, or hypothermia in infants 4 months or younger).

The primary outcome in this study (rUTI associated VUR) was defined as any VUR diagnosed on VCUG and a recurrent febrile UTI during the study period. Recurrent rUTI was defined as described as fever (38°C or greater). Subjects with VUR but no rUTI, with rUTI but no VUR and those with neither condition were defined as being negative for the primary outcome.

Statistical Analysis and Model Development

Bivariate analyses were performed to compare potential predictors of subjects with vs without rUTI associated VUR. We used the chi-square, Fisher exact or Wilcoxon rank sum test, or the t-test as appropriate based on data characteristics and distribution.

Supplementary Appendix 2 (https://www.jurology.com) shows the details of machine learning model development. Briefly, missing data were imputed using a novel technique, namely optimal tree imputation.14 Figure 1, B shows the flow of oversampling, train/test set splitting, model training and performance evaluation (the AUC). OCTs were chosen as the technique due to high performance and interpretability.15

Statistical significance was considered at α = 0.05 and the 95% CI. All analyses were performed with Julia, version 0.6.0 (package OptimalTrees, OptImpute), Python 2.7.13 (package Scikit-learn) and SAS®, version 9.4.

RESULTS

Demographics

We identified 500 participants without exposure to prophylactic antibiotics, including 305 in RIVUR and 195 in CUTIE. Mean ± SD age was 21 ± 19 months. Female patients comprised 90% of the cohort.

Compared with children without rUTI associated VUR, those with rUTI associated VUR were significantly more likely to be white (91% vs 72%, chi-square test vs nonwhites p < 0.01), taking over-the-counter or prescription medication (74% vs 49%, p < 0.01) and have a higher index UTI temperature (mean 39.8°C vs 39.4°C, p < 0.03). Additionally, children with rUTI associated VUR were at a lower weight (median 57th vs 72nd percentile, p < 0.05), and had a prior antibiotic treatment history (median 1 vs 0 month, p = 0.07) and a dilated right ureter (6% vs 1%, p = 0.05). Table 1 lists full demographics by outcome.

Prediction Model

Figure 2, A shows the prediction model. Each patient was categorized in a terminal leaf comprising those who shared a similar probability of rUTI associated VUR. Baseline variables included BBD, defined as positive (equal to 1) if the Dysfunctional Voiding Questionnaire score was 6 or greater in
## Table 1. Patient characteristics by outcome

|                          | Overall | Recurrent UTI Associated VUR | p Value |
|--------------------------|---------|-----------------------------|---------|
| No. pts                  | 500     | 53                          | 447     | —       |
| No. mos age at enrollment (%): |         |                             |         |
| 2—11                     | 238     | 26                          | 212     | 0.41    |
| 12—23                    | 91      | 9                           | 82      | 0.18    |
| 24—35                    | 48      | 2                           | 46      | 0.13    |
| 36—71                    | 123     | 16                          | 107     | 0.29    |
| Missing                  | 0       |                             | —       |         |
| No. gender (%):          |         |                             |         |
| F                        | 452     | 50                          | 402     | 0.46    |
| M                        | 48      | 3                           | 45      | 0.10    |
| Missing                  | 0       |                             | —       |         |
| No. race (%):            |         |                             |         |
| White                    | 368     | 48                          | 320     | <0.01*  |
| Black                    | 52      | 0                           | 52      | 0.11    |
| Mixed                    | 37      | 2                           | 35      | 0.78    |
| Other                    | 35      | 3                           | 32      | 0.72    |
| Missing                  | 8       |                             | —       |         |
| Mean ± SD index UTI temperature (F):† | 103.6 ± 1.4 | 102.9 ± 1.8 | 0.03 |
| No. index UTI organism (%): |         |                             |         |
| Escherichia coli         | 451     | 47                          | 404     | 0.61    |
| Other                    | 46      | 6                           | 40      | 0.89    |
| Missing                  | 3       |                             | —       |         |
| No. index UTI symptoms (%): |         |                             |         |
| Febrile                  | 160     | 21                          | 135     | 0.47    |
| Symptomatic              | 83      | 3                           | 81      | 0.79    |
| Febrile + symptomatic    | 257     | 29                          | 228     | 0.51    |
| Missing                  | 0       |                             | —       |         |
| No. index UTI (%)        |         |                             |         |
| Susceptible              | 248     | 29                          | 219     | 0.47    |
| Resistant                | 252     | 24                          | 228     | 0.51    |
| Missing                  | 0       |                             | —       |         |
| Median No. antibiotic treatments in last 6 mos (IQR):‡ | 1 | (0—2) | 0 | (0—1) | 0.07 |
| No. receiving any medication (%): |         |                             |         |
| Yes                      | 260     | 39                          | 221     | <0.01   |
| No                       | 239     | 14                          | 225     | 0.50    |
| Missing                  | 1       |                             | —       |         |
| No. family history (%)   |         |                             |         |
| Sibling VUR              | 14      | 3                           | 11      | 0.32    |
| Sibling recurrent UTI     | 28      | 4                           | 24      | 0.70    |
| Missing                  | 1       |                             | —       |         |
| No. constipation history (%) |         |                             |         |
| Yes                      | 139     | 12                          | 127     | 0.37    |
| No                       | 359     | 41                          | 318     |         |
| Missing                  | 2       |                             | —       |         |
| No. ever treated for constipation (%) |         |                             |         |
| Yes                      | 79      | 5                           | 74      | 0.23    |
| No                       | 419     | 48                          | 371     | 0.30    |
| Missing                  | 2       |                             | —       |         |
| No. bladder bowel dysfunction (%) |         |                             |         |
| Yes                      | 63      | 10                          | 53      | 0.05    |
| No                       | 57      | 4                           | 53      | 0.11    |
| Not toilet trained       | 373     | 39                          | 334     | 0.72    |
| Missing                  | 7       |                             | —       |         |
| Median wt percentile (IQR):§ | 57 (38—80) | 72 (45—88) | 0.05 |
| No. systolic blood pressure 90th percentile or greater (%): |         |                             |         |
| Yes                      | 115     | 14                          | 101     | 0.72    |
| No                       | 203     | 30                          | 253     | 0.50    |
| Missing                  | 102     |                             | —       |         |
| No. ultrasound findings (%): |         |                             |         |
| Dilated rt ureter        | 8       | 3                           | 5       | 0.05    |
| Dilated lt ureter        | 9       | 2                           | 7       | 0.26    |
| Thickened bladder wall   | 6       | 0                           | 6       | 0.50    |
| Missing                  | 40      |                             |         |

* Chi-square test significant for white vs nonwhite and Fisher exact test white vs black vs others vs mixed.
†Missing 54 patients.
‡Missing 1 patient.
§Missing 0 patients.
Figure 2. A, full prediction OCT model with high-low risk cutoff at 0.5. SBP, systolic blood pressure. B, example 1. C, example 2. UCx, urine culture.
female patients, or 9 or greater in male patients, with all nontoliet trained children treated as negative (equal to 0) (supplementary table, https://www.jurology.com). Further baseline variables included patient age in months, sex, race, weight percentile, antibiotic resistance number in urine culture, ACR, dysuria, receiving prescription or over-the-counter medication (yes or no), antibiotics within the last 6 months in those without a UTI and systolic blood pressure at the 90th percentile or greater.

The tree structure was intuitive and interpretable for clinical use. For example, patient A presented as a 20-month black male with no BBD (fig. 2, B). No BBD (no = 0) and age 20 months would give an initial BBD × age = 0, which was less than the cutoff at 42. At the next node (race × sex) he would go down further left as a black male and end up over the low risk group. As another example, a 5-year-old girl had BBD and a first UTI urine culture showed bacteria with multiple antibiotic resistance (fig. 2, C). She had BBD with an age of 60 months and, therefore, the first value was greater than 42, which led to the right. Multiple resistance on urine culture further led to a high risk group. VCUG should be strongly considered in this case. Table 2 lists all leaves and associated characteristics (fig. 2, A).

Supplementary figure 1 (https://www.jurology.com) shows the ROC curve of the proposed OCT model in the testing set. In the OCT model the AUC was 0.761 (95% CI 0.714-0.808). This demonstrated that the predictive model had good performance. A perfect predictive model would have an AUC of 1.0 while a model no better than a coin toss would have an AUC of 0.5. Sensitivity analysis was performed to compare logistic regression, random forest and gradient boosted tree algorithms. OCT was chosen because of good performance, a tighter AUC CI and interpretability (supplementary Appendix 2, https://www.jurology.com).

**DISCUSSION**

To our knowledge this is the first machine learning model created to predict clinical outcomes in children with a UTI. Our model effectively sorted children into probabilistic groups for rUTI associated VUR. By quantifying the risk of rUTI and VUR in a given child our model allowed for data driven management. In children predicted to be at very high risk for rUTI associated VUR providers may order a VCUG after the initial fUTI despite the 2011 AAP guideline recommendation. Conversely, in patients predicted to be at very low risk for rUTI associated VUR deferring the VCUG would seem reasonable. VCUG in such children is likely to be low yield even in those with rUTI. The model also offered the capability to quantify the probability of the outcome to allow for individual interpretation.

Unlike many machine learning techniques with a black box reputation OCT models enable physicians to look under the hood while maintaining high performance. This allows the incorporation of medical knowledge into the conceptual model framework, ensuring a clinically sound model with real world applicability. For example, during the model building phase serum parameters were initially included. With the goal of reducing unnecessary invasive testing analysis was performed with and without the serum data. Model performance was minimally affected and, therefore, serum related variables were removed. Additionally, we were able to reduce the number of variables from more than 50 to fewer than 8 needed per patient while maintaining performance. The variables ultimately included are easy to obtain in a typical clinical setting. The only specimen needed to fully apply the model prediction power was urine ACR, which is a common test which does not require sterile urine collection.

Encouragingly most splits in the OCT model correlated well with clinical intuition. For example, BBD has been found to be highly associated with VUR and UTI. While BBD has the limitation of applicability only in toilet trained children, our model overcame this issue by combining BBD and age, which resulted in identifying older children with BBD as at higher risk. Our model also showed a higher risk of rUTI associated VUR in white and female children, which was consistent with reported data. Similarly, previous antibiotic exposure and resistance were highly related to rUTI in patients with VUR. Unfortunately circumcision was too rare in our cohort to be incorporated into the model meaningfully. Hypertension was also a known sequela of reflux nephropathy and pyelonephritis, and it was selected by the algorithm.

During model development we also noted several interesting findings. Urine ACR stood out in the final model and subsequent sensitivity analyses. Despite relatively scarce urology literature this test is commonly done in nephrology cases to screen for albuminuria. Multiple groups have reported a significant association between high grade VUR, UTI and urine ACR. Although to our knowledge the exact mechanism is unknown, it is hypothesized that retrograde urine flow, glomerulosclerosis and subsequent hyperfiltration are significantly associated with this finding.

Similar to urine ACR, weight was consistently chosen as an important tree splitting predictor. The association between weight and VUR or UTI is poorly defined in the literature and conflicting data
have been reported. Our hypothesis is that weight may be associated with VUR and UTI in nonlinear fashion and its influence may depend on complex interactions with other variables.

The association of dysuria with a higher risk of rUTI associated VUR may seem counterintuitive. However, since our primary outcome was VUR with recurrent rUTI, we hypothesized that in older children dysuria alone was more likely an indicator of BBD or lower tract nonfebrile UTI instead of pyelonephritis. This hypothesis was supported by the relatively weak association between rUTI associated VUR and symptom only, nonfebrile UTI in our study. These findings demonstrate that a robust machine learning model can potentially detect biologically plausible but previously underappreciated clinical associations.

The findings of our study should be viewed in the context of its design limitations. The RIVUR and CUTIE studies enrolled children between 2 months and 6 years old with a heavy female predominance and children with congenital anatomical abnormalities were excluded. This may have impacted the generalizability of our model, especially in patients out of the range of the cohort. However, we believe that the original cohort captured the majority of children of interest, and the RIVUR and CUTIE studies represented the most comprehensive and best described cohort available.

Many anatomical abnormalities such as ureterocele would likely be detected by screening ultrasound and, therefore, be diverted out of the algorithm since decision making for VCUG in such patients is not addressed by the AAP guidelines. Additionally, the cohort enrolled a few children after a second UTI if they otherwise met study inclusion criteria. These 47 subjects represented 9% of the cohort and a second index UTI was not significantly associated with rUTI (p = 0.19) or VUR (p = 0.43). Therefore, we were not surprised that this variable did not make it into the model.

Furthermore, model power was limited by the relatively small size of the cohorts. This limitation further restricted the evaluation of factors such as BBD since nontoilet trained children could not be evaluated and ureteral dilatation, which was noted in only 17 participants. We were able to stabilize the model and provide good performance with the combination of weighting and oversampling techniques. Nevertheless, the model would be more accurate and useful with broader generalizability if the cohort were larger, supplying additional data to train and validate the algorithm. It is important to recognize that this prediction model is imperfect, primarily due to the inherent size limitation.

One of the most essential insights provided by this study is that building such a prediction model using robust data and state-of-the-art analytics is achievable and would potentially impact current practice. We built a free webpage and app (pending application store approval) to permit rUTI associated VUR prediction (supplementary fig. 2, https://www.jurology.com). The tool would aid clinical
counseling and decision making by clinicians who see children after an initial UTI and it may also facilitate data collection for further studies. We hope that this study can serve as an impetus to incorporate machine learning techniques to advance our ability to care for our patients in a more individualized, quantitative and data driven fashion.

CONCLUSIONS

We developed a predictive model using novel machine learning algorithms and robust trial data to estimate the risks of rUTI associated VUR after an initial UTI in children. This information may facilitate more selective performance of VCUG after an initial UTI than current guidelines permit, reserving VCUG for patients in whom it is likely to be high yield while allowing VCUG to be safely deferred in those determined to be at very low risk.

Further validation, especially for novel factors such as urine ACR, is warranted and requires additional data collection.

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REFERENCES

1. Hellstrom A, Hanson E, Hansson S et al: Association between urinary symptoms at 7 years old and previous urinary tract infection. Arch Dis Child 1991; 66: 232.

2. Smellie JM, Normand IC and Katz G: Children with urinary infection: a comparison of those with and those without vesicoureteric reflux. Kidney Int 1981; 20: 717.

3. Downs SM: Technical report: urinary tract infections in febrile infants and young children: the Urinary Tract Subcommittee of the American Academy of Pediatrics Committee on Quality Improvement. Pediatrics 1999; 103: e54.

4. Committee on Quality Improvement, Subcommittee on Urinary Tract Infection: Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. Pediatrics 1999; 103: 843.

5. Estrada CR Jr, Passerotti CC, Graham DA et al: Nomograms for predicting annual resolution rate of primary vesicoureteral reflux: results from 2,462 children. J Urol 2009; 182: 1535.

6. Shaikh N, Hoberman A, Wise B et al: Dysfunctional elimination syndrome: is it related to urinary tract infection or vesicoureteral reflux diagnosed early in life? Pediatrics 2003; 112: 1134.

7. Soccorso G, Wagstaff J, Blakey K et al: Investigating febrile UTI in infants: is a cystogram necessary? J Pediatr Urol 2010; 6: 148.

8. Roberts KB: Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. Pediatrics 2011; 128: 595.

9. Logvinenko T, Chow JS and Nelson CP: Predictive value of specific ultrasound findings when used as a screening test for abnormalities on VCUG. J Pediatr Urol 2015; 11: 176.e1.

10. Juliano TM, Stephany HA, Clayton DB et al: Incidence of abnormal imaging and recurrent pyelonephritis after first febrile urinary tract infection in children 2 to 24 months old. J Urol 2013; 190: 1505.

11. Bertsimas D, Kung J, Trichakis N et al: Accept or decline? An analytics-based decision tool for kidney offer evaluation. Transplantation 2017; 101: 2988.

12. Hoberman A, Greenfield SP, Mattoo TK, et al: Antimicrobial prophylaxis for children with vesicoureteral reflux. RIVUR Trial Investigators. N Engl J Med 2014; 371: 1072.

13. Carpenter MA, Hoberman A, Mattoo TK et al: The RIVUR trial: profile and baseline clinical associations of children with vesicoureteral reflux. Pediatrics 2013; 132: e34.

14. Bertsimas D, Pawlowski C and Zhuo YD: From predictive methods to missing data imputation: an optimization approach. J Mach Learn Res 2018; 18: 1.

15. Bertsimas D and Dunn J: Optimal classification trees. Mach Learn 2017; 106: 1039.

16. RIVUR Data Dictionary and Analysis Manual. RIVUR Data Coordinating Center, C. S. C. C., Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, 2010.

17. Farhat W, Bagli DJ, Capolicchio G et al: The dysfunctional voiding scoring system: quantitative standardization of dysfunctional voiding symptoms in children. J Urol 2000; 164: 1011.

18. Shaikh N, Morone NE, Bost JE et al: Prevalence of urinary tract infection in childhood: a meta-analysis. Pediatr Infect Dis J 2008; 27: 302.

19. Chand DH, Rhodes T, Poe SA et al: Incidence and severity of vesicoureteral reflux in children related to age, gender, race and diagnosis. J Urol 2003; 170: 1548.

20. Wu TH, Huang FL, Fu LS et al: Treatment of recurrent complicated urinary tract infections in children with vesicoureteral reflux. J Microbiol Immunol Infect 2016; 49: 717.

21. Paschke AA, Zaoutis T, Conway PH et al: Previous antimicrobial exposure is associated with drug-resistant urinary tract infections in children. Pediatrics 2010; 126: 664.

22. Farnham SB, Adams MC, Brock JW III et al: Pediatric urological causes of hypertension. J Urol 2005; 173: 697.

23. Cendron M: Reflux nephropathy. J Pediatr Urol 2008; 4: 414.

24. Garcia Nieto V, Gonzalez Cerrato S, Garcia Rodriguez VE et al: Should a cystography be performed on all breastfeeding infants with mild to moderate dilatation of the urinary tract? Renal function tests can help to answer this question. Nefrologia 2011; 31: 192.

25. Basic J, Golubic B, Miljovic P et al: Microalbuminuria in children with vesicoureteral reflux. Ren Fail 2008; 30: 639.

26. Takeda M, Komeyama T, Katayama Y et al: Measurement of urinary endothelin-1-like immunoreactivity and comparison with other urinary parameters in patients with primary
EDITORIAL COMMENTS

Traditionally VCUG has been routine in the evaluation of children with a febrile UTI as up to 40% may have VUR. More recently the utility of aggressive diagnosis and management of reflux has been questioned with a more selective approach gaining favor.\(^1,2\) Consensus is that management should be based on factors including patient age, the likelihood of subsequent infections, the risk of renal injury, the projected clinical course of a given child and parental preference. These considerations can determine whether to perform invasive imaging in the first place.

In simple terms machine learning is a technique for recognizing complex patterns believed to be important in making predictions or diagnoses of interest, often with great success. Using data from 2 large multicenter trials the authors created a high performance model predicting the likelihood of recurrent infection and VUR in children who present with an initial UTI, thus, allowing for judicious VCUG use. Many variables included in the model are the same factors discussed by clinicians when considering the need for additional testing. Whether computer algorithms are superior to physicians at identifying children at risk remains to be seen but reserving VCUG for those most likely to benefit warrants strong consideration.

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REFERENCES

1. Roberts KB, Downs SM, Finnell SM et al: Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 2011; 128: 595.
2. Bandari J and Docimo SG: Vesicoureteral reflux is a phenotype, not a disease: a population-centered approach to pediatric urinary tract infection. J Pediatr Urol 2017; 13: 378.

The diagnosis of VUR in the setting of febrile UTI in young children remains controversial despite multiple guidelines and studies. Clinicians must strike a balance between over testing and delaying diagnosis of VUR. The authors of this study addressed this dilemma using modern machine learning techniques.

Machine learning algorithms are an integral part of our daily lives, predicting online searches, targeting advertisements, providing online movie recommendations, etc. The authors used robust data sets from the RIVUR and CUTIE trials to create a practical algorithm that predicts which children presenting with febrile UTI are at high risk for VUR with rUTI. However, the algorithm reflects limitations related to the machine learning need for large sample sizes. For instance, a history of constipation or its treatment and BBD were interestingly not independently related to rUTI associated VUR. Furthermore, right but not left ureteral dilatation was associated with rUTI associated VUR. The authors rightfully discuss that these findings were likely related to the relatively small cohort sizes.

This study highlights how pediatric urologists can effectively partner with data scientists to construct algorithms to better guide clinical decisions. However, the need for large data sets can hinder the use of machine learning in clinical research. Even in multicenter studies such as the RIVUR and CUTIE trials some data subsets existed which proved to be too small. If we hope to incorporate machine learning techniques in pediatric urology, increased collaboration and multicenter studies are needed.

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