

**PEDIATRIC UROLOGY** \_\_\_\_\_**Recurrent Urinary Tract Infections in Children: Risk Factors and Association with Prophylactic Antimicrobials.**

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**Context:** The evidence regarding risk factors for recurrent urinary tract infection (UTI) and the risks and benefits of antimicrobial prophylaxis in children is scant.

**Objectives:** To identify risk factors for recurrent UTI in a pediatric primary care cohort, to determine the association between antimicrobial prophylaxis and recurrent UTI, and to identify the risk factors for resistance among recurrent UTIs.

**Design, Patients and Setting:** From a network of 27 primary care pediatric practices in urban, suburban, and semirural areas spanning 3 states, a cohort of children aged 6 years or younger who were diagnosed with first UTI between July 1, 2001, and May 31, 2006, was assembled. Time-to-event analysis was used to determine risk factors for recurrent UTI and the association between antimicrobial prophylaxis and recurrent UTI, and a nested case-control study was performed among children with recurrent UTI to identify risk factors for resistant infections.

**Main Outcome Measures:** Time to recurrent UTI and antimicrobial resistance of recurrent UTI pathogens.

**RESULTS:** Among 74 974 children in the network, 611 (0.007 per person-year) had a first UTI and 83 (0.12 per person-year after first UTI) had a recurrent UTI. In multivariable Cox time-to-event models, factors associated with increased risk of recurrent UTI included white race (0.17 per person-year; hazard ratio [HR], 1.97; 95% confidence interval [CI], 1.22-3.16), age 3 to 4 years (0.22 per person-year; HR, 2.75; 95% CI, 1.37-5.51), age 4 to 5 years (0.19 per person-year; HR, 2.47; 95% CI, 1.19-5.12), and grade 4 to 5 vesicoureteral reflux (0.60 per person-year; HR, 4.38; 95% CI, 1.26-15.29). Sex and grade 1 to 3 vesicoureteral reflux were not associated with risk of recurrence. Antimicrobial prophylaxis was not associated with decreased risk of recurrent UTI (HR, 1.01; 95% CI, 0.50-2.02), even after adjusting for propensity to receive prophylaxis, but was a risk factor for antimicrobial resistance among children with recurrent UTI (HR, 7.50; 95% CI, 1.60-35.17).

**Conclusion:** Among the children in this study, antimicrobial prophylaxis was not associated with decreased risk of recurrent UTI, but was associated with increased risk of resistant infections.

**Editorial Comment**

This is a very large network of 27 primary care pediatric practices using a common electronic health record attempting to identify: the risk factors for recurrent UTI's in pediatrics, the association between prophylactic antimicrobials and recurrent UTI's and the risk factors for resistance of recurrent UTI's in patients six years or younger

This is a retrospective study and the authors tried to review data on their patients that were outside their health care network and laboratory and x-ray data were reviewed manually. There was a 5% random sampling of the actual charts to validate the study. Patients had to have at least two clinic visits in the health network. Positive cultures were defined at 50,000 colony forming units and these were all catheterized specimens and they excluded voided or bagged urine specimens. Patients were excluded that had significant other comorbidities. It is important to note that a resistant culture was defined as a pathogen, resistant to "any" antimicrobial. They reviewed VCUG's that were performed on their patients and did a highly credible job of analyzing the statistics.

They had a total of 74,974 patients six years or under who had at least two clinic visits. Six-hundred sixty-six of them had a confirmed UTI and 611 were in the study group. There was a 13.6% recurrence rate resulting in 12% recurrence per year. 61% of the recurrences were due to a pathogen with antimicrobial resistance. 88.9% with a first UTI were female and 65.5% of all patients did not undergo a VCUG even though under two years of age the American Academy of Pediatrics recommends the VCUG to be performed. 58% of the children under two years-of-age in the study had a VCUG performed. Antimicrobial prophylaxis considered as a time-varying covariate had no significant effect on the risk of recurrent urinary tract infection in a multivariate analysis. Conversely exposure to prophylactic antimicrobials significantly increased the likelihood of resistant infections.

Their data showed the cumulative incidence from 0-6 years of having a first UTI was 4.2% and the rate of recurrence per year was 12%. Their conclusions were that Caucasians from three to five years of age with Grade IV-V vesicoureteral reflux were associated with increased risk of recurrent urinary tract infection. Sex of the patient and Grade I-III vesicoureteral reflux were not associated with increased risk of recurrence. An antimicrobial prophylaxis was not associated with lower risk of recurrent UTI but prophylaxis was associated with increased risk of resistant infections.

Electronic medical record data from insurance networks have significant study difficulties especially with missed results from outside the network and with a large group of physicians treating a large group of patients, the patterns of care may vary significantly. Noted in this study was the absence of VCUG in nearly 70% of patients in spite of the recommendations of the American Academy of Pediatrics to do so. Also all patients had catheterized specimens and yet most physicians would accept a clean-catch negative specimen or a clean-catch single organ positive specimen. Antibiotic exposure is difficult to judge especially since patients may have had antibiotics for different etiologies prior to joining the network and having their first UTI.

One of my biggest concerns about the data is the definition of antibiotic resistance as the pathogen having resistance to any of the antibiotics tested for sensitivity. It almost seems unusual in my practice to have urine cultures that are pan-sensitive, even in first time UTI patients on an outpatient basis. A second large concern was no attempt to ask questions about bladder or bowel function and it is well-known that constipation and voiding dysfunction have a large impact on vesicoureteral reflux and urinary tract infection occurrences and this is a significant oversight in their study. This study still has produced provocative data and should be read and studied because of its wide circulation.

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### **Is Antibiotic Prophylaxis Necessary in Infants with Obstructive Hydronephrosis?**

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Purpose: We investigated the relationship between the level of obstruction of the upper urinary tract and the risk and onset of urinary tract infection in infants with severe obstructive hydronephrosis to determine the need for antibiotic prophylaxis.

**Materials and Methods:** A total of 105 patients were prenatally diagnosed with severe hydronephrosis (Society for Fetal Urology grade III or IV) due to upper urinary tract obstruction between 1994 and 2004. Of these patients 75 had ureteropelvic junction obstruction and 30 had lower ureteral obstruction. We retrospectively evaluated the clinical course and incidence of urinary tract infection during the first 12 months postnatally without antibiotic prophylaxis.

**Results:** The incidence of overall urinary tract infection during followup was 36.2% (38 of 105 patients), and it demonstrated a higher trend with lower ureteral obstruction than with ureteropelvic junction obstruction (50% vs 30.7%,  $p=0.063$ ). Most cases of urinary tract infection (92.8%) occurred before age 6 months, with a mean age at onset of 2.6 months. Of 105 patients 77 (73.3%) underwent corrective surgery at a mean age of 3.8 months. The incidence of urinary tract infection before surgical correction was 33.8% at a mean age of 2.1 months. The incidence of urinary tract infection in surgical cases was significantly higher with lower ureteral obstruction than with ureteropelvic junction obstruction (54.2% vs 24.5%,  $p=0.011$ ).

**Conclusions:** Urinary tract infection in infants with severe obstructive hydronephrosis has a high incidence, occurs before age 6 months and is more common with lower ureteral obstruction than with ureteropelvic junction obstruction. These findings indicate that infants with severe hydronephrosis due to obstruction of the upper urinary tract should receive antibiotic prophylaxis.

### **Editorial Comment**

105 congenital hydronephroses due to upper urinary tract blockages were evaluated during a ten year period. 99 were unilateral and six were bilateral. Forty-seven had SFU Grade III hydronephrosis and 58 had Grade IV. None of the 82 males were circumcised. All patients were followed without prophylactic antibiotics. Seventy-five had ureteropelvic junction obstruction and 30 patients had lower urinary tract obstruction, 18 of which had ureterovesical junction obstruction. There were 10 ureteroceles and 2 ectopic ureters. Surgery was performed if a UTI occurred, or when there was an increased anterior and posterior pelvis diameter or an increased drainage time with worsening obstructive curve or decreasing relative renal function less than 40.

The overall incidence of UTI during follow up was 36.2% (38/105 patients), 50% of the lower urinary tract obstructions and 30.7% of the upper urinary tract obstructions had a UTI. 92.8% of these infections occur before six months of age with a mean age of onset of 2.6 months. Of the 105 patients, 77 underwent corrective surgery at a mean age of 3.8 months. Their data suggested that there is a higher risk of infection for obstructions near the bladder and they recommended prophylactic antibiotics for infants with SFU Grade III and IV obstruction during observation periods.

This is a higher rate of infection than is sometimes reported and a much higher surgery rate at earlier ages than is usually recommended. For ureteropelvic junction obstructions, half of the patients will resolve spontaneously by waiting 18 months or more. It is surprising that their patients either had infections or other indications for surgery by a mean age of 3.8 months. This probably indicates that this is a highly selective group of patients but still suggests that prophylactic antibiotics may be required.

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