

ORIGINAL ARTICLE

Antibiotic Prophylaxis in Infants with Grade III, IV, or V Vesicoureteral Reflux

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ABSTRACT

BACKGROUND

The efficacy of continuous antibiotic prophylaxis in preventing urinary tract infection (UTI) in infants with grade III, IV, or V vesicoureteral reflux is controversial.

METHODS

In this investigator-initiated, randomized, open-label trial performed in 39 European centers, we randomly assigned infants 1 to 5 months of age with grade III, IV, or V vesicoureteral reflux and no previous UTIs to receive continuous antibiotic prophylaxis (prophylaxis group) or no treatment (untreated group) for 24 months. The primary outcome was the occurrence of the first UTI during the trial period. Secondary outcomes included new kidney scarring and the estimated glomerular filtration rate (GFR) at 24 months.

RESULTS

A total of 292 participants underwent randomization (146 per group). Approximately 75% of the participants were male; the median age was 3 months, and 235 participants (80.5%) had grade IV or V vesicoureteral reflux. In the intention-to-treat analysis, a first UTI occurred in 31 participants (21.2%) in the prophylaxis group and in 52 participants (35.6%) in the untreated group (hazard ratio, 0.55; 95% confidence interval [CI], 0.35 to 0.86; $P=0.008$); the number needed to treat for 2 years to prevent one UTI was 7 children (95% CI, 4 to 29). Among untreated participants, 64.4% had no UTI during the trial. The incidence of new kidney scars and the estimated GFR at 24 months did not differ substantially between the two groups. *Pseudomonas* species, other non-*Escherichia coli* organisms, and antibiotic resistance were more common in UTI isolates obtained from participants in the prophylaxis group than in isolates obtained from those in the untreated group. Serious adverse events were similar in the two groups.

CONCLUSIONS

In infants with grade III, IV, or V vesicoureteral reflux and no previous UTIs, continuous antibiotic prophylaxis provided a small but significant benefit in preventing a first UTI despite an increased occurrence of non-*E. coli* organisms and antibiotic resistance. (Funded by the Italian Ministry of Health and others; PREDICT ClinicalTrials.gov number, NCT02021006; EudraCT number, 2013-000309-21.)

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CONTINUOUS ANTIBIOTIC PROPHYLAXIS is routinely used in infants with grade III, IV, or V vesicoureteral reflux. The aim is to prevent urinary tract infections (UTI) and potential long-term sequelae associated with kidney scarring.¹⁻³

Previous pediatric trials on UTI prevention have focused mainly on children with absent or low-grade vesicoureteral reflux, predominantly in girls with associated bladder or bowel dysfunction.³⁻⁶ In the large Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial, in which young children underwent randomization after a first or second UTI, more than 90% were female, with a wide age range, and 80% had grade II or III vesicoureteral reflux.⁷ Although continuous antibiotic prophylaxis was effective in preventing recurrent UTIs,⁷⁻⁹ there was no apparent effect on kidney scarring,^{2,7} a finding that raises questions about the clinical significance of this intervention.¹⁰ The role of primary continuous antibiotic prophylaxis in infants with grade III, IV, or V vesicoureteral reflux (grades that have often been associated with congenital kidney damage) and no previous UTI is unclear.

The use of continuous antibiotic prophylaxis in infants must be weighed against the potential emergence of multidrug-resistant isolates^{11,12} and adverse effects on gut microbiota.¹³⁻¹⁵ Both are important public health issues.

We now report results from the Antibiotic Prophylaxis and Renal Damage in Congenital Abnormalities of the Kidney and Urinary Tract (PREDICT) trial. In the trial, we assessed whether continuous antibiotic prophylaxis would be effective in preventing the occurrence of a first symptomatic UTI and would avert secondary kidney damage in infants with grade III, IV, or V vesicoureteral reflux and no previous UTIs.

METHODS

TRIAL DESIGN AND OVERSIGHT

This investigator-initiated, phase 3, multicenter, prospective, randomized, open-label trial was performed in 39 European centers within the ESCAPE Network.¹⁶ Institutional review boards at all the participating sites approved the trial. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org. There was no agreement re-

garding the confidentiality of the data between the sponsors and the authors.

TRIAL POPULATION

The inclusion criteria were an age of 1 to 5 months; vesicoureteral reflux with a grade of III, IV, or V as assessed by voiding cystourethrography or voiding ultrasonography¹⁷; a gestational age of 35 weeks or more; and an estimated glomerular filtration rate (GFR) of more than 15 ml per minute per 1.73 m² of body-surface area (2009 Schwartz formula).¹⁸ Infants with previous UTI, posterior urethral valves, neurogenic bladder, or ureteropelvic-junction or ureterovesical-junction obstruction were excluded. At baseline, all the infants were assessed by kidney and bladder ultrasonography, a dimercaptosuccinic acid (DMSA) scan, measurement of the serum creatinine level, and urinalysis.

STRATIFICATION, RANDOMIZATION, AND INTERVENTION

Eligible children were randomly assigned (in a 1:1 ratio) to receive continuous antibiotic prophylaxis (prophylaxis group) or no treatment (untreated group) for 2 years. The randomization was stratified according to the presence or absence of kidney parenchymal damage (Table S1 in the Supplementary Appendix, available at NEJM.org).

The antibiotic choice for continuous antibiotic prophylaxis was left to the site investigators, according to local *Escherichia coli* resistance patterns. Treatment options included nitrofurantoin at a dose of 1.5 mg per kilogram of body weight per day, amoxicillin-clavulanate at a dose of 15 mg per kilogram per day (expressed in amoxicillin-equivalent units), cefixime at a dose of 2 mg per kilogram per day, and trimethoprim-sulfamethoxazole at a dose of 2.5 mg per kilogram per day (expressed in trimethoprim-equivalent units and preferably prescribed after 3 months of life).

Prophylaxis was administered as a single daily dose, with the option of changing the antibiotic in the event that unacceptable side effects occurred. After a first UTI, continuous antibiotic prophylaxis could be modified among one of the four possible options, according to the antibiotic sensitivities, in order to overcome resistance.

FOLLOW-UP PROCEDURES

Participants were monitored at baseline and at 4, 8, 12, 18, and 24 months. In the event of symp-

tomatic UTIs or adverse events, additional visits occurred (Table S2). Adherence to continuous antibiotic prophylaxis was evaluated at each visit with diaries filled out by families.

Participants were assessed by means of ultrasonography, DMSA scan, and voiding cystourethrography or voiding ultrasonography at baseline and 2 years. Images were uploaded to a central database, and DMSA scans with centrally available images were reevaluated in a blinded fashion by three of the authors (nuclear medicine physicians at different institutions) to assess possible focal uptake defects (number and position), global reduction of isotope uptake, and possible kidney asymmetry. In case of disagreement, images were reassessed and discussed and a final joint decision was made.

OUTCOMES

The primary outcome was the occurrence of a first symptomatic UTI during the 24-month trial. Secondary outcomes were the total number of UTIs during the 24-month trial, new kidney scars, the estimated GFR at 24 months, causative organisms and antibiotic resistance in UTI isolates, and serious adverse events.

TRIAL DEFINITIONS

Symptomatic UTI was defined as the concomitant presence of acute symptoms (e.g., fever of $\geq 38^{\circ}\text{C}$, unwell appearance, irritability, or loss of appetite), leukocyte esterase or nitrites on urinalysis, and a positive urine culture. A positive urine culture was defined as any growth from a suprapubic bladder aspirate, the growth of a single organism to at least 10,000 colony-forming units (CFU) per milliliter from a catheter sample, or the growth of a single organism to at least 100,000 CFU per milliliter from a midstream voided sample. Bagged specimens were not allowed. Local DMSA defects on a renal scan were defined as focal areas of reduced tracer uptake that were associated with loss of contours or cortical thinning.¹⁹

STATISTICAL ANALYSIS

On the basis of previous trials,²⁰ we anticipated a risk of symptomatic UTIs of approximately 35% among untreated participants during the 2 years of study. For sample-size calculation, we considered a between-group difference of 15 percentage points (with a risk of approximately 20% among participants receiving continuous antibiotic pro-

phylaxis) to be clinically important. With an alpha error of 0.05, a power of 90%, and an estimated dropout rate of 25%, the sample-size calculation was 436 participants (218 per group).

A prespecified interim analysis was conducted 1 year after the randomization of 200 participants (November 27, 2018). We conducted the analysis in 116 participants with complete follow-up (60 in the prophylaxis group and 56 in the untreated group), using an alpha of 0.01 and the outcome at 24 months. The criteria for early interruption for efficacy or futility were not met (z -test for proportions; one-sided P value of 0.33; $z=0.43$), and no safety issues were observed. The steering committee agreed to continue the trial and to reduce the power to 80%, in view of the steady accrual rate of 50 participants per year, which resulted in a required sample size of 218 participants (109 per group), with 290 participants (145 per group) to be recruited under the assumption of an unchanged 25% dropout rate.

In the efficacy assessment, all the participants who underwent randomization were included in the intention-to-treat analysis. The first UTI was considered to be the event. Data for participants who did not have a symptomatic UTI were censored either at 24 months (those with the final visit) or at the time that they were lost to follow-up. A time-to-event Cox regression model was used to include data from all the participants who underwent randomization, in order to avoid potential bias. Several sensitivity analyses were performed to detect possible bias in the intention-to-treat analysis (Table S3). Cox and logistic-regression models included analysis for possible confounding and effect modifiers.

RESULTS

PARTICIPANT CHARACTERISTICS

From October 2013 through January 2020, a total of 867 infants were screened and 292 underwent randomization, 146 to each group. Reasons for screening failure were an age of more than 5 months (26.8%), absent or low-grade vesicoureteral reflux (35.0%), previous UTI (32.9%), and a lack of parental consent (5.4%) (Fig. S1). Participants were recruited from 39 European centers in Italy (42.8%), Turkey (24.0%), Poland (17.5%), Lithuania (7.9%), Belgium (4.8%), and other European countries (3.0%).

The 292 enrolled participants included 227 boys

(77.7%), of whom 5 (2.2%) had been circumcised for religious reasons. At recruitment, the median age was 3.4 months (interquartile range, 2.4 to 4.1), 80.5% of the participants had grade IV or V vesicoureteral reflux, and 48.3% had bilateral vesicoureteral reflux (Table 1). Focal congenital defects were identified in 83 participants (28.4%) on the baseline DMSA scan. In addition, DMSA abnormalities, including diffuse decreased uptake and unbalanced kidney function, were detected in 154 participants (52.7%). Congenital kidney defects were not associated with the grade of vesicoureteral reflux. Ten participants had a solitary kidney. Before enrollment, 150 participants (51.4%) had received previous antibiotic prophylaxis. The clinical characteristics of the participants at baseline did not differ substantially between the two groups.

In the prophylaxis group, amoxicillin–clavulanate was the antibiotic used most often for prophylaxis (72 participants [49.3%]). That was followed by trimethoprim–sulfamethoxazole (35 participants [24.0%]), nitrofurantoin (24 [16.4%]), and cefixime (15 [10.3%]).

PRIMARY OUTCOME

A first symptomatic UTI occurred in 31 participants (21.2%) in the prophylaxis group and in 52 participants (35.6%) in the untreated group (hazard ratio, 0.55; 95% confidence interval [CI], 0.35 to 0.86; $P=0.008$ by log rank test). The percentage of febrile UTIs was similar in the two groups (25 of 31 [81%] in the prophylaxis group and 41 of 52 [79%] in the untreated group; rate ratio, 1.02; 95% CI, 0.82 to 1.28). Urine cultures were collected by midstream voided samples in 49 of 83 cases (59%) and by catheter in 34 of 83 cases (41%). The time to the first UTI was 6.4 months in the prophylaxis group and 5.2 months in the untreated group (mean difference, 1.2 months; 95% CI, -1.3 to 3.6). Figure 1 shows the UTI-free survival among the 292 participants according to trial group. UTI-free survival was uninfluenced by the type of antibiotic used (Fig. S2).

All baseline data were checked in the Cox regression models to verify their possible association with the outcome (Table S4). Sex was a strong predictor of first UTIs, with male participants having a hazard ratio of 0.46 (95% CI, 0.29 to 0.73). When we controlled for sex, continuous antibiotic prophylaxis was still associated with the outcome (hazard ratio, 0.51; 95% CI,

0.33 to 0.80) (Table S5). The number needed to treat was 7 (95% CI, 4 to 29) to prevent one UTI within 2 years.

A total of 49 participants (16.8%) were lost to follow-up, 29 in the prophylaxis group and 20 in the untreated group. Of these, 13 (27%) had a first UTI before being lost to follow-up (5 in the prophylaxis group and 8 in the untreated group). Results of the sensitivity analyses were consistent with the results of the primary intention-to-treat analysis. The effect of treatment was similar, with similar effect sizes. The hazard ratio, rate ratio, and odds ratio in the prophylaxis group ranged from 0.53 to 0.64, with similar 95% confidence intervals (Table S3).

In the subgroup analysis of the treatment effect in all six combinations of participant sex and grade of vesicoureteral reflux, continuous antibiotic prophylaxis was associated with the outcome in female participants with grade IV or V vesicoureteral reflux. In male participants, a weak association was observed only in those with grade IV vesicoureteral reflux (Fig. 2).

SECONDARY OUTCOMES

Total UTIs

A total of 139 symptomatic UTIs occurred during the 24-month trial period, 60 in the prophylaxis group and 79 in the untreated group (rate ratio, 0.76; 95% CI, 0.59 to 0.97). Although participants with 1 or 2 UTIs were more common in the untreated group, participants with 3 or more UTIs were more common in the prophylaxis group (Fig. S3). The percentage of symptomatic UTIs that resulted in hospitalization was similar in the two groups (16 of 60 [27%] in the prophylaxis group and 24 of 79 [30%] in the untreated group; rate ratio, 0.88; 95% CI, 0.51 to 1.50). Most of the first symptomatic UTIs (50 of 82 cases with available data [61%]) were treated with oral antibiotics. The percentage of UTIs that were treated intravenously was similar in the two groups (13 of 30 [43%] in the prophylaxis group and 19 of 52 [37%] in the untreated group; rate ratio, 1.19; 95% CI, 0.69 to 2.04).

New Kidney Scars

DMSA data at both baseline and 24 months were available for 201 participants (83.7% of those with complete follow-up). At baseline, before any UTI, congenital kidney defects were present in 83 infants, 43 in the prophylaxis group and 40 in the

Table 1. Clinical and Demographic Characteristics of Enrolled Infants at Baseline.*

| Characteristic | Prophylaxis Group (N=146) | Untreated Group (N=146) | Total (N=292) |
|---|------------------------------|----------------------------|-------------------|
| Male sex — no. (%) | 110 (75.3) | 117 (80.1) | 227 (77.7) |
| White race — no. (%) | 140 (95.9) | 141 (96.6) | 281 (96.2) |
| Median age (IQR) — mo | 3.4 (2.4–4.1) | 3.4 (2.3–4.1) | 3.4 (2.4–4.1) |
| Coexisting condition at screening — no. (%)† | 11 (7.5) | 9 (6.2) | 20 (6.8) |
| Parental consanguinity — no./total no. (%) | 6/141 (4.3) | 4/143 (2.8) | 10/284 (3.5) |
| Previous antibiotic prophylaxis — no. (%)‡ | 69 (47.3) | 81 (55.5) | 150 (51.4) |
| Phimosis in male infants — no./total no. (%)§ | 20/110 (18.2) | 31/117 (26.5) | 51/227 (22.5) |
| Abnormality on prenatal ultrasonography — no./total no. (%) | 107/141 (75.9) | 111/139 (79.9) | 218/280 (77.9) |
| Hydronephrosis on prenatal ultrasonography — no./total no. (%) | 95/141 (67.4) | 105/139 (75.5) | 200/280 (71.4) |
| Grade of vesicoureteral reflux — no. (%)¶ | | | |
| III | 29 (19.9) | 28 (19.2) | 57 (19.5) |
| IV | 60 (41.1) | 59 (40.4) | 119 (40.8) |
| V | 57 (39.0) | 59 (40.4) | 116 (39.7) |
| Bilateral vesicoureteral reflux — no. (%)¶ | 65 (44.5) | 76 (52.1) | 141 (48.3) |
| Split function on DMSA scan — no. (%) | | | |
| Absent: 0 to 10% | 13 (8.9) | 11 (7.5) | 24 (8.2) |
| Reduced: >10 to <45% | 72 (49.3) | 76 (52.1) | 148 (50.7) |
| Normal: ≥45% | 61 (41.8) | 59 (40.4) | 120 (41.1) |
| Overall DMSA abnormalities — no. (%) | 80 (54.8) | 74 (50.7) | 154 (52.7) |
| Bilateral overall DMSA abnormalities — no. (%) | 17 (11.6) | 15 (10.3) | 32 (11.0) |
| Local defects on DMSA scan — no. (%)** | 43 (29.5) | 40 (27.4) | 83 (28.4) |
| Bilateral local defects on DMSA scan — no. (%) | 5 (3.4) | 7 (4.8) | 12 (4.1) |
| Solitary kidney — no. (%) | 2 (1.4) | 8 (5.5) | 10 (3.4) |
| Hyperechogenicity in one kidney on baseline ultrasonography — no. (%) | 24 (16.4) | 22 (15.1) | 46 (15.8) |
| Pelvic dilatation ≥5 mm on baseline ultrasonography — no. (%) | 108 (74.0) | 99 (67.8) | 207 (70.9) |
| Bilateral pelvic dilatation ≥5 mm on baseline ultrasonography — no. (%) | 41 (28.1) | 33 (22.6) | 74 (25.3) |
| Ureteric dilatation on baseline ultrasonography — no. (%) | 77 (52.7) | 64 (43.8) | 141 (48.3) |
| Bilateral ureteric dilatation on baseline ultrasonography — no. (%) | 25 (17.1) | 18 (12.3) | 43 (14.7) |
| Bladder-wall irregularity on baseline ultrasonography — no. (%) | 12 (8.2) | 8 (5.5) | 20 (6.8) |
| Systolic blood pressure >90th percentile — no./total no. (%) | 7/126 (5.6) | 8/125 (6.4) | 15/251 (6.0) |
| Diastolic blood pressure >90th percentile — no./total no. (%) | 27/123 (22.0) | 29/122 (23.8) | 56/245 (22.9) |
| Median estimated GFR (IQR) — ml/min/1.73 m ² †† | 81.3 (59.1–109.9) | 83.2 (62.1–111.2) | 82.6 (61.0–110.6) |

* Participants in the prophylaxis group were assigned to receive continuous antibiotic prophylaxis for 24 months. Participants in the untreated group were assigned to receive no prophylaxis. DMSA denotes dimercaptosuccinic acid, GFR glomerular filtration rate, and IQR interquartile range.

† Coexisting conditions at screening were defined as separate medical conditions, other than vesicoureteral reflux, that were simultaneously present in the enrolled participants (syndromic features, intrauterine growth retardation, cardiac defects, gastrointestinal defects, genital abnormalities, hematologic disorders, lung disease, endocrinopathies, and maternal diabetes).

‡ Previous antibiotic prophylaxis was defined as the use of antibiotic prophylaxis before enrollment.

§ Phimosis was defined as the inability to retract the foreskin with bulging or ballooning during urination.

¶ This characteristic was assessed by voiding cystourethrography in 283 participants and by voiding ultrasonography in 9 participants.

|| Overall DMSA abnormalities were defined as the presence of local defects, diffuse defects, or both on a DMSA scan.

** The number of local defects ranged from one to three per participant.

†† The estimated glomerular filtration rate (GFR) was calculated according to the 2009 Schwartz formula.¹⁸

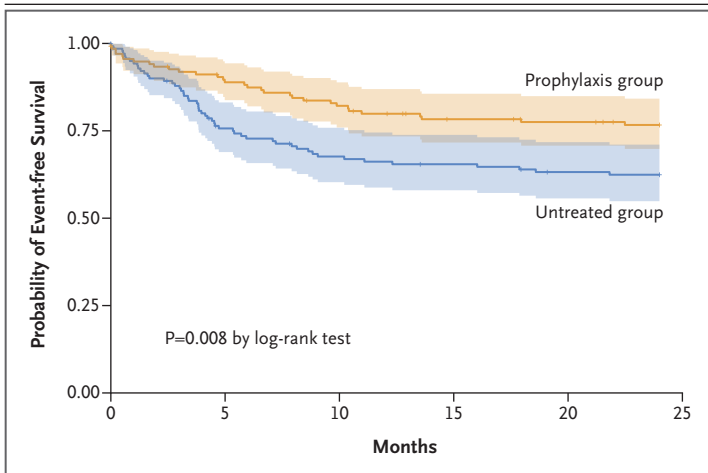


Figure 1. Urinary Tract Infection (UTI)-free Survival during the 24-Month Trial.

Participants in the prophylaxis group were assigned to receive continuous antibiotic prophylaxis for 24 months. Participants in the untreated group were assigned to receive no prophylaxis. The shaded areas represent 95% pointwise confidence intervals. Confidence intervals were not adjusted for multiplicity and should not be used to infer definitive treatment effects.

untreated group (Table 1). At 24 months, new kidney defects were identified in 21 participants in the prophylaxis group and 17 participants in the untreated group (rate ratio, 1.22; 95% CI, 0.69 to 2.18). The number of new lesions ranged from one to five per child. The change in the number of focal defects from baseline to 24 months was similar in the two groups in our sample (Fig. S4).

The number of new lesions was independent of the occurrence of UTIs during the trial period. New defects were identified in 27 of 144 participants (18.8%) who had no UTI and in 11 of 57 (19%) who had at least one UTI (rate ratio, 0.97; 95% CI, 0.52 to 1.83). Participants with kidney defects at baseline were not at greater risk for UTIs during the 24-month follow-up in our sample. These results were confirmed in the blinded evaluation of 108 participants with centrally available images (Fig. S5).

Estimated GFR

Data on the estimated GFR at both baseline and 24 months were available for 228 participants (93.8% of those with complete follow-up). The estimated GFR was similar in the two groups at baseline (Table 1) and at 24 months (mean, 112.3 ml per minute per 1.73 m² in the prophylaxis

group and 109.5 ml per minute per 1.73 m² in the untreated group; mean difference, 2.8 ml per minute per 1.73 m²; 95% CI, -4.8 to 10.3). Serum creatinine values at 24 months were also similar in the two groups (228 participants; mean, 0.37 in the prophylaxis group and 0.37 in the untreated group; mean difference, 0.00; 95% CI, -0.04 to 0.04). The estimated GFR at 24 months was similar in participants with a UTI and those without a UTI (mean, 105.8 ml per minute per 1.73 m² and 112.8 ml per minute per 1.73 m², respectively; mean difference, -7.0 ml per minute per 1.73 m²; 95% CI, -18.0 to 1.0).

UTI Isolates and Antibiotic Resistance

Isolates differed according to trial group, with *E. coli*, klebsiella species, and proteus species more commonly found in untreated participants, whereas all pseudomonas infections and an increased percentage of non-*E. coli* isolates were observed in participants who received continuous antibiotic prophylaxis (Table 2). Resistance to at least two first-line antibiotics (including amoxicillin, amoxicillin-clavulanate, and second- or third-generation cephalosporin) was present in 16 of 31 isolates (52%) in the prophylaxis group and 9 of 52 isolates (17%) in the untreated group, with a rate ratio of 2.98 (95% CI, 1.50 to 5.92) (Table S6).

Serious Adverse Events

Serious adverse events were reported in 9 of 146 participants (6.2%) in the prophylaxis group and 6 of 146 participants (4.1%) in the untreated group ($P=0.43$). No events of special interest were reported. Table 3 summarizes all serious adverse events that occurred during the trial, according to trial group.

REPRESENTATIVENESS OF THE TRIAL POPULATION

Our population was representative of infants with high-grade vesicoureteral reflux with associated kidney hypodysplasia and no previous UTI, with the expected male-to-female ratio. The percentage of non-White participants was small (3.8%), owing both to the pooled European population and the lower incidence of vesicoureteral reflux among Black persons than among non-Black persons. The results may not be applicable to children who receive a diagnosis of vesicoureteral reflux after a first UTI or to older female children (Table S7).

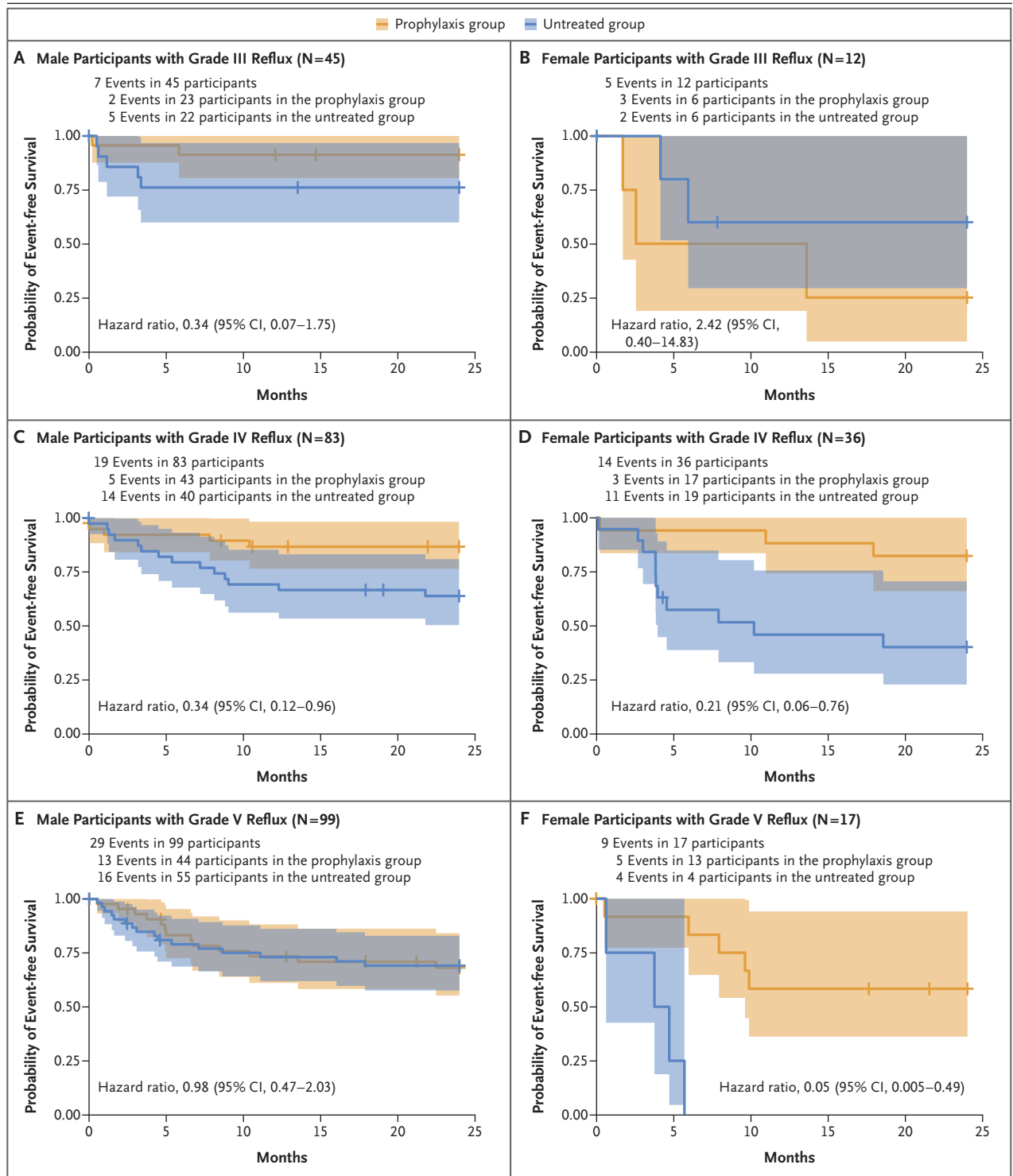


Figure 2. Subgroup Analysis According to Participant Sex and Grade of Vesicoureteral Reflux.

Shown is the probability of survival free from a first UTI. Shaded areas represent 95% pointwise confidence intervals. Confidence intervals were not adjusted for multiplicity and should not be used to infer definitive treatment effects.

Table 2. Urinary Tract Infection (UTI) Isolates.

| Isolate | Prophylaxis Group | Untreated Group |
|---|-------------------|-----------------|
| | number (percent) | |
| Total | 31 (100) | 52 (100) |
| <i>Candida albicans</i> | 1 (3) | 0 |
| Citrobacter species | 1 (3) | 1 (2) |
| <i>Escherichia coli</i> | 13 (42) | 29 (56) |
| <i>Enterobacter cloacae</i> | 2 (6) | 1 (2) |
| <i>Enterococcus faecalis</i> or <i>E. faecium</i> | 2 (6) | 2 (4) |
| Klebsiella species | 5 (16) | 13 (25) |
| <i>Morganella morganii</i> | 0 | 1 (2) |
| Proteus species | 0 | 4 (8) |
| Pseudomonas species | 6 (19) | 0 |
| Undetermined | 1 (3) | 1 (2) |

DISCUSSION

In this multicenter, randomized, controlled trial, we assessed and quantified the efficacy of continuous antibiotic prophylaxis administered before the occurrence of any UTI in infants with grade III, IV, or V vesicoureteral reflux. The incidence of a first symptomatic UTI was lower by 14.4 percentage points among participants who received continuous antibiotic prophylaxis for 24 months than among untreated participants. However, a UTI did not develop in 64.4% of the untreated participants; thus, the number needed to treat was seven children for 2 years to prevent one UTI. Continuous antibiotic prophylaxis was not associated with the occurrence of new kidney scars or with the estimated GFR at 24 months, but an increased occurrence of pseudomonas and other non-*E. coli* organisms as well as increased antibiotic resistance were observed. No substantial difference in the percentage of UTIs that resulted in hospitalization was noted.

Our trial cohort of young (median age, 3.4 months), predominantly male (77.7%) infants with grade III, IV, or V vesicoureteral reflux (grades that are often associated with innate kidney damage) and no previous UTI represents a population of children with congenital abnormalities of the kidney and urinary tract who are at increased risk for chronic kidney disease.¹ The cohort differs from the cohorts of earlier trials, which consisted

predominantly of older female children who had already had a UTI, with low-grade or absent vesicoureteral reflux, normal kidneys, and a favorable long-term outcome.

In the Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts (PRIVENT) trial involving 576 children under the age of 18 years who had had a previous UTI, the incidence of UTI recurrence was lower by 6 percentage points among those who received continuous antibiotic prophylaxis than among those who received placebo. However, 41% of the children in that trial who underwent urinary tract imaging had no vesicoureteral reflux.²¹ The Swedish Reflux Trial, in which 203 children 1 year of age with grade III or IV vesicoureteral reflux were randomly assigned to one of three groups (continuous antibiotic prophylaxis, endoscopic reflux correction, or clinical observation), showed lower incidences of UTI recurrence and kidney damage among girls receiving continuous antibiotic prophylaxis, with no differences in boys.²² The RIVUR trial⁷ evaluated the efficacy of trimethoprim-sulfamethoxazole in 607 children (92% female) 2 to 72 months of age with grade I to IV vesicoureteral reflux (92% with grade I, II, or III reflux) and normal kidneys, after a first or second UTI. The risk of UTI recurrence was lower by 11.9 percentage points in the prophylaxis group than in the placebo group, and the number needed to treat was 8 children for 2 years to prevent one UTI (a finding similar to that in our trial).

Our results show a significant effect of continuous antibiotic prophylaxis in preventing the occurrence of a first UTI, but no substantial differences were observed in the appearance of new scar formation, the estimated GFR at 24 months, or hospitalizations for UTIs. These findings support the results of previous trials and a meta-analysis of seven trials involving 1076 children with vesicoureteral reflux,² in which continuous antibiotic prophylaxis did not prevent kidney scarring in otherwise healthy children. Furthermore, in the current trial, the occurrence of new kidney defects was not associated with the presence or absence of UTIs.

The small but significant effect of continuous antibiotic prophylaxis in preventing UTI, with no evident effect on kidney scarring in the sample enrolled, must be weighed against the develop-

ment of antibiotic resistance^{4,11} and change in the developmental trajectory of eubiotic gut microbiota.^{13,14} In our trial, UTIs in participants in the prophylaxis group were associated with a greater number of non-*E. coli* isolates, including six infections with pseudomonas species, and increased antibiotic resistance. The increased resistance of bacterial isolates to antibiotics in the prophylaxis group probably reflects the selection of resistant strains. This occurrence should not be underestimated, in light of the major health concerns associated with the emergence of multidrug-resistant bacteria.²³⁻²⁵

Our results indicate that only one third of untreated infants with grade III, IV, or V vesicoureteral reflux will have a UTI during their first 2 years of life. The 53 female participants with grade IV or V reflux showed a benefit from continuous antibiotic prophylaxis, in accordance with the results of the Swedish Reflux Trial,²² whereas in the largest subgroup, the 99 male participants with grade V reflux, continuous antibiotic prophylaxis was not associated with any relevant benefit. For these reasons, we believe that the routine use of continuous antibiotic prophylaxis is not justified and should be considered only in female patients with grade IV or V vesicoureteral reflux or to prevent reinfections that may occur after a first UTI.

In our trial cohort, all the infants had congenital abnormalities of the kidney and urinary tract, as shown by prenatal or postnatal ultrasonography. In the absence of symptomatic UTI, our data cast doubt on the need for invasive procedures for the detection of vesicoureteral reflux, particularly voiding cystourethrography, when the result may not influence subsequent management. These findings suggest that further imaging should be reserved to rule out posterior urethral valves or ureterocele.

Our trial has several limitations. One is its open-label design, although the unequivocal and well-defined primary outcome may indicate a minimum of investigator or parent bias and expectations affecting results. The inclusion of participants from different European countries with different resistance patterns of *E. coli*²⁶ precluded the universal designation of a single antibiotic for UTI prophylaxis. Moreover, only a subset of DMSA images were available for central reading. More than 95% of our participants were White; that

Table 3. Serious Adverse Events in the Intention-to-Treat Population.

| Serious Adverse Event | Prophylaxis Group (N=146) | Untreated Group (N=146) |
|--|---------------------------|-------------------------|
| Total | 9 | 6 |
| Bronchiolitis* | 0 | 3 |
| Gastroenteritis* | 1 | 2 |
| Diarrhea* | 2 | 0 |
| Sepsis* | 1 | 0 |
| Pneumonia* | 1 | 0 |
| Fever* | 1 | 0 |
| Febrile seizure* | 1 | 0 |
| Sudden infant death syndrome | 1 | 0 |
| Cardiac surgery* | 0 | 1 |
| Implantation of prosthetic eye socket* | 1 | 0 |

* The event was considered to be serious because it resulted in hospitalization or prolonged an existing hospitalization.

fact may affect applicability to infants of other racial backgrounds. Finally, our results cannot be generalized to children with previous UTI, who were excluded from the trial.

The strengths of the trial include a large, multicenter, diverse population of participants with similar characteristics in both groups. The trial retention rate was high, with low nonadherence and dropout rates. Furthermore, our trial succeeded in addressing the efficacy of continuous antibiotic prophylaxis as a therapeutic strategy in a real-life scenario, in which the antibiotic for continuous antibiotic prophylaxis was selected by physicians according to local patterns of bacterial resistance, thus providing results that we speculate can be generalized to all children with grade III, IV, or V vesicoureteral reflux.

Although our trial showed a numerical benefit of primary continuous antibiotic prophylaxis in young infants with vesicoureteral reflux without preceding UTI, the results are of doubtful clinical benefit and we believe do not support the routine use of continuous antibiotic prophylaxis in this population. A UTI did not develop in almost two thirds of the untreated participants, and the number needed to treat to prevent a UTI was 7, with a small difference in primary-outcome events; no apparent difference in kidney scarring, kidney function, or hospitalization for UTIs; and unfavorable effects on the spectrum of causative organisms and their resistance patterns.

In our trial, we found a small but significant benefit of primary continuous antibiotic prophylaxis in preventing a first UTI in young infants with vesicoureteral reflux and without preceding UTI.

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APPENDIX

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REFERENCES

- Hewitt I, Montini G. Vesicoureteral reflux: is it important to find? *Pediatr Nephrol* 2021;36:1011-7.
- Hewitt IK, Pennesi M, Morello W, Ronfani L, Montini G. Antibiotic prophylaxis for urinary tract infection-related renal scarring: a systematic review. *Pediatrics* 2017;139(5):e20163145.
- Garin EH. Primary vesicoureteral reflux: what have we learnt from the recently published randomized, controlled trials? *Pediatr Nephrol* 2019;34:1513-9.
- Tullus K. Vesicoureteric reflux in children. *Lancet* 2015;385:371-9.
- Hajiyev P, Burgu B. Contemporary management of vesicoureteral reflux. *Eur Urol Focus* 2017;3:181-8.
- Montini G, Hewitt I. Urinary tract infections: to prophylaxis or not to prophylaxis? *Pediatr Nephrol* 2009;24:1605-9.
- The RIVUR Trial Investigators. Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med* 2014; 370:2367-76.
- Williams G, Craig JC. Long-term antibiotics for preventing recurrent urinary

- tract infection in children. *Cochrane Database Syst Rev* 2019;4:CD001534.
9. de Bessa J Jr, de Carvalho Mrad FC, Mendes EF, et al. Antibiotic prophylaxis for prevention of febrile urinary tract infections in children with vesicoureteral reflux: a meta-analysis of randomized, controlled trials comparing dilated to nondilated vesicoureteral reflux. *J Urol* 2015;193: Suppl:1772-7.
 10. Hewitt I, Dall'Amico R, Montini G. Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med* 2014;371:1071.
 11. Selekmán RE, Shapiro DJ, Boscardin J, et al. Uropathogen resistance and antibiotic prophylaxis: a meta-analysis. *Pediatrics* 2018;142(1):e20180119.
 12. Morello W, La Scola C, Alberici I, Montini G. Acute pyelonephritis in children. *Pediatr Nephrol* 2016;31:1253-65.
 13. Bokulich NA, Chung J, Battaglia T, et al. Antibiotics, birth mode, and diet shape microbiome maturation during early life. *Sci Transl Med* 2016;8(343):343ra82.
 14. Gibson MK, Crofts TS, Dantas G. Antibiotics and the developing infant gut microbiota and resistome. *Curr Opin Microbiol* 2015;27:51-6.
 15. Morello W, D'Amico F, Serafinelli J, et al. Low-dose antibiotic prophylaxis induces rapid modifications of the gut microbiota in infants with vesicoureteral reflux. *Front Pediatr* 2021;9:674716.
 16. The ESCAPE Trial Group. Strict blood-pressure control and progression of renal failure in children. *N Engl J Med* 2009;361:1639-50.
 17. Ntoulia A, Aguirre Pascual E, Back SJ, et al. Contrast-enhanced voiding urosonography. 1. Vesicoureteral reflux evaluation. *Pediatr Radiol* 2021;51:2351-67.
 18. Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009;20:629-37.
 19. Finkelstein JB, Rague JT, Chow J, et al. Accuracy of ultrasound in identifying renal scarring as compared to DMSA scan. *Urology* 2020;138:134-7.
 20. Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, 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. *Pediatrics* 2011;128:595-610.
 21. Craig JC, Simpson JM, Williams GJ, et al. Antibiotic prophylaxis and recurrent urinary tract infection in children. *N Engl J Med* 2009;361:1748-59.
 22. Brandström P, Jodal U, Sillén U, Hansson S. The Swedish reflux trial: review of a randomized, controlled trial in children with dilating vesicoureteral reflux. *J Pediatr Urol* 2011;7:594-600.
 23. Arias CA, Murray BE. Antibiotic-resistant bugs in the 21st century — a clinical super-challenge. *N Engl J Med* 2009;360:439-43.
 24. Kadri SS, Boucher HW. U.S. efforts to curb antibiotic resistance — are we saving lives? *N Engl J Med* 2020;383:806-8.
 25. Branswell H. WHO releases list of world's most dangerous superbugs. Boston: STAT, February 27, 2017 (<https://www.statnews.com/2017/02/27/who-list-bacteria-antibiotic-resistance/>).
 26. Alberici I, Bayazit AK, Drozd D, et al. Pathogens causing urinary tract infections in infants: a European overview by the ESCAPE study group. *Eur J Pediatr* 2015;174:783-90.

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