Short Course Therapy for Urinary Tract Infections in Children: The SCOUT Study

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Background

- Urinary tract infections (UTI) are one of the most common bacterial infections of childhood
- The American Academy of Pediatrics recommends antimicrobial therapy for 7 to 14 days; most physicians routinely prescribe at least 10 days of therapy
- Prior observational studies suggest that courses shorter than 10 days might be effective

Objective

- To determine if 5 days of therapy (short course) results in a similar failure rate as 10 days (standard course) in children who are clinically improved by day 5 of therapy

Methods

Study design and population: Randomized, double-blind, placebo-controlled non-inferiority clinical trial of children aged 2 months to 10 years diagnosed with UTI at two centers. Children treated with 1 of 5 antibiotics (trimethoprim-sulfamethoxazole, amoxicillin-clavulanate, cefixime, cefdinir or cephalexin) and who experienced clinical improvement by day 5 of therapy were eligible. Children were stratified by presence or absence of fever at presentation, antibiotic, and study site. Full study description at clinicaltrials.gov.

Exclusion criteria:

- >1 uropathogen cultured (>10,000 CFU/mL collected via catheter or >50,000 collected via clean void)
- Hospitalization with bacteremia, urosepsis, or in the ICU
- Resistance to the initially prescribed antibiotic
- Known anatomic abnormality of the genitourinary tract
- History of UTI within 30 days

Study Schedule: Children were screened and recruited by phone on day 2-5, followed by an enrollment visit on day 2-6, and a test of cure (ToC) visit day 11-14. A symptom assessment, clinical evaluation, pain assessment, and stool sample collection were carried out at each visit.

Study definitions:

- Day 1: Initiation of antimicrobial treatment
- Urinary Tract Infection: Culture proven infection with a single uropathogen (≥50,000 CFU/mL if catheterized OR ≥100,000 CFU/mL if clean void) AND pyuria (≥10 WBC/mm^3 [uncentrifuged] OR ≥5 WBC/hpf [centrifuged] OR leukocyte esterase >trace on dipstick) AND the presence of at least one of the following symptoms:
  - Fever (any age)
  - Dysuria (any age)
  - Suprapubic, abdominal, or flank pain or tenderness (children >2 years of age)
  - Urinary urgency, frequency, or hesitancy (children >2 years of age)
  - Poor feeding or vomiting (children >2 months to 2 years of age)

Primary outcome: Comparison of efficacy, based on symptomatic UTI assessed up to or at the ToC visit, between short course and standard course therapies.

Secondary outcomes: Comparison between arms of number of children with recurrent UTI, colonization with antimicrobial resistant *Escherichia coli* or *Klebsiella pneumoniae*, asymptomatic bacteriuria, or clinical symptoms.

Sample size and analysis: Sample estimates and power calculations were based on a clinically acceptable interval of equivalence of 5%, with an expected success rate of 95% for the standard course arm and 90% for the short course arm. Primary analysis was a non-inferiority test comparing the proportion of children with symptomatic UTI at the ToC visit between treatment arms to evaluate whether the difference was within the 5% equivalence interval. This test was conducted by calculating the one-sided 95% upper confidence limit for the difference in symptomatic UTI (treatment failure) rates between the short course and standard course therapies.

Results

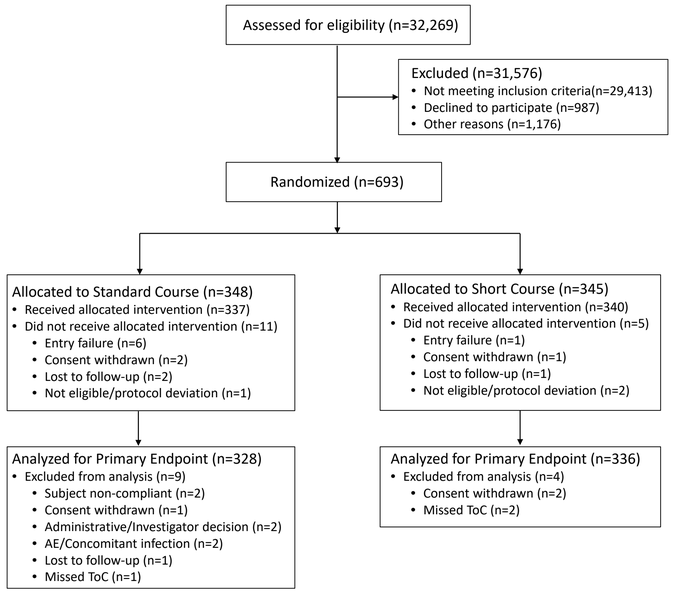

Figure 1. Consort Diagram

Table 1. Selected Demographic Characteristics of Children According to Treatment Group

Characteristic at entry	Treatment Group	
	Standard Course N=328 No(%)	Short Course N=336 No(%)
Age Group		
2 month – 35 months	95 (29.0)	89 (26.5)
3 – 6 years	148 (45.1)	177 (52.7)
7 - 10 years	85 (25.9)	70 (20.8)
Sex		
Female	316 (96.3)	323 (96.1)
Male	12 (3.7)	13 (3.9)
Race		
Black/African American	73 (22.3)	83 (24.7)
Multi-Racial	23 (7.0)	25 (7.4)
White	217 (66.2)	210 (62.5)
Other	14 (4.3)	18 (5.4)
Unknown	1 (0.3)	0 (0.0)
Hispanic		
Yes	33 (10.1)	27 (8.0)
No	295 (89.9)	309 (92.0)
Febrile at Presentation		
Yes	122 (37.2)	128 (38.1)
No	206 (62.8)	208 (61.9)
Medication		
Amoxicillin-Clavulanate	4 (1.2)	2 (0.6)
Cefdinir	183 (55.8)	185 (55.1)
Cefixime	2 (0.6)	1 (0.3)
Cephalexin	103 (31.4)	112 (33.3)
TMP-SMX	36 (11.0)	36 (10.7)
Study Site		
CHOP	143 (43.6)	152 (45.2)
PITT	185 (56.4)	184 (54.8)

Table 2. Primary Endpoint
Symptomatic UTI: Clinical Failure Rates Prior to or at the TOC Visit, According to Treatment Group

Measure	Treatment Group		
	Standard Course N=328	**Short Course N=336**	**Difference of Proportion and One-sided 95% Confidence Limit**
Evaluable Subjects	328 (100%)	336 (100%)	
Treatment Failure	2 (0.6%)	14 (4.2%)	0.035 (0.016, 0.054)

Key Results

- A total of 693 children were randomized, 345 to short course and 348 to standard course. Median age was 4 years (IQR; 2-6), 652 (96.3%) were female and 255 (37%) were febrile. There were no statistically significant differences between treatment groups after randomization (Table 1).
- We found no significant differences between treatment groups in rates of adverse events, recurrent UTI, clinical symptoms related to UTI, or emergence of antimicrobial resistance.
- Children in the short course arm were more likely to have asymptomatic bacteriuria between days 10-14 (29/336 [8.6%] vs 11/328 [3.4%]).
- Treatment failure rate was 14/336 (4.2%) for the short course arm and 2/328 (0.6%) for the standard course arm (Table 2). The 95% upper CI limit for the difference was 0.054. Treatment failure was not related to age group, fever at presentation, antibiotic type, or study site.

Discussion

- In children aged 2 months to 10 years with UTI, both 5 days and 10 days of therapy resulted in high success rates. However, the 5 day course was inferior the 10 day course.
- With these treatment failure rates, approximately 28 children would need to be treated with an additional 5 days of antibiotics to prevent one treatment failure.
- The unique strength and novelty of this study is that it addressed the practical and significantly generalizable question of whether antibiotics can be discontinued once clinical improvement has been established, a potential paradigm shift from the traditional practice of completing an antibiotic course unrelated to whether symptoms have resolved.

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