Evaluating the benefits of antimicrobial prophylaxis to prevent urinary tract infections in children: a systematic review

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Abstract

Background: The recurrence rate for urinary tract infections in children is estimated at between 30% and 40%. The use of low doses of antibiotics as prophylaxis for recurrent urinary tract infections is common clinical practice. However, prolonged antimicrobial therapy has the potential to contribute to problems of bacterial resistance and antimicrobial side effects. The aim of this review was to systematically examine the available evidence for the effectiveness of this intervention.

Methods: We conducted a literature search of 3 electronic databases for the period 1966 to 1999. We also searched bibliographies from conference proceedings and contacted content experts to ensure completeness of our database. Each trial was evaluated on the basis of the following inclusion criteria: target population (children), intervention (antibiotic v. no antibiotic), outcome (number of urinary tract infections) and study design (randomized controlled trial). Quality was assessed for the studies that met these criteria.

Results: Most of the studies identified were case series and cohort studies. Only 6 randomized trials fulfilled the inclusion criteria. All were of low quality (median 2, range 0 to 2 [maximum quality score 5]). Three trials dealt with children who had anatomically normal urinary tracts, and three included children with neurogenic bladder. The rate of infections for patients with normal urinary tracts ranged from 0 to 4.0 per 10 patient-years for the treatment groups and from 4.0 to 16.7 for the control groups. The recurrence rates for patients with neurogenic bladders in 2 trials were 2.9 and 17.1 per 10 patient-years for the treatment groups and 1.5 and 33.0 for the control groups.

Interpretation: The available evidence for using antimicrobial prophylaxis to prevent urinary tract infection in children with normal urinary tracts or neurogenic bladder is of low quality. This suggests that the magnitude of any benefit should at best be questioned. The surprising lack of data for children with reflux is of concern. Well-designed trials are needed to optimize the use of antimicrobials in children with recurrent urinary tract infection.

Approximately 1% to 8% of children between 1 month and 11 years of age will experience at least one urinary tract infection.[1–3] In school-aged girls the recurrence rate for urinary tract infection within 1 year of the original infection has been estimated at 40%, whereas for boys it is slightly less, at 30%.[1,2] Renal scarring may occur in 5% to 10% of children after a febrile urinary tract infection in infancy. Because scarring is an important risk factor for subsequent hypertension, prevention of febrile infection is important.

The aim of prophylactic antimicrobial therapy is to provide levels of antimicrobial agents in the bladder sufficient to prevent bacterial multiplication should organisms ascend from the urethra into the bladder or upper urinary tract. Standard textbooks emphasize ensuring regular bladder- and bowel-emptying habits as a first measure in preventing recurrences.[4,5] Prophylaxis with antimicrobials is also mentioned as an effective prevention strategy, but guidelines for children with normal

Research

Recherche

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urinary tracts are not firm as to indication or effectiveness.[4–6] One pediatric nephrology textbook[5] emphasizes that prophylaxis is indicated for patients at high risk of renal scarring (patients with vesicoureteral reflux with dilatation of the upper urinary tract, and those who are prone to acute pyelonephritis) and suggests that recurrent cystitis is a questionable indication. The American Urological Association has recommended antimicrobial prophylaxis for children who have any documented reflux after a urinary tract infection.[4] These recommendations differ from recently published Swedish guidelines,[7] which did not recommend prophylaxis for lower grades of reflux but did recommend prophylaxis for 1 year in children with higher grades of reflux. Prophylaxis regimens for patients with neurogenic bladder are not clearly defined.

The risk of adverse events with prolonged antimicrobial therapy is between 8% and 10%, but most are not serious;[8] these include nausea, vomiting and skin reactions. However, the use of antimicrobials for prophylaxis raises the possibility of development of antimicrobial resistance in both enteric and oropharyngeal flora.[9,10] The aim of our review was to determine whether antimicrobial prophylaxis for recurrent urinary tract infection in children significantly decreases the frequency of such infections.

Methods

We searched 3 electronic databases: MEDLINE (January 1966 to April 1999), EMBASE (January 1980 to April 1999) and the Cochrane Library (fourth quarter, 1999). There was no language restriction. Bibliographies from relevant articles and standard textbooks,[5] as well as conference proceedings[11–13] on the management of urinary tract infections in children, were also searched by hand. Content experts in the field were contacted. The MEDLINE search strategy is shown in Appendix 1. The EMBASE strategy was translated from the MEDLINE strategy.

The population of interest consisted of boys and girls up to 18 years of age who had a history of recurrent urinary tract infection or who had had one symptomatic infection. Studies of covert or asymptomatic bacteriuria were not included. Underlying renal condition was classified into 3 categories: normal, presence of reflux or neurogenic bladder. Studies of patients whose urinary tract abnormality could not be characterized were not included in the analysis, because the generalizability of such findings would be limited. Interventions of interest were any type of antibiotic therapy for the purpose of preventing urinary tract infection (administered for a period of 3 months or longer) compared with placebo or "no treatment" or "non-antibiotic arm." Studies that included surgery of the urinary tract were excluded. Only randomized controlled trials were included in the final selection.

The outcome of interest was comparison of the number of urinary tract infections in children who received antibiotic prophylaxis with the number of such infections in those who received a placebo or a "non-antibiotic" treatment.

All trials identified in the search were screened. Trials dealing with adults were excluded. Reviews were excluded, but the bibliographies from such articles were scanned for relevant trials. The remaining trials were evaluated for inclusion on the basis of 4 criteria: target population (age up to 18 years); intervention (comparison of an antimicrobial agent with a placebo or "no treatment" or "non-antimicrobial agent"); outcome (presence of urinary tract infection as defined by standard criteria); and study design (randomized controlled trial).

The quality of the reports was assessed by means of the scale developed by Jadad and associates.[14] Allocation concealment (knowledge of treatment assignment by people running the trial) was also assessed and rated as adequate, inadequate or unclear.[15] Quality was assessed by one person (N.L.S.).

Two of the authors (N.L.S. and B.P.) used a standard data abstraction form to abstract data from the 6 studies that met all of our criteria. In the case of crossover studies, only data from the first parallel arm of the study were abstracted, if possible.

We assumed that the frequency of urinary tract infections, our primary outcome, followed a Poisson distribution. The variance for each rate ratio was calculated according to Hasselblad and McCrory.[16] The rate ratio was considered our estimate of treatment effectiveness (which is presented along with 95% confidence intervals).

Results

From the searches of the electronic databases, 71 potential studies were identified. Fig. 1 illustrates the search strategy results.[17–47] One person (N.L.S.) screened the abstracts of the articles and excluded reviews, trials involving adults and trials dealing with prolonged treatment of acute infections. One trial published in Switzerland was not retrieved because it dealt with immunomodulation and appeared to include both adults and children.[48] In all, 26 potentially relevant trials were retrieved from the searches of the electronic databases.

Hand-searching of review articles and conference proceedings resulted in a further 5 trials, which were also reviewed for consideration. Thus, 31 trials or studies were determined potentially relevant.

Two of the authors (N.L.S. and D.M.) examined the 31 trials for inclusion in the systematic review using a standard relevance form based on the inclusion criteria. There was complete agreement about eligibility for 23 of the trials. Disagreements related to study design for 7 publications and to inclusion criteria for 1 study. These disagreements were resolved by consensus.

Of the 31 potentially relevant studies, 6 fulfilled the inclusion criteria.[42–47] These studies are described in Table 1, and their shortcomings are presented in Table 2. The trials were small, with a mean of 28 (range 10 to 56) children per trial. The quality scores of all 6 trials were low (median 2, range 0 to 2, on a scale of 0 to 5, where a score of 3 or above indicates sufficient quality). Allocation concealment was unclear for all 6 trials.

Data on children with normal urinary tracts were available from 3 of the studies.[42–44] The children with normal urinary tracts in the trial by Ray and colleagues[46] could not be included in our analysis because of the study design, whereby patients were switched from one treatment group to another during the trial.[46] The urinary tract infection rates are shown in Table 3. There were substantial differ-

ences in the rate of urinary tract infection reported in the three trials. The rate of urinary tract infection ranged from 0 to 4.0 per 10 patient-years for the groups that received prophylaxis and from 4.0 to 16.7 per 10 patient-years for the control groups.

The study by Smellie and colleagues[42] did not define urinary tract infection, and therefore it is unknown whether both asymptomatic and symptomatic episodes were included. This study had statistically significant results, but the 95% confidence intervals were large. In the study by Lohr and colleagues,[43] data on symptomatic episodes during the first parallel arm of the study could not be derived from the data presented, so the combined data set, which used only symptomatic episodes, was used. The study by Lettgen[44] compared an oral immunogen with nitrofurantoin and reported approximately 4 recurrences per 10 patient-years, at the same rate in the two treatment groups (rate ratio of 1.0, 95% confidence interval 0.3–4.0). Smellie and colleagues[42] and Lettgen[44] reported the number of children with urinary tract infections, whereas Lohr and colleagues[43] reported the number of episodes per patient. The heterogeneity of outcome measures and the lack of parallel data from the crossover study by Lohr and colleagues[43] prevented us from combining data in a meaningful way for the purpose of a meta-analysis.

Three trials dealt entirely or partially with children who had neurogenic bladders.[45–47] The results of two of these trials[45,47] are shown in Table 3. The trial by Ray and colleagues[46] shifted patients from one treatment group to another, a process that resulted in an unclear data set that could not be used for analysis. Data for symptomatic urinary tract infection in the first parallel arm of the study by Schlager and colleagues[45] were available, but the data from the first parallel arm of the trial by Johnson and colleagues[47] could not be extracted; hence the entire data set was used. In the 2 randomized trials involving patients with neurogenic bladder, the rates of urinary tract infection were 2.9 and 17.0 episodes of urinary tract infection per 10 patient-years for the groups who received prophylaxis and 1.5 and 33.0 for the control groups. The data were not combined because of the fundamental differences in study design and outcome.

In the trial by Ray and colleagues[46] children with vesicoureteral reflux were combined with children who had normal urinary tracts, which made an analysis of children with reflux impossible.

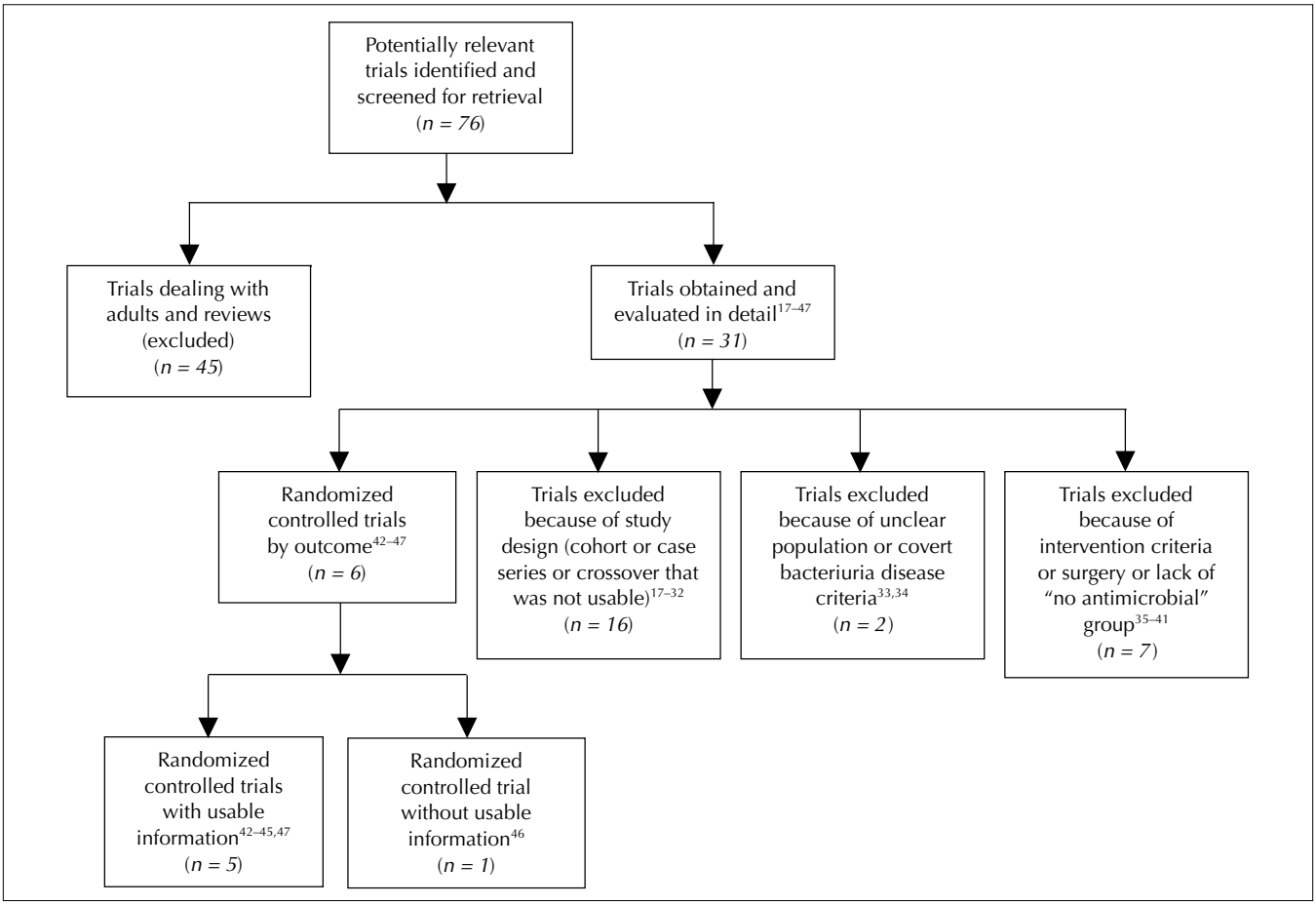

Fig. 1: Flow diagram outlining the results of literature search and review of studies retrieved. Of the trials excluded because of study design, Jodal and Winberg[22] was mainly a review article, but it did include some cohort data.

Interpretation

The goal of medical therapy for children with recurrent urinary tract infections is to prevent symptomatic episodes of infection and potentially minimize long-term sequelae. The American Academy of Pediatrics *Red Book*,[49] which is used by pediatricians and infectious disease specialists, indicates that the efficacy of prophylaxis for recurrent urinary infection has been established. Standard textbooks of pediatrics and nephrology have put forth similar views.[4,5] A recent publication on clinical evidence[50] summarized the issue by saying that routine prophylaxis may be warranted since it is not possible to identify children at high risk of renal damage from urinary tract infections. Given such endorsements, we expected to find fairly strong and widespread evidence to support these recommendations. However, we found only limited data, despite an extensive search of the literature.

Most of the studies were case series or cohort studies. Such observational studies are associated with substantial bias and are considered to represent the lowest quality of evidence, since the investigators are not blinded as to outcome.[51] These studies used historical data as the control arm and did not clearly distinguish episodes of cystitis from pyelonephritis. Interventions during antimicrobial therapy

Table 1: Trials of antibiotic prophylaxis for urinary tract infection (UTI) in children that met criteria for inclusion in systematic review

						Antimicrobial (treatment) arm			Control arm		
Author(s)	Year	Study design	UT status	QS	Criteria for UTI	Agent (and study duration)	No. of patients	No. of UTIs	Agent (and study duration)	No. of patients	No. of UTIs
Studies of children with normal urinary tract											
Lohr et al[43]*	1977	Cross-over	NUT	2	Symptomatic episodes only included	Nitrofurantoin (6 months)	18	0†	Placebo (6 months)	18	14†
Smellie et al[42]	1978	RCT	NUT	2	Not defined	Co-trimoxazole or nitrofurantoin (10 months)	25	0‡	No treatment (10 months)	22	11‡
Lettgen[44]§	1996	Cross-over	NUT	2	Clinical signs plus a positive urine culture (not defined)	Nitrofurantoin (6 months)	15	3‡	OM-89§ (6 months)	20	4‡
Studies of children with neurogenic bladder											
Ray et al[46]¶	1970	Cross-over	NB	0	Symptoms of infection in conjunction with "significant" bacteriuria	Sulfisoxazole (possibly 6 months, but exact duration unclear)	10	1.5**	Placebo (possibly 6 months, but exact duration unclear)	10	1**
Johnson et al[47]††	1994	Cross-over	NB	2	One or more of abdominal or flank pain, pyrexia or incontinence, as diagnosed by a physician at the time of the UTI	Nitrofurantoin (3 months)	56	4‡‡	Placebo (3 months)	56	2‡‡
Schlager et al[45]	1998	Cross-over	NB	2	Bacteriuria with fever, abdominal pain, change in continence or change in urine colour or odour	Nitrofurantoin (5 months)	7	5‡‡	Placebo (5 months)	8	11‡‡

Note: UT = urinary tract, QS = quality score (maximum value 5), NUT = normal urinary tract (no reflux or neurogenic bladder) as reported in the study, RCT = randomized controlled trial, NB = neurogenic bladder.

*The number of patients who were symptomatic during the first arm of the crossover study could not be determined from the data presented. Therefore, data from both arms were used for symptomatic episodes.

†Number of symptomatic bacteriuric episodes per patient.

‡Number of children with recurrent UTI.

§Data from first parallel arm of study was used for analysis. These patients received OM-89 orally, which is a lyophilized bacterial proteinic extract obtained from soluble components of alkalinized secretions of *Escherichia coli* marketed in Germany as Uro-Vaxom.

¶Only patients with neurogenic bladder were included in the analysis. The group that underwent treatment for symptomatic bacteriuria was included.

**Mean number of symptomatic episodes per 100-week period per patient.

††There were only 6 instances of clinical infection, but it could not be determined in which phase of the crossover trial they occurred. Therefore, combined results were used for analysis.

‡‡Number of symptomatic infections.

also included "correction of constipation" and "instruction in bowel and bladder control"; these measures left in question the attributable effect of the antimicrobial therapy, since constipation is a major risk factor for recurrence.[29–31] To overcome these difficulties, we limited our review to randomized trials. Of the 6 included trials, 5 had crossover designs. Although crossover studies are randomized, they suffer from carryover and sequence effects and hence have a greater chance than simple parallel-group trials of producing biased results.[52] The 6 studies that met our inclusion criteria were, at best, methodologically weak and, at worst, unusable.

Overall, the quality of the trials was poor, and the number of patients studied was small. In the only parallel-group randomized trial involving children with normal urinary tracts,[42] no blinding took place. The quality score for this trial was only 2 out of 5. That trial also included children who had had only one prior urinary tract infection, so the group was less generalizable to children with recurrent infections, and the study may have overestimated the beneficial effect of antibiotics.[42] Some evidence suggests that when

Table 2: Shortcomings of randomized controlled trials meeting inclusion criteria

Author(s)	Year	Shortcomings
Studies of children with normal urinary tract		
Lohr et al[43]	1977	Crossover trial (18 patients) without a "wash-out" period 1 of 18 patients had high-pressure reflux Data on symptomatic UTI not presented for parallel arms No attempt to control for other risk factors
Smellie et al[42]	1978	Not blinded, "placebo" group received no treatment Precise past history of UTI was not given UTI diagnostic criteria not stated
Lettgen[44]	1996	Crossover trial (15 patients) without a "wash-out" period Patients in "no-antibiotic" arm received oral proteinic extract of fractions of *Escherichia coli* Not known if protocol was blinded Endpoint was number of patients with UTI
Studies of children with neurogenic bladder		
Ray et al[46]	1970	Crossover trial (19 patients); blinding and randomization not maintained Random shifting of patients to different treatment arms depending on success of initial treatment Outcome measure was mean number of infections per 100-week period; data for parallel arms of trial could not be assessed
Johnson et al[47]	1994	Crossover trial (56 patients) without a "wash-out" period Data presented as "average percentage of infections per urine sample per patient" 6 instances of clinical infection reported for entire data set (4 in patients receiving nitrofurantoin and 2 in the placebo group)
Schlager et al[45]	1998	Crossover trial with 8 and 7 children in the initial parallel arms Data presented as total number of UTI

Table 3: UTI rates and rate ratios

	Prophylactic treatment			Control			
Trials	No. of patients	No. of UTI episodes (and no. of patient-months)	UTI rate per 10 patient-years (and 95% CI)	No. of patients	No. of UTI episodes (and no. of patient-months)	UTI rate per 10 patient-years (and 95% CI)	Rate ratio* (and 95% CI)
Studies of children with normal urinary tract							
Smellie et al[42]	25	0 (243)	0.0†	22	11 (220)	6.0 (3.4–10.7)	24.3 (3.2–187.5)
Lohr et al[43]	18	0 (108)	0.0†	18	14 (99)	16.7 (10.1–28.4)	30.6 (4.0–231.8)
Lettgen[44]	15	3 (90)	4.0 (1.6–10.1)	20	4 (120)	4.0 (1.4–11.4)	1.0 (0.3–4.0)
Studies of children with neurogenic bladder							
Schlager et al[45]	7	5 (35)	17.1 (7.4–39.5)	8	11 (40)	33.0 (18.5–58.8)	1.9 (0.7–5.3)
Johnson et al[47]	56	4 (168)	2.9 (1.1–7.2)	56	2 (168)	1.5 (0.4–4.9)	0.5 (0.1–2.3)

Note: CI = confidence interval.
*Rate ratio = treatment rate / control rate.
†For cases with zero-cell count, a correction for continuity factor of 0.5 was applied to both the numerator and the denominator to derive a UTI rate per 10 patient-years, and subsequently the rate ratio.

the quality of a study is poor, the effectiveness of a given strategy is likely to be exaggerated.[53] Therefore, we question the magnitude of benefit of antimicrobial prophylaxis in children with no underlying urinary tract abnormality.[15,53,54] In children with neurogenic bladder one trial showed benefit[45] but the other did not.[47] Given this conflicting evidence, confidence in this intervention is not robust.

The prevalence of vesicoureteral reflux among children with recurrent urinary tract infections ranges from 20% to 50%.[1,55] The natural history of this condition is resolution with age, and only 5% of adults have evidence of reflux.[56,57] Given the prevalence of antibiotic prophylaxis in this unique group, there is a surprising lack of data to support the intervention. This view is shared by the authors of a recently published review.[58] Since the aim of management is to minimize the risk of renal scarring due to pyelonephritis, the attributable benefits of prophylactic antibiotics and other measures should be quantified in groups with different risks. As a recent editorial[59] pointed out, changing attitudes toward antibiotics may make a placebo group acceptable in a study setting in children with reflux.[59]

Because the magnitude of benefit of prophylactic antimicrobials may be small and a potential for harboring resistant bacteria may exist, they should be used only after careful consideration and only after attempts have been made to correct conditions that predispose to urinary stasis (e.g., voiding dysfunction or constipation). Optimally, the practice should be re-evaluated in the setting of well-designed randomized trials focusing on groups with different risk stratifications.

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Appendix 1: MEDLINE search strategy

1. *Vesico-ureteral reflux*/
2. *Bladder, neurogenic*/
3. Exp *urinary tract infections*/
4. Exp *anti-infective agents, urinary*/or exp *antibiotics*/ or *antibiotic prophylaxis*/
5. tu.fs.
6. ((1 or 2) and 5) or (3 and 4)
7. Limit 6 to (*clinical trial* or *clinical trial, phase i* or *clinical trial, phase iii* or *clinical trial, phase iv* or *multicenter study* or *randomized controlled trial*)
8. Exp *clinical trials*/ or *multicenter studies*/ or *randomized controlled trials*/
9. 7 or (6 and 8)
10. 9 not exp *adult*/

Note: The search terms used are shown in italic type. Exp = explode, tu.fs. = retrieve every instance of the subheading therapeutic use no matter where it occurs.