Antibiotics and Cure Rates in Childhood Febrile Urinary Tract Infections in Clinical Trials: A Systematic Review and Meta-analysis

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Antibiotics and cure rates in childhood febrile urinary tract infections in clinical trials: a systematic review and meta-analysis

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Running title: Antibiotics and cure rates in childhood febrile urinary tract infections in clinical trials

ABSTRACT

Purpose: Urinary tract infections (UTIs) are common bacterial infections among children.

Objective: To systematically review the antimicrobials used for febrile urinary tract infections in pediatric clinical trials and meta-analyze the observed cure rates and reasons for treatment failure.

Materials and Methods: We searched Medline, Embase and Cochrane central databases between January 1, 1990, and November 24, 2016, combining MeSH and free-text terms for: "urinary tract infections", AND "therapeutics", AND "clinical trials" in children (age range 0–18 years). Two independent reviewers assessed study quality and performed data extraction. The major outcome measures were clinical and microbiological cure rates according to different antibiotics.

Results: We identified 2,762 published studies and included 30 clinical trials investigating 3913 cases of pediatric febrile urinary tract infections. Children with no underlying condition were the main population included in the trials (n=2,602; 66.5%). Cephalosporins were the most frequent antibiotics studied in trials (22/30, 73.3%). Only a few antibiotics active against resistant urinary tract infections have been tested in randomised clinical trials, mainly aminoglycosides. The average point cure rate of all investigational drugs was estimated to 95.3% [95% CI 93.5-96.9%]. Among 3,002 patients for whom cure and failure rates were reported, only 3.9% (3.9%; 118/3,002) were considered clinically to have treatment failure, while 135 (4.5%; 135/3,002) had microbiological failure.

Conclusions: We observed high treatment cure rates, regardless of the investigational drug chosen, the route of administration, duration and dosing. This suggests that future research should prioritise observational studies and clinical trials on children with multi-drug resistant infections.

Key points

- We observed high treatment cure rates for childhood urinary tract infections in clinical trials, regardless of the investigational drug used.
- Paediatric UTI trials excluded children with underlying disease or multi drug resistant pathogens.
- Future research should focus on observational or interventional studies of children with multi-drug resistant infections.

1. INTRODUCTION

Urinary tract infections (UTIs) are common among children, with an increased incidence in infants.[1] UTIs can be associated with acute complications, such as renal abscesses and urosepsis [2], as well as long-term renal scarring [3-5, 2]. The successful treatment of UTIs is complicated by the increasing prevalence of extended spectrum beta-lactamase (ESBL) carriage in children worldwide [6-9]. Currently, there are limited oral antibiotics available to treat ESBL UTIs [8, 10] and these antibiotics (such as fosfomycin) have not yet been adequately studied in children [11, 12]. The consequence of the inappropriate treatment of resistant UTIs may lead to high rates of hospital admission, long hospital stays, increased healthcare costs and mortality rates [13, 14].

We have recently demonstrated marked heterogeneity in study design and endpoints assessed in childhood febrile UTIs clinical trials (CTs) [15]. In the current review, our main aim was to: i) review the antimicrobials used for febrile UTIs treatment, in terms of route of administration, dosage and duration; ii) estimate cure rates with different antibiotic regimens, in children with susceptible or resistant UTIs, with or without underlying conditions; iii) identify the reasons for treatment failure.

2. METHODS

2.1 Search strategy and selection criteria.

This systematic review was conducted according to the PRISMA guidelines [16]. We searched Medline, Embase and Cochrane central databases between January 1, 1990, and November 24, 2016, combining MeSH and free-text terms for: “urinary tract infections”, AND “therapeutics”, AND “clinical trials” in children (age range 0–18 years).The full search strategy and PRISMA checklist are available in the Supplementary appendix. We included randomized CTs reporting on the clinical and/or microbiological efficacy of antibiotics or other type of antibacterial or anti-inflammatory agents in children presenting with acute febrile UTI. We excluded trials including any cases of uncomplicated UTI, cystitis, or lower UTI, in order to focus exclusively on febrile UTIs (presumed upper UTIs, pyelonephritis). The rationale for the latter was that we aimed to analyse antibiotics selection and dosing, as well as cure rates, which potentially differ significantly between febrile and afebrile UTIs (presumed lower UTIs, cystitis). Studies were also excluded if they included only: a) patients with underlying conditions (e. g. known major urinary tract abnormalities, immunodeficiency, diabetes, and spinal cord injury), b) long-term efficacy endpoints (> 1 month).

Two reviewers (KV and RB) independently extracted the following data according to pre-specified criteria: year of publication, study design, participants' characteristics (age, gender, medical history, and diagnosis), pathogen distribution, intervention protocols (drugs, route, dose, duration), cure and failure rates. Disagreements were resolved in discussion with a third reviewer (JB).

2.2 Statistical analysis

The definition of cure rates varied across included studies, assessing clinical and/or microbiological endpoints alone or both [15]. Cure could be assessed during any of the following timings: on antibiotic-therapy (OAT) and/or at the end of treatment (EOT) and/or after the EOT (often defined as the test of cure (TOC)), and/or during follow-up [15]. In this study, we extracted clinical and microbiological data separately. For most studies, the principal cure rates were either provided for OAT or EOT/TOC timings. In the studies where there were discrepancies between the rates for these timings, the lowest cure rates were used to estimate the average cure rates, providing more conservative estimates.

Data from both arms of each included trial were extracted and a meta-analysis was performed to estimate the average cure rate in paediatric CTs. A random-effect meta-analysis model was used to obtain an average estimate of the cure rate across studies. This model was selected to control for the inter-study variability effect in the meta-analysis of cure rates. The proportions obtained from each study were pooled using the Freeman-Tukey double arcsine transformation and generated forest plots [17, 18]. I^2 statistic was used to determine heterogeneity [19]. A P value < 0.05 was defined as the presence of statistical significance. Low, moderate, and high heterogeneity was defined to levels of I^2 values of 25%, 50%, and 75% respectively [19].We assessed the risk of bias using the Cochrane Collaboration's tool [20]. To further explore possibility reasons for heterogeneity, we carried out subgroup meta-analysis on the type of cure assessed (microbiological or clinical), timing for endpoints assessment (OAT and EOT/TOC), and drug class of the initial antibiotic therapy. In addition, we analysed cure rates for the intention-to-treat (ITT) populations and the per-protocol populations when data was available.

All statistical analyses were performed with R statistical package 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). A p-value <0.05 was considered statistically significant.

3. RESULTS

3.1 Trial selection description

We identified 2,762 published studies and 30 were included in the final analysis [21-50] (Figure 1 and Supplementary Table 1). Four trials (13.3%) were double-blinded [21, 23, 33, 49] and one (3.3%) was single-blinded [22], while 10 (33.3%) were multicentre trials [24, 26, 30, 31, 36-38, 41, 44, 45].

3.2 Population characteristics

A total of 3,913 children aged from 1 week to 18 years were included in the 30 CTs. The patient characteristics are reported in Table 1. Overall, 22.4% of the patients were male and 59.1% female while the gender distribution was not reported for 722 (18.5%) patients. Nine studies (30.0%) included children without any underlying conditions [42, 29, 40, 22, 36, 39, 43, 49, 50], while 17 studies (55.7%) included a mixed population of children with or without underlying conditions [21, 28, 27, 26, 23, 25, 30-33, 35, 37, 38, 41, 46, 47, 34]. Patients with no underlying conditions represented the main population included in paediatric clinical trials (n=2,602; 66.5%). A urinary tract-related underlying condition was the most common medical condition reported (71.8%; 903/1,258) (Table 1).

A total of 3,158 pathogens were reported in 25 studies [21-24, 26-32, 51, 33-38, 40-46], *E. coli* was the predominantly isolated pathogen in 2,822 (89.4%; 2,822/3,158) children with a febrile UTI. Non- *E. coli* identified pathogens represented 179 (5.7%) of isolates, while 157 (4.9%) isolates were not specified in the CTs (Table 1).

3.3 Antibiotic treatment

A total of 10 intravenous and 12 oral antibiotics were used in the paediatric febrile UTIs CTs. Table 2 shows the antibiotics used for febrile UTIs treatment. Penicillins, cephalosporins, and aminoglycosides were the most commonly used antibiotic classes.[22-26, 31, 37-40, 47-50, 30, 32, 36, 41, 27, 29, 33, 34, 42, 45, 46, 35, 43, 44] Cephalosporins were the most frequent antimicrobial class studied, with 12 different drugs being evaluated in 22 trials (73.3%), [22-26, 31, 37-40, 47-50, 30, 32, 36, 41, 44] while aminoglycosides and penicillins were assessed in 11 (36.7%)[27, 29, 31, 33, 34, 39, 40, 42, 43, 45, 46] and 6 (20.0%) [35, 37, 39, 42-44] studies, respectively (Table 2). There were only 3 antibiotics belonging to different antibiotic classes that were used for febrile UTIs treatment, mainly cotrimoxazole, which was used in 5 studies [22, 29, 30, 36, 41] (Table 2). Six supplemental drugs were prescribed in addition to antibiotics [21, 33, 42, 48-50] (Table 2). In terms of intravenous agents with potential activity against ESBL-producing bacteria, only isepamicin, netilmicin, amikacin and temocillin were prescribed for treatment. Only one oral agent potentially active against ESBL-producers (amoxicillin-clavulanic acid, though with limited activity) was tried in four trials as the initial antibiotic intervention [35, 37, 44, 43]. No carbapenem was used as an interventional drug in the included randomised CTs. The details of dosages prescribed for treatment are presented in Table 2. The length of treatment for each antibiotic varied, ranging from 1 day to 18 days (Table 2).

3.4 Risk of bias

The assessment of risk of bias is shown in Supplementary Table 1, Supplementary Figure 1 and Supplementary Figure 2. Supplementary Figure 1 shows the proportion of studies assessed as low, high or unclear risk of bias for each risk of bias indicator. Supplementary Figure 2 shows the risk of bias indicators for individual studies. The highest risk of bias was observed in the blinding of participants/personnel (27/30, 90.0%) [22-32, 34-48, 50] and other potential sources of bias (17/30, 56.7%) [21-23, 30, 32, 34, 36, 38-44, 47, 49, 50] . We observed lower risk of bias (18/30, 60.0%) in the amount of incomplete outcome data [22, 23, 25, 27-29, 31-36, 39, 43, 44, 46, 47, 50] and in the selective reporting of outcome data (19/30, 63.3%) [22, 23, 25, 27, 29-34, 36, 37, 40, 41, 43, 44, 47, 49, 50]. Bias was predominantly unclear in the concealment of allocations in participants in 60.0% (18/30) of studies [23, 24, 26, 27, 29, 31, 32, 34, 35, 40, 41, 43, 44, 46-50]. The risk of bias is presented in full detail in Supplementary Table 1.

3.5 Cure rates

In 30 included CTs, the clinical and/or microbiological cure rates were extractable in 24 studies [22, 23, 25, 27-41, 43, 44, 46, 47, 49, 50]. We divided 24 studies into 47 independent arms (Supplementary Table 1); in one study patients received the same antibiotic in both groups in different healthcare settings (inpatients versus outpatients) [40]. Overall, the cure rates varied from 80% to 100% with the average point cure rate estimate being 95.3% [95% CI 93.5-96.9%] (Figure 2), with a prediction interval of 82.8% - 100.0%. We observed high heterogeneity with an I^2 of 76.7% [95% CI: 69.2%-82.3%; between study standard error = 0.018] ($P<0.0001$). In order to explore the high heterogeneity, subgroup analyses were carried out. Subgroup analysis revealed heterogeneity was high when assessing clinical or microbiological cures, as well as when the cure rate was assessed during on-antibiotic therapy (OAT) or during the end of treatment (EOT) or the test of cure (TOC) (Table 3). This suggests that the type of cure assessed or the timing of the assessment may have been potential sources of heterogeneity. Nonetheless, heterogeneity was low when using aminoglycosides (I^2 = 0.0%) as the initial interventional drug, in contrast to studies assessing cephalosporins (I^2 = 70.9%) (Table 3). Similar results were observed with aminoglycosides in all subgroups, while low heterogeneity was observed for studies assessing clinical cure when cephalosporins were used (Table 3). Subgroup analysis regarding other interventional drugs (penicillins, sulphonamides, or combinations) have to be interpreted cautiously due to the low number of studies in each subgroup. Finally, three studies [27, 31, 36] assessed the cure in the ITT population and 16 [25, 27-30, 33, 35-38, 40, 41, 46, 47, 49, 50] in the per-protocol population. The average estimate for clinical and microbiological cure rates in the ITT population were 96.5% [91.1-99.6%, I^2 = 87.3%, p=0] and 97.3% [95.7-98.6%, I^2 = 0%, p=0.784], respectively; while they were 95.7% [93.7-97.3%, I^2 = 54.4%, p=0.006] and 97.0% [95.4-98.4%, I^2 = 69.7%, p=0], respectively, when assessed in the per-protocol population.

3.6 Antibiotic treatment failure

Overall, among 3,002 patients identified in 24 paediatric febrile UTI CTs reporting cure and failure rates, only 3.9% of patients (3.9%; 118/3,002) were considered clinically to have treatment failure. Of those, 20 (16.9%; 20/118) patients had persisting signs of a UTI during treatment, and 33 (28.0%; 33/118) patients had recurrent UTI signs. Moreover, there were 135 patients (4.5%; 135/3,002) considered to have microbiological failure. A total of 9 patients (6.7%; 9/135) had persistence of a positive urine culture and 77 patients (57.0%; 77/135) had recurrence or relapse of a urinary pathogen. Among microbiological failure patients, 24 (17.8%; 24/135) were identified growing pathogens resistant to the study drug and 40 (29.6%; 40/135) pathogens susceptible to the study drug, while data regarding resistance was missing in 69 (51.1%; 69/135) patients. Only 70% (21/30) of studies [21, 22, 26, 27, 29-31, 34-39, 41-47, 49] reported resistance patterns for the investigational antibiotic. Even fewer studies (13.3%; 4/30) [35, 36, 40, 49] reported the resistance patterns for the recurrent UTI episodes in their CTs. Of note, 11 studies [24, 26, 27, 29, 30, 34-36, 44, 45, 49] excluded patients with resistance to the study drug.

4. DISCUSSION

4.1 Principal findings

Paediatric febrile UTIs CTs have mostly included beta-lactams and aminoglycosides, whereas only a few antibiotics active against multi-drug resistant UTIs have been tested. In this review, we observed very high treatment cure rates for childhood UTIs in CTs, regardless of the investigational drug chosen, the route of administration, duration and dosing. However, in these CTs, the population consisted mainly of patients with no underlying conditions, while isolates resistant to the main investigational drug have been predominantly excluded.

4.2 Strengths and limitations

In the studied CTs, we estimated the average treatment cure rate to 95.3% [95% CI 93.5-96.9%]. Although the lowest cure rates were selected to provide a conservative approach, high cure rates were consistently observed for most of the antibiotics used, even when subgroup analysis was performed to assess heterogeneity. The provided cure rates in this paper can potentially be used to better inform the future design, sample size calculations and analysis in childhood febrile UTIs non-inferiority trials. However, the design of such trials appears limited as the paediatric UTIs population is mainly represented from children with no comorbidities (66.5%) and susceptible UTIs as UTIs resistant to the study drug were either primarily or secondarily excluded. Such populations of predominantly healthy children consistently exhibit high rates of clinical and microbiological cure.

Reporting of outcome data in UTIs CTs was fairly complete (up to 63.3%), while blinding of participants represents a challenge in paediatric CTs. The poor reporting of the initial resistance patterns, as also shown in our study, did not allow us to infer any estimates for the ESBL-producing or other resistant UTIs. Most studies did not also report resistance patterns separately by control and intervention groups, which made it impossible to analyse their effect on acquisition of resistance, especially in cases of recurrence of a UTI.

The main limitation of our study is the potential overestimation of the average point cure rate estimate which may be associated with the point that in 11 (36.7%) studies [24, 26, 27, 29, 30, 34-36, 44, 45, 49], patients infected with a pathogen resistant to the study drug were secondarily excluded, resulting in an *E. coli* isolates overrepresentation, as compared with previous reviews on paediatric UTIs [52-55]. In this way, rates of resistance have been underestimated suggesting the limited use of this data for studies on ESBL-producing or other resistant UTIs and the potential overestimation of the clinical and microbiological success of the study drugs. Moreover, about 30% of included studies also assessed the cure rates during OAT when urine sterilisation is expected to be higher during treatment due to the active presence of the antibiotic. Finally, some antibiotic studies may have been missed as CTs before 1990 have been excluded due to perceived lack of quality reporting prior to this date. High heterogeneity was observed in our meta-analysis, which is probably due to the variable studies design, definitions of cure rates, various timings for therapy endpoints assessment (OAT or EOT or TOC), and different intervention antibiotics used as we have previously noted [15].

4.3 Results in the context of existing research

Recent reviews on paediatric febrile UTIs focused on diagnosis [52, 54], antibiotic treatment duration, prophylaxis for the risk of renal scarring development [56], or guidelines for management of paediatric febrile UTIs. Several studies included meta-analyses to compare different antimicrobials regimens used in the CTs. Those studies mainly evaluated the efficacy of oral antibiotic therapy versus initial IV therapy followed by oral therapy; or the efficacy of short duration versus long duration therapy [57, 58, 55, 59]. To our knowledge, this is the first review providing a comprehensive description of all antibiotic treatments providing point estimates for clinical and microbiological cure rates in paediatric febrile UTI CTs.

High rates of resistance to 3rd generation cephalosporins [6, 7] and increased prevalence of ESBL infections is being observed in children worldwide [9]. Carbapenems are widely used to treat such infections [11]. However, there are no CTs, currently, evaluating the effectiveness of carbapenems against paediatric ESBL UTIs and any evidence for carbapenems use for ESBL UTIs treatment comes mainly from observational studies [60-63]. Two on-going clinical trials are assessing safety and efficacy of doripenem, cefepime or ceftazidime-avibactam (https://clinicaltrials.gov/; NCT01110408, NCT02497781), but the results are not yet available at this stage.

Of note, in our meta-analysis, the average cure rate was estimated to 95.3%, which seems higher than in adult complicated UTIs, where the microbiological eradication rate has been historically estimated to 70% [64] and recently 80% for doripenem, levofloxacin and imipenem-cilastatin [65]. This is most likely related to the different background of adult patients with a complicated UTI. Adults with a complicated UTI usually have an underlying functional or anatomic abnormality of the urinary tract or a permanent urinary catheter [66], while pyelonephritis is only a fraction of complicated UTIs.

5. FUTURE STEPS

Our findings support the need for the conduct of pragmatic trials on MDR infections in children, including ESBL-producers and carbapenemase resistant organisms. These trials should explore the efficacy of oral and intravenous antibiotics against childhood febrile UTIs. These agents may be either newly developed (e.g. new beta-lactam/BLI combinations) or revived older off-patent antibiotics (e.g. fosfomycin). Observational, prospective cohort studies are required to inform the study design, treatment and outcomes for MDR febrile UTIs trials.

Authors Contributions: KV, RB and YH conceptualized and designed the work. KV, RB, JB and LF identified eligible studies. KV, RB and LF appraised study quality; data were extracted, transformed and analyzed by KV and RB. Data analysis was guided by YH. MS and TZ contributed substantially to data interpretation. KV and RB drafted the initial manuscript. JB, LF, TZ, MS and YH critically revised the manuscript for important intellectual content. All authors contributed to, reviewed, and approved the final version to be published. All authors received access to all the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. YH is the guarantor.

Compliance with Ethical Standards

Funding: No external funding for this manuscript.

Conflict of interest: MS reports grants from GlaxoSmithKline, Pfizer and Cubist Pharmaceuticals, outside the submitted work. JB's husband is senior corporate counsel at Novartis International AG, Basel, Switzerland, and holds Novartis stock and stock options. The other authors have no conflicts of interest to disclose.

Ethical approval: Not required.

Figures Legends

Figure 1. Diagram for study selection

UTI, urinary tract infection

*Excluded publication types were: review, meta-analysis, observational study, case report, not randomized trials, editorial, comment

**Excluded population were: Cystitis, urinary tract abnormalities, underlying disorders, inconsistent pathogen, mixed infections with no specific data on urinary tract infections

Figure 2. Forest plot of the standardised cure rates observed in each arm of the febrile UTIs CTs

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Table 1. Clinical and microbiological characteristics of the patients included in the paediatric febrile urinary tract infections clinical trials

Features	**Number (%)**
Demographics	
Total patients	**3913**
Male	878 (22.4%)
Female[a]	2313 (59.1%)
Unspecified	722 (18.5%)
Medical Background	
Patients without any underlying condition/comorbidity	**2602 (66.5%)**
Underlying conditions/comorbidities[c]	**1258**
UT-related conditions	903 (71.8%)
History of recurrent UTIs	216 (17.2%)
VUR, hydronephrosis, pelvic dilation	487 (38.7%)
Urolithiasis, obstructive uropathy	36 (2.9%)
Anatomic abnormalities (kidney duplication, polycystic kidney, single kidney, vesicoureteric stenosis, urethrocele, hypospadias, bladder diverticulae)	20 (1.6%)
Neurogenic bladder	24 (1.9%)
Urologic surgery/indwelling catheter	22 (1.7%)
Unspecified UT-related abnormalities	98 (7.8%)
Chronic underlying conditions (Still's diseases, diabetes, cancer, paralysis, myelomeningocele, prematurity)	15 (1.2%)
Concurrent infections (bronchiolitis)	1 (0.1%)
Unspecified pathological conditions	339 (26.9%)
Pathogen distribution	
Total pathogens	**3158**
Escherichia coli[d]	2822 (89.4%)

Proteus sp.	69 (2.2%)
Klebsiella sp.	49 (1.6%)
Enterococcus sp.	17 (0.5%)
Enterobacter sp.	13 (0.4%)
Pseudomonas sp.	13 (0.4%)
Staphylococcus sp.	7 (0.2%)
Other	11 (0.3%)
Unspecified	157 (5%)

UT, urinary tract; UTI, urinary tract infection; VUR, vesicoureteral reflux

a: Yousefichaijan et al [50] (n=152) considered only girls for inclusion

c: Each patient could have more than one pathological conditions

d: Bocquet et al [27] (n=171) considered only *E. coli* for inclusion

Table 2. Intervention drugs assessed in the paediatric febrile urinary tract infection clinical trials

Drug Category	Drug name	Route	Dosage in mg/kg/d	Dosage in IU/d	Duration in days (range)	Cure rate† % (CI)	Number of arms assessed	Number of studies (%)	Reference
Penicillins	Amoxicillin or ampicillin	po	50-100	-	4-18	na		3 (10.0)	[36,40,43]
	Co-amoxiclav	po	50-150**	-	4-18	98.327 (94.6 – 100.0)	5	4 (13.3)	[36,38,44,45]
	Temocillin	IV	na	-	3-7	94.3 (88.1 - 98.5)	2	1 (3.3)	[36]
1st generation cephalosporins	Cefadroxil	po	30	-	7-10	Na		1 (3.3)	[41]
	Cefalothin	po	100	-	3-10	Na		2 (6.6)	[34,43]
	Cefalexin	po	na	-	10-14	Na		1 (3.3)	[30]
2nd generation cephalosporins	Cefuroxime axetil	po	30	-	7-10	Na		1 (3.3)	[41]
3rd generation cephalosporins	Ceftibuten	po	9	-	9-14	Na		3 (10.0)	[37,39,48]
	Cefetamet pivoxil	po	20-40	-	7-10	Na		1 (3.3)	[45]
	Cefixime	po	8-16	-	6-14	96.1 (93.6 - 98.0)	11	9 (30.0)	[23-27,31-33,40,49-51]
	Ceftriaxone	IV	50-75	-	1-14	95.8 (92.8- 98.1)	13	14 (46.7)	[26,27,32,38-41,48,50,51]

	Cefotaxime	IV	100-200	-	5-14	80.8 (63.1 - 94.0)	1	2 (6.6)	24,25
	Ceftizoxime	IV	100	-	2	na		1 (3.3)	33
	Ceftazidime	IV	150	-	≥2	na		1 (3.3)	42
4th generation cephalosporins	Cefepime	IV	150	-	3	na		1 (3.3)	42
Aminoglycosides	Isepamicin	IV	15	-	4-14	na		2 (6.6)	35,46
	Amikacin	IV	15	-	2-14	93.5 (58.9-100.0)	1	5 (16.7)	35,40,41,43,46
	Gentamicin	IV	3-7.5	-	3-10	99.3 (97.6 - 100.0)	6	5 (16.7)	28,30,34,40,44
	Netilmicin	IV	5-7.5	-	5-10	(99.0 96.3-100.0)	2	2 (6.6)	32,47
Others	Cotrimoxazole	po	6-10/30-50*	-	7-14	88.4 (78.5 - 95.8)	3	5 (16.7)	23,30,31,37,42
	Nitrofurantoin	po	7	-	7-10	na		1 (3.3)	41
	Ciprofloxacin	po	20	-	7-10	na		1 (3.3)	41
Antibiotic not specified	-	-		-	-	na		1 (3.3)	29
Supplemental therapies	Vitamin A	po	-	1500/kg	10	na		1 (3.3)	43
	Vitamin E	po	-	20-100	10-14	na		2 (6.6)	43,50
	Vitamin C	po	250mg/d	-	14	na		1 (3.3)	49

	Zinc	po	1	-	14	na		1 (3.3)	[51]
	N-acetyl-cysteine	po	70 (or 600mg/d or 900mg/d based on age)	-	5	na		1 (3.3)	[22]
	Methylprednisolone	po	1.6	-	3	na		1 (3.3)	[34]

Abbreviations: po, per os; IV, intravenous; na, not available

*presented as trimethoprim/sulfamethoxazole; ** of amoxicillin

† Cure rates are presented for the investigational drugs only if they represented the initial treatment given for those patients.

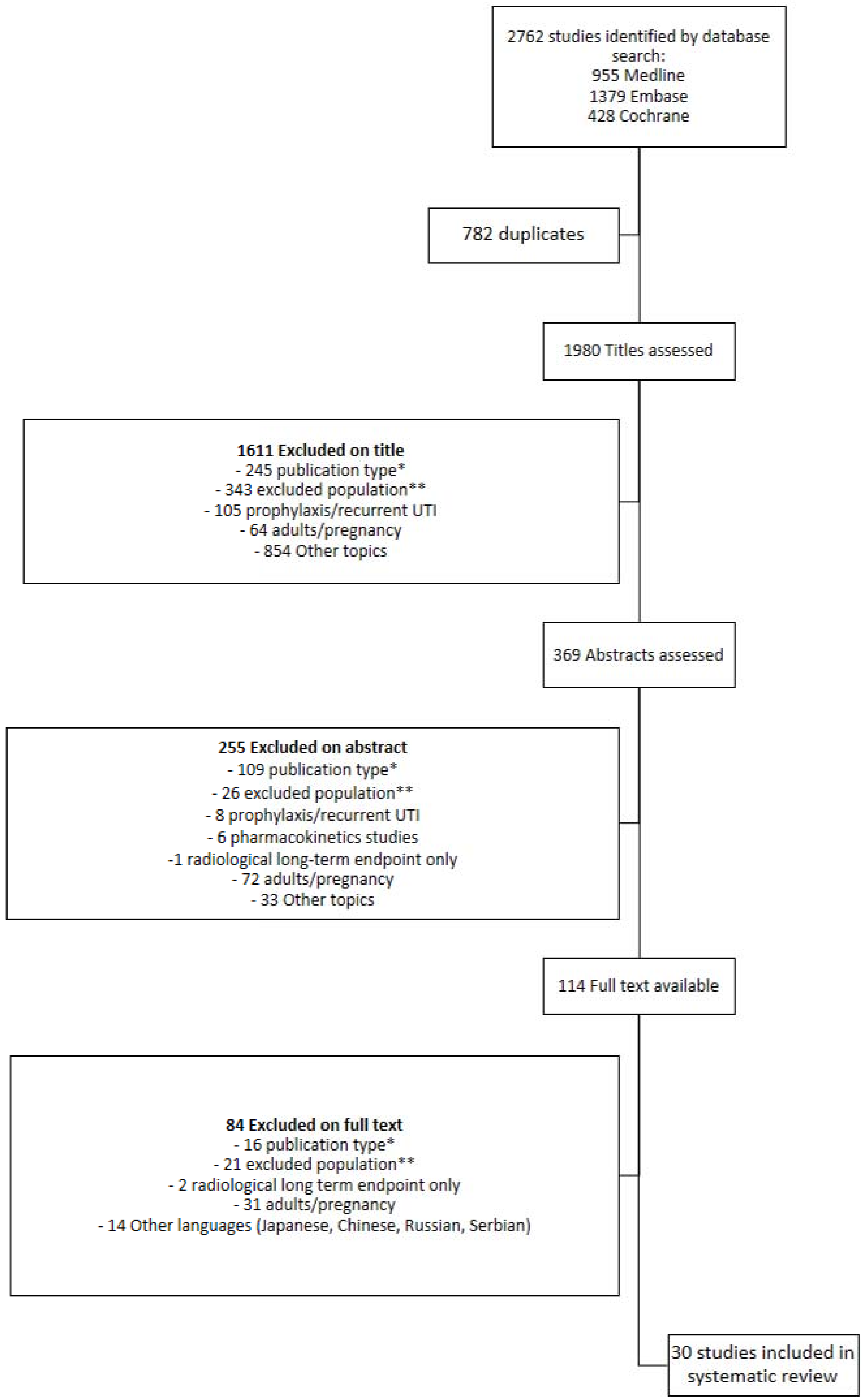
Antibiotics and Cure Rates in Childhood Febrile Urinary Tract Infections in Clinical Trials: A Systematic Review and Meta-analysis

Konstantinos Vazouras, Romain Basmaci, Julia Bielicki, Laura Folgori, Theoklis Zaoutis, Mike Sharland, Yingfen Hsia

Table 3. Meta-analysis assessing the cure rate in paediatric febrile UTI clinical trials by subgroup

Variable	Proportion (RE model)	Lower 95% CI	Upper 95% CI	I^2 (%)	P value	Number of arms assessed
Average	95.31	93.51	96.87	70.74	5.23E-16	47
Cephalosporins	93.78	91.13	96.04	70.88	6.23E-09	23
Aminoglycosides	99.62	98.39	100	0	0.743033	10
Penicillin	98.27	94.58	100	53.29	0.081091	5
Sulfonamide	88.4	78.45	95.75	62.73	0.071478	3
Aminoglycosides+Penicillin	80	63.53	92.69	0	1	1
Aminoglycosides+Cephalosporin	98.18	95.12	99.91	0	0.530762	3
Unspecified	92.6	71.12	100	84.93	0.009986	2
Clinical cure	94.78	92.64	96.63	61.61	1.06E-05	30
Cephalosporins	93.99	92.07	95.68	29.95	0.098301	19
Aminoglycosides	100	98.96	100	0.07	0.379945	4
Penicillin	99.71	95.81	100	0	0.318869	2
Sulfonamide	90.33	73.05	99.6	82.73	0.016117	2
Aminoglycosides+Penicillin	80	63.53	92.69	0	1	1
Aminoglycosides+Cephalosporin	NA	NA	NA	NA	NA	0
Unspecified	97.15	91.84	99.95	0	0.396146	2
Microbiological cure	96.29	94.7	97.64	67.94	1.33E-12	47
Cephalosporins	95.07	92.44	97.23	75.04	1.03E-10	23
Aminoglycosides	99.62	98.39	100	0	0.743033	10
Penicillin	98.27	94.58	100	53.29	0.081091	5
Sulfonamide	94.83	90.77	97.89	0.11	0.330007	3
Aminoglycosides+Penicillin	80	63.53	92.69	0	1	1
Aminoglycosides+Cephalosporin	98.18	95.12	99.91	0	0.530762	3
Unspecified	92.6	71.12	100	84.93	0.009986	2
End Of Treatment (EOT)/ Test Of Cure (TOC)	94.79	92.7	96.6	64.93	1.79E-08	37
Cephalosporins	93.75	90.9	96.15	66.19	3.39E-05	19

Aminoglycosides	99.7	97.41	100	0	0.605186	6
Penicillin	97.16	92.55	99.83	27.52	0.317962	4
Sulfonamide	90.1	73.24	99.43	80.94	0.022002	2
Aminoglycosides+Penicillin	80	63.53	92.69	0	1	1
Aminoglycosides+Cephalosporin	98.18	95.12	99.91	0	0.530762	3
Unspecified	92.6	71.12	100	84.93	0.009986	2
On Antibiotic Therapy (OAT)	96.51	92.89	99.01	80.46	2.51E-06	10
Cephalosporins	93.66	85.06	98.96	84.32	1.62E-05	4
Aminoglycosides	98.82	97.01	99.9	0	0.586312	4
Penicillin	99.46	97.71	100	0	1	1
Sulfonamide	85.71	71.87	95.69	0	1	1
Aminoglycosides+Penicillin	NA	NA	NA	NA	NA	0
Aminoglycosides+Cephalosporin	NA	NA	NA	NA	NA	0
Unspecified	NA	NA	NA	NA	NA	0


2762 studies identified by database search:
955 Medline
1379 Embase
428 Cochrane
782 duplicates
1980 Titles assessed
1611 Excluded on title
- 245 publication type*
- 343 excluded population**
- 105 prophylaxis/recurrent UTI
- 64 adults/pregnancy
- 854 Other topics
369 Abstracts assessed
255 Excluded on abstract
- 109 publication type*
- 26 excluded population**
- 8 prophylaxis/recurrent UTI
- 6 pharmacokinetics studies
-1 radiological long-term endpoint only
- 72 adults/pregnancy
- 33 Other topics
114 Full text available
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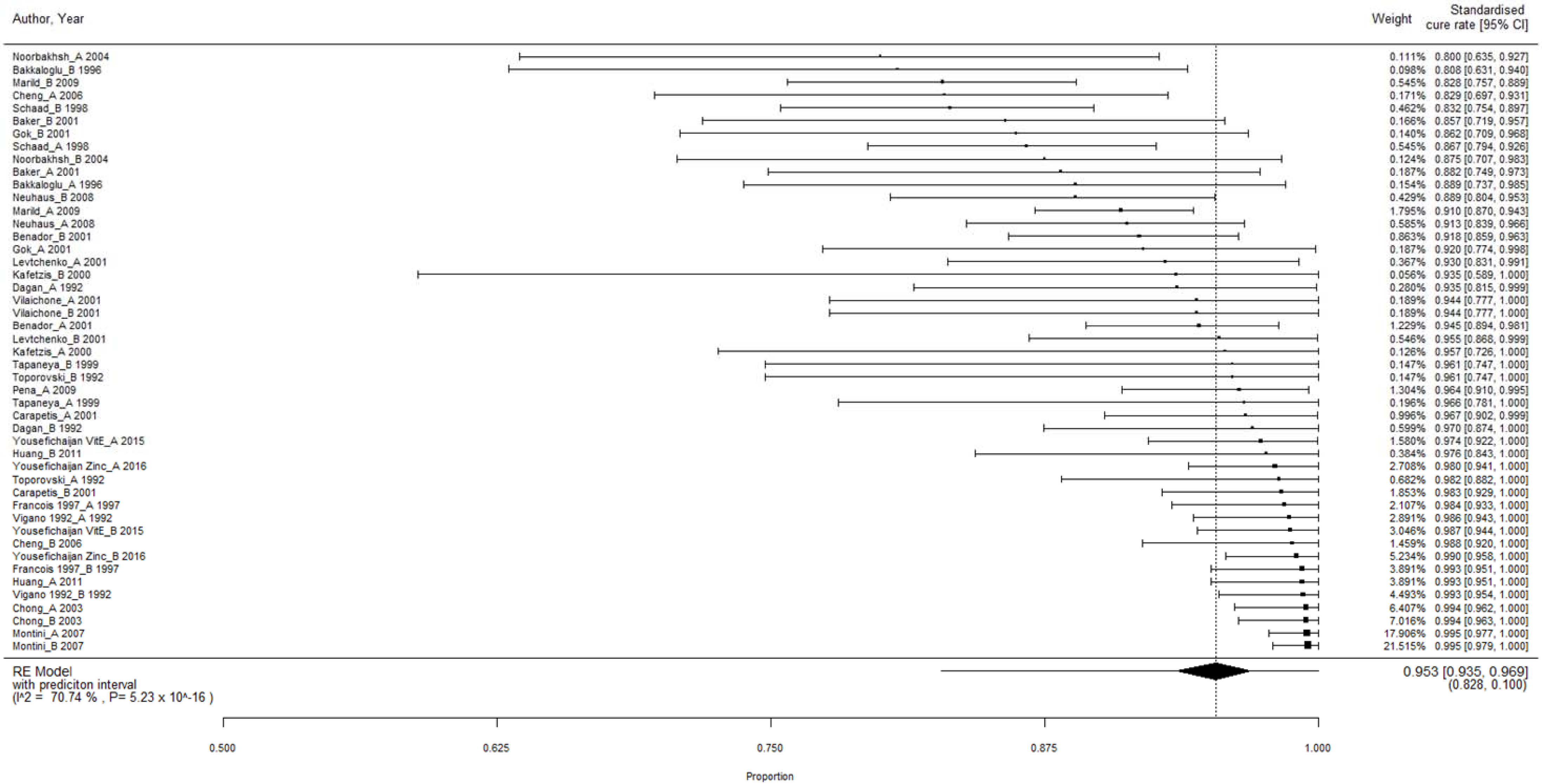
- 21 excluded population**
- 2 radiological long term endpoint only
- 31 adults/pregnancy
- 14 Other languages (Japanese, Chinese, Russian, Serbian)
30 studies included in systematic review


Author, Year
Weight
Standardised cure rate [95% CI]
Noorbakhsh_A 2004 0.111% 0.800 [0.635, 0.927]
Bakkaloglu_B 1996 0.098% 0.808 [0.631, 0.940]
Marild_B 2009 0.545% 0.828 [0.757, 0.889]
Cheng_A 2006 0.171% 0.829 [0.697, 0.931]
Schaad_B 1998 0.462% 0.832 [0.754, 0.897]
Baker_B 2001 0.166% 0.857 [0.719, 0.957]
Gok_B 2001 0.140% 0.862 [0.709, 0.968]
Schaad_A 1998 0.545% 0.867 [0.794, 0.926]
Noorbakhsh_B 2004 0.124% 0.875 [0.707, 0.983]
Baker_A 2001 0.187% 0.882 [0.749, 0.973]
Bakkaloglu_A 1996 0.154% 0.889 [0.737, 0.985]
Neuhaus_B 2008 0.429% 0.889 [0.804, 0.953]
Marild_A 2009 1.795% 0.910 [0.870, 0.943]
Neuhaus_A 2008 0.585% 0.913 [0.839, 0.966]
Benador_B 2001 0.863% 0.918 [0.859, 0.963]
Gok_A 2001 0.187% 0.920 [0.774, 0.998]
Levtchenko_A 2001 0.367% 0.930 [0.831, 0.991]
Kafetzis_B 2000 0.056% 0.935 [0.589, 1.000]
Dagan_A 1992 0.280% 0.935 [0.815, 0.999]
Vilaichone_A 2001 0.189% 0.944 [0.777, 1.000]
Vilaichone_B 2001 0.189% 0.944 [0.777, 1.000]
Benador_A 2001 1.229% 0.945 [0.894, 0.981]
Levtchenko_B 2001 0.546% 0.955 [0.868, 0.999]
Kafetzis_A 2000 0.126% 0.957 [0.726, 1.000]
Tapaneya_B 1999 0.147% 0.961 [0.747, 1.000]
Toporovski_B 1992 0.147% 0.961 [0.747, 1.000]
Pena_A 2009 1.304% 0.964 [0.910, 0.995]
Tapaneya_A 1999 0.196% 0.966 [0.781, 1.000]
Carapetis_A 2001 0.996% 0.967 [0.902, 0.999]
Dagan_B 1992 0.599% 0.970 [0.874, 1.000]
Yousefichaijan VitE_A 2015 1.580% 0.974 [0.922, 1.000]
Huang_B 2011 0.384% 0.976 [0.843, 1.000]
Yousefichaijan Zinc_A 2016 2.708% 0.980 [0.941, 1.000]
Toporovski_A 1992 0.682% 0.982 [0.882, 1.000]
Carapetis_B 2001 1.853% 0.983 [0.929, 1.000]
Francois 1997_A 1997 2.107% 0.984 [0.933, 1.000]
Vigano 1992_A 1992 2.891% 0.986 [0.943, 1.000]
Yousefichaijan VitE_B 2015 3.046% 0.987 [0.944, 1.000]
Cheng_B 2006 1.459% 0.988 [0.920, 1.000]
Yousefichaijan Zinc_B 2016 5.234% 0.990 [0.958, 1.000]
Francois 1997_B 1997 3.891% 0.993 [0.951, 1.000]
Huang_A 2011 3.891% 0.993 [0.951, 1.000]
Vigano 1992_B 1992 4.493% 0.993 [0.954, 1.000]
Chong_A 2003 6.407% 0.994 [0.962, 1.000]
Chong_B 2003 7.016% 0.994 [0.963, 1.000]
Montini_A 2007 17.906% 0.995 [0.977, 1.000]
Montini_B 2007 21.515% 0.995 [0.979, 1.000]
RE Model
with prediciton interval
(I^2 = 70.74 % , P= 5.23 x 10^-16)
0.953 [0.935, 0.969]
(0.828, 0.100)
0.500
0.625
0.750
0.875
1.000
Proportion