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SYSTEMATIC REVIEW

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

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Abstract

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

Objective To systematically review the antimicrobials used for febrile UTIs in paediatric clinical trials and meta-analyse 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 2762 published studies and included 30 clinical trials investigating 3913 cases of paediatric febrile urinary tract infections. Children with no underlying condition were the main population included in the trials ($n = 2602$; 66.5%). Cephalosporins were the most frequent antibiotics studied in trials (22/30, 73.3%). Only a few antibiotics active against resistant UTIs 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 3002 patients for whom cure and failure rates were reported, only 3.9% (3.9%; 118/3002) were considered clinically to have treatment failure, while 135 (4.5%; 135/3002) 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.

Konstantinos Vazouras and Romain Basmaci contributed equally to the work and are co-first authors.

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Key Points

We observed high treatment cure rates for childhood UTIs 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 [2–5]. 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 UTI clinical trials (CTs) [15]. In the current review, our main aim was to: (i) review the antimicrobial drugs used for febrile UTI 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 types of antibacterial or anti-inflammatory agents in children presenting with acute febrile UTI. We excluded trials with 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 antibiotic 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 provided for either 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 were 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 2762 published studies and 30 were included in the final analysis [21–50] (Fig. 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 3913 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 [22, 29, 36, 39, 40, 42, 43, 49, 50], while 17 studies (55.7%) included a mixed population of children with or without underlying conditions [21, 23, 25–28, 30–33, 37, 38, 41, 46, 47]. Patients with no underlying conditions represented the main population included in paediatric clinical trials ($n = 2602$; 66.5%). A urinary tract-related underlying condition was the most common medical condition reported (71.8%; 903/1258) (Table 1).

A total of 3158 pathogens were reported in 25 studies [21–24, 26–38, 40–46, 51], *Eschrichia coli* was the predominantly isolated pathogen in 2822 (89.4%; 2822/3158) 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 UTI CTs. Table 2 shows the antibiotics used for febrile UTI treatment. Penicillins, cephalosporins, and aminoglycosides were the most commonly used antibiotic classes [22–27, 29–50]. Cephalosporins were the most frequent antimicrobial class studied, with 12 different drugs being evaluated in 22 trials (73.3%), [22–26, 30–32, 36–41, 44, 47–50] 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 UTI 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, 43, 44]. 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 Fig. 1 and Supplementary Fig. 2. Supplementary Fig. 1 shows the proportion of studies assessed as low, high or unclear risk of bias for each risk of bias indicator. Supplementary Fig. 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 vs 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%) (Fig. 2), with a prediction interval of 82.8–100.0%. We observed high heterogeneity

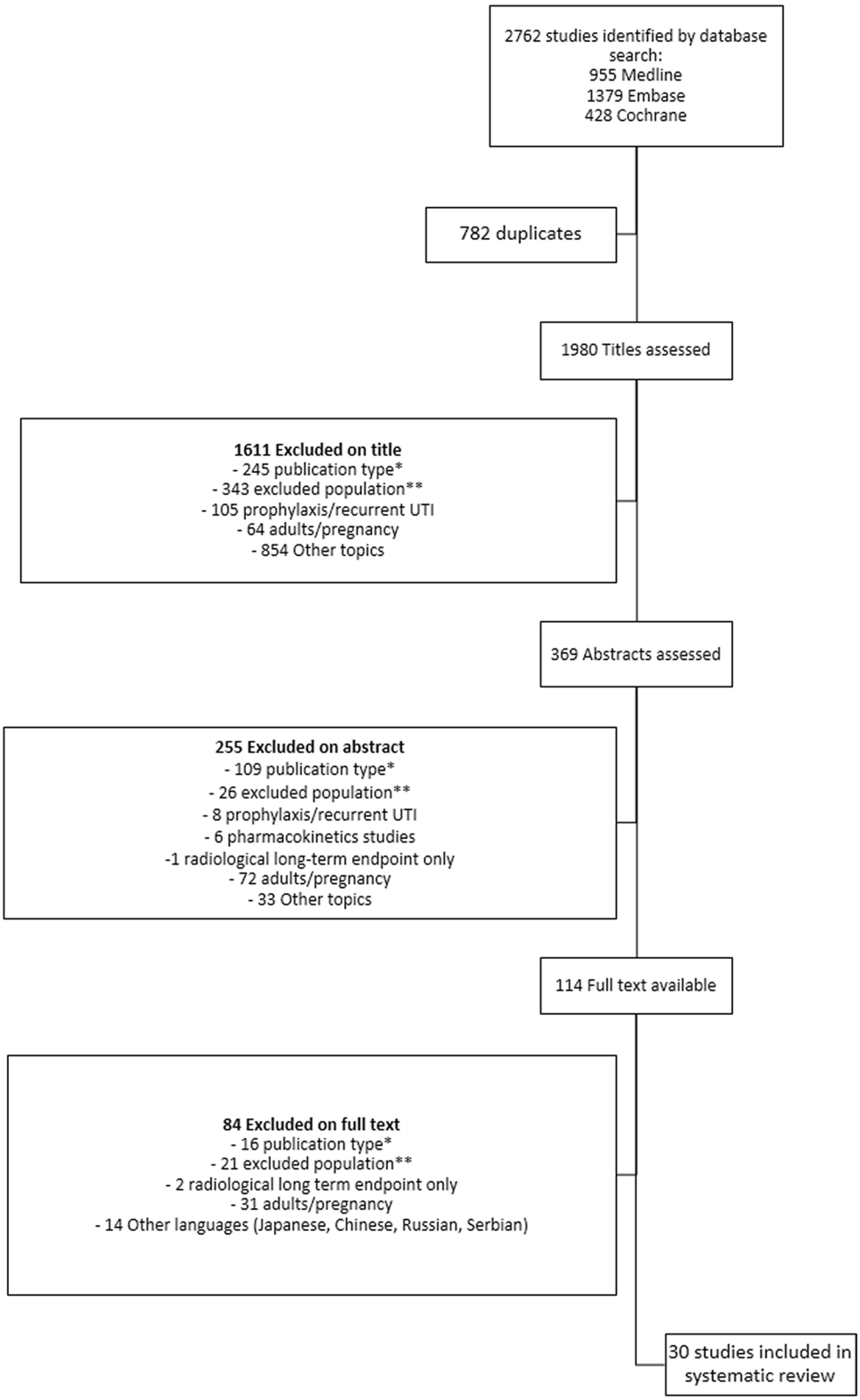

Fig. 1 Diagram for study selection. *UTI* urinary tract infection. *Excluded publication types were: review, meta-analysis, observational study, case report, not randomized trials, editorial, comment. **Excluded population were: cystitis, urinary tract abnormalities, underlying disorders, inconsistent pathogen, mixed infections with no specific data on urinary tract infections

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

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[b]	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[c]	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%)

CI confidence interval, *NA* not available, *UT* urinary tract, *UTI* urinary tract infection

VUR vesicoureteral reflux

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

[b]Each patient could have more than one pathological condition

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

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.

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

Drug category	Drug name	Route	Dosage (mg/kg/d)	Dosage (IU/d)	Duration in days (range)	Cure rate[a] % (CI)	Number of arms assessed	Number of studies (%)	References
Penicillins	Amoxicillin or ampicillin	po	50–100	–	4–18	NA		3 (10.0)	[36, 40, 43]
	Co-amoxiclav	po	50–150[b]	–	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[c]	–	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]

Table 2 (continued)

Drug category	Drug name	Route	Dosage (mg/kg/d)	Dosage (IU/d)	Duration in days (range)	Cure rate[a] % (CI)	Number of arms assessed	Number of studies (%)	References
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	250 mg/d	–	14	NA		1 (3.3)	[49]
	Zinc	po	1	–	14	NA		1 (3.3)	[51]
	N-acetyl-cysteine	po	70 (or 600 mg/d or 900 mg/d based on age)	–	5	NA		1 (3.3)	[22]
	Methylprednisolone	po	1.6	–	3	NA		1 (3.3)	[34]

CI confidence interval, *IV* intravenous, *NA* not available, *po* oral

[a]Cure rates are presented for the investigational drugs only if they represented the initial treatment given for those patients

[b]Of amoxicillin

[c]Presented as trimethoprim/sulfamethoxazole

3.6 Antibiotic Treatment Failure

Overall, among 3002 patients identified in 24 paediatric febrile UTI CTs reporting cure and failure rates, only 3.9% of patients (3.9%; 118/3002) 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%; 135/3002) 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 were 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 UTI 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 be 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 UTI non-inferiority trials. However, the design of such trials appears limited as the paediatric UTI population is mainly represented from children with no comorbidities

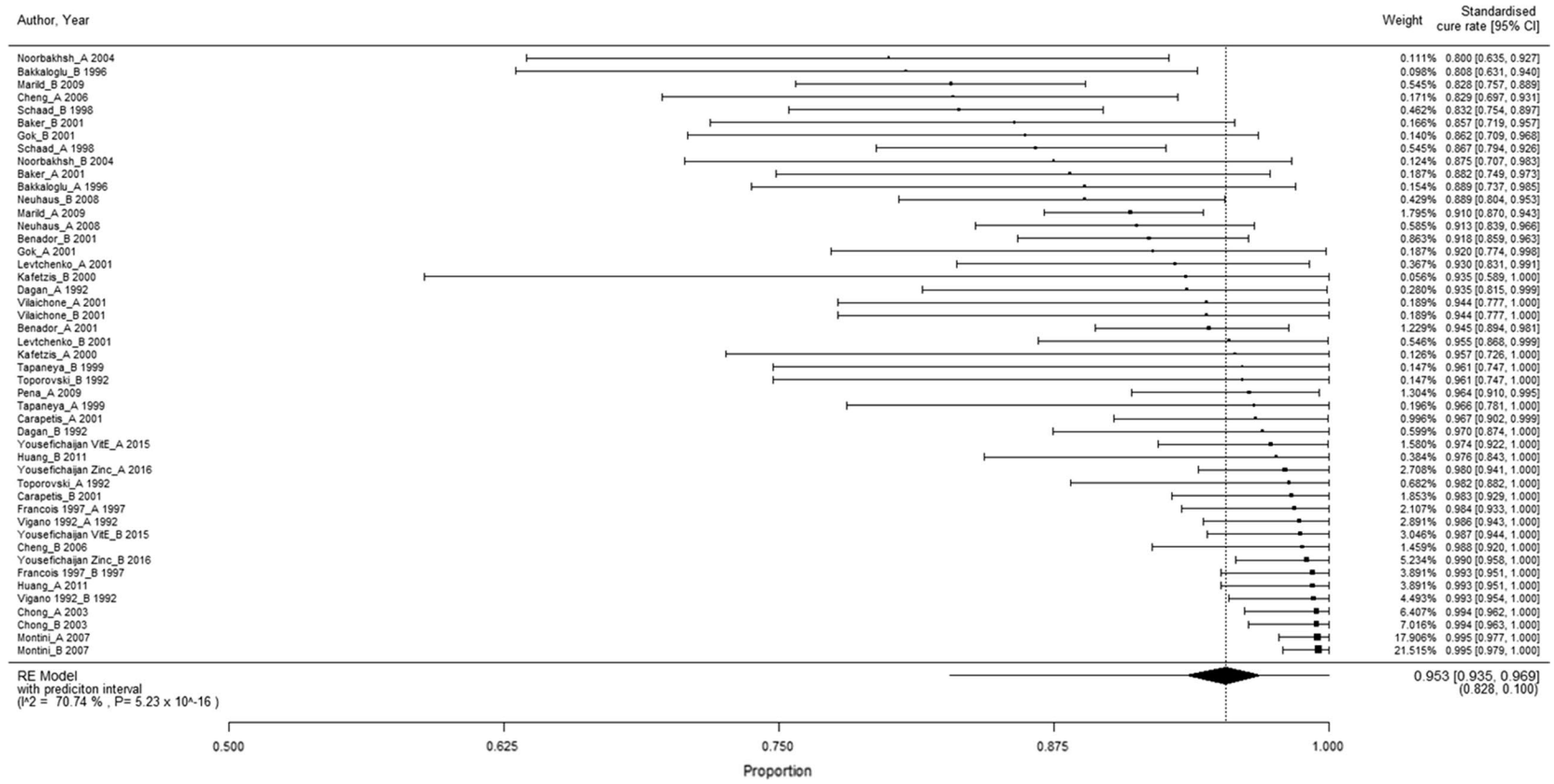

Fig. 2 Forest plot of the standardised cure rates observed in each arm of the febrile urinary tract infection clinical trials (UTI CTs)

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

CI confidence interval, *NA* not available, *UTI* urinary tract infection

(66.5%) and susceptible UTIs such 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 UTI CTs was fairly complete (up to 63.3%) in our study, while blinding of the participants and the concealment of allocations proved challenging in paediatric CTs. The risk of bias regarding blinding participants/personnel was high (90.0%) as compared to another

systematic review of antibiotic trials in neonatal infections [52] where the risk was high or unclear in 46.0% of studies. The allocation bias was quite unclear in both paediatric (60.0%) and neonatal CTs (54.0%) [52].

Finally, 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 [53–56]. In this way, rates of resistance have been underestimated suggesting the limited use of the data for studies on ESBL-producing or other resistant UTIs and the potential overestimation of the clinical and microbiological success of the study drugs. 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. Moreover, some antibiotic studies may have been missed as CTs before 1990 have been excluded due to the perceived lack of regulatory guidance for antibiotic CTs in the paediatric population prior to this date. A recent systematic review on antibiotic clinical trials in children has pointed out that the quality of outcomes reporting for clinical trials is inadequate and adheres poorly to the CONSORT guidelines [57]. Finally, 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 endpoint 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 [53, 55], antibiotic treatment duration, prophylaxis for the risk of renal scarring development [58], or guidelines for management of paediatric febrile UTIs. Several studies included meta-analyses to compare different antimicrobial 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 [56, 59–61]. 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 third-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 currently no CTs evaluating the effectiveness of carbapenems against paediatric ESBL UTIs and any evidence for carbapenem use for ESBL UTI treatment comes mainly from observational studies [62–65]. 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.

Of note, in our meta-analysis, the average cure rate was estimated to be 95.3%, which seems higher than in complicated UTIs in adults, where the microbiological eradication rate has been historically estimated to be 70% [66] and recently 80% for doripenem, levofloxacin and imipenem-cilastatin [67]. 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 [68], 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 UTI 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 analysed 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

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