**Supplementary Appendix**

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

**DRUGS**

Konstantinos Vazouras, MD, MPH, Romain Basmaci, MD, PhD; Julia Bielicki, MD , Laura Folgori, MD, Theoklis Zaoutis, MD, PhD, Mike Sharland, MD, Yingfen Hsia, PhD

**Correspondence to:** K Vazouras, Paediatric Infectious Diseases Research Group, St George’s University of London, Cranmer Terrace, London SW17 0RE, United Kingdom; [k.vazouras@cleoresearch.org](mailto:k.vazouras@cleoresearch.org); Tel.: +442087252804, ORCID: 0000-0002-5278-0083

**Supplementary Methods 1. Search strategy**

**Supplementary Methods 2. PRISMA Checklist for Systematic Review and Meta-analysis**

**Supplementary Table 1. Characteristics of included studies**

**Supplementary Table 2. Risk of bias in included studies**

**Supplementary Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies**

**Supplementary Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study**

**Supplementary Methods 1. Search strategy**

**The following strategy was used to search EMBASE (1980 to 2016 Week 47) from January 1, 1990 to November 24, 2016 [search conducted on November 24, 2016]: Results = 1379**

#1 exp Urinary Tract Infections/ or exp Pyelonephritis/ or pyelonephrit\*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]

#2 (UTI or UTIs).mp.

#3 (urin\* adj1 tract adj1 infect\*).mp.

#4 (urin\* adj1 infect\*).mp.

#5 (urinary?tract adj1 infect\*).mp.

#6 exp Anti-Infective Agents/ or exp Anti-Bacterial Agents/ or exp Anti-Inflammatory Agents/

#7 (anti bact\* or anti microb\* or anti infect\* or anti inflammat\*).mp.

#8 (anti?bact\* or anti?microb\* or anti?infect\* or anti?inflammat\*).mp.

#9 exp Therapeutics/

#10 (therap\* or treat\*).mp.

#11 exp Clinical Trial/

#12 exp Clinical Trials as Topic/

#13 (clinic\* adj1 trial\*).mp.

#14 Clinical Trial.pt.

#15 malaria.mp. or exp Malaria/

#16 exp HIV/ or HIV.mp.

#17 exp Tuberculosis/ or tuberculosis.mp.

#18 (parasit\* adj1 infect\*).mp.

#19 exp Pregnancy/ or pregnancy.mp.

#20 1 or 2 or 3 or 4 or 5

#21 6 or 7 or 8 or 9 or 10

#22 11 or 12 or 13 or 14

#23 15 or 16 or 17 or 18 or 19

#24 20 and 21 and 22

#25 24 not 23

#26 limit 25 to humans

#27 limit 26 to yr="1990 -Current"

#28 limit 27 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

**The following strategy was used to search MEDLINE (Ovid Medline® 1946 to November Week 2 2016) from January 1, 1990 to November 24, 2016 [search conducted on November 24, 2016]: 955 results**

The same strategy used to search EMBASE was used, except for #28, which was altered to be valid in MEDLINE as: “limit 27 to all child (0 to 18 years)”.

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

**The following strategy was used to search CENTRAL (Issue 10 of 12, October 2016) from January 1, 2000 to November 24, 2016 [search conducted November 24, 2016]: 428 results**

#1 urinary tract infection\*:ti,ab,kw (Word variations have been searched)

#2 MeSH descriptor: [Urinary Tract Infections] explode all trees

#3 MeSH descriptor: [Pyelonephritis] explode all trees

#4 pyelonephriti\*:ti,ab,kw (Word variations have been searched)

#5 "UTI":ti,ab,kw (Word variations have been searched)

#6 UTIs:ti,ab,kw (Word variations have been searched)

#7 urin\* near tract\* near infect\*:ti,ab,kw (Word variations have been searched)

#8 urin\* near infect\*:ti,ab,kw (Word variations have been searched)

#9 urinary?tract near infect\*:ti,ab,kw (Word variations have been searched)

#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

#11 MeSH descriptor: [Therapeutics] explode all trees

#12 MeSH descriptor: [Anti-Bacterial Agents] explode all trees

#13 MeSH descriptor: [Anti-Infective Agents] explode all trees

#14 MeSH descriptor: [Anti-Inflammatory Agents] explode all trees

#15 #11 or #12 or #13 or #14

#16 #10 and #15

#17 MeSH descriptor: [Malaria] explode all trees

#18 MeSH descriptor: [HIV] explode all trees

#19 MeSH descriptor: [Tuberculosis] explode all trees

#20 MeSH descriptor: [Pregnancy] explode all trees

#21 #17 or #18 or #19 or #20

#22 #16 not #21

Limited Publication Year from 1990 to 2016, in Trials

#23 MeSH descriptor: [Child] explode all trees

#24 MeSH descriptor: [Infant] explode all trees

#25 MeSH descriptor: [Adolescent] explode all trees

#26 #23 or #24 or #25

#27 #22 and #26

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

**Supplementary Methods 2. PRISMA Checklist for Systematic Review and Meta-analysis**

|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic** | **#** | **Checklist item** | **Reported on page #** |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | |  |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2-3 |
| **INTRODUCTION** | | |  |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 3-4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| **METHODS** | | |  |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | Not applicable |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 4 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 4 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Supplementary appendix |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 4 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 4 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 4-5 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 10-11, no formal method |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 5 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis. | 5 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 6 and Supplement |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 5 |
| **RESULTS** | | |  |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Figure 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 6-9 and figures |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | no formal method used |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Table 2 & Figure 2 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Figure 2 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 8 and Supp Figure 1 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 8-9, Table 3 |
| **DISCUSSION** | | |  |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 10-11 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 10-11 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 12-13 |
| **FUNDING** | | |  |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | Not applicable |

**Supplementary Table 1. Characteristics of included studies**

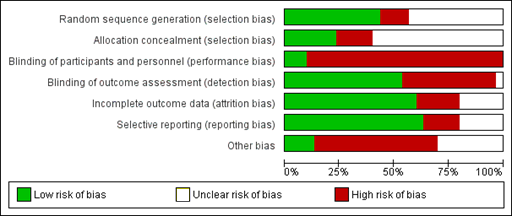
|  |  |
| --- | --- |
| ***Allameh*** |  |
|  |  |
| Methods | * Year of publication: 2015 * Study design: double-blind randomized placebo-controlled * Study period: na * Condition: pyelonephritis * Power calculation: based on the expected changes to the procalcitonin (as primary variable) assuming a power equal to 80% |
| Participants | * Country: Iran * Setting: university-affiliated children’s hospital (infectious and nephrology units), (inpatients/outpatients) * Inclusion Criteria: children with a definite or probable diagnosis of acute pyelonephritis confirmed by clinical symptoms, blood and urine laboratory findings, and results of the dimercaptosuccinic acid (DMSA) scan, age between 1 and 14 years * Exclusion criteria: concurrent acute or chronic inflammatory and infectious diseases * Age group: 1 year – 14 years * Gender (m/f): 8/62 * Numbers: Treatment group (35), Placebo group (35) |
| Interventions | * N-acetylcysteine, weight > 30 kg, 900 mg/d; weight 30 kg-8.5 kg, 600 mg/d; weight <8.5kg, 70 mg/kg/d for 5d+ routine antimicrobial drug regimen (ceftriaxone,cefotaxime, ceftizoxime, ceftazidime, amikacin, meropenem) * placebo for 5d + routine antimicrobial drug regimen (ceftriaxone,cefotaxime, ceftizoxime, ceftazidime, amikacin, meropenem) |
| Relevant outcomes | * Type of cure assessed: Mean day of resolving of pyuria, bacteriuria * Population analysed (cure/failure): 70 (NS/NS) * Timing of assessment: calculation of the mean day |
|  |  |
| ***Baker*** |  |
|  |  |
| Methods | * Year of publication: 2001 * Study design: prospective, randomized, single-blind * Study period: 09/1996 - 03/1998 * Condition: febrile UTI * Power calculation: this study achieved a 75% power to detect a true difference of 30% in treatment failures |
| Participants | * Country: United States of America * Setting: tertiary hospital (outpatients) * Inclusion Criteria: Children 6 months to 12 years; temperature > 38°C and diagnosed as having a UTI based on presenting history, physical examination and urinalysis findings * Exclusion criteria: patients with known uropathy; current antibiotic therapy; * allergy to study antibiotics; clinically unstable patients * Age group: 6 months - 12 years * Gender (m/f): 7/62 * Numbers: Treatment group (34), treatment group (35) |
| Interventions | * TMP-SMX p.o. (5 mg/Kg of TMP twice daily) 10 days * TMP-SMX p.o. 10 days plus ceftriaxone im (50 mg/Kg) 1 day |
| Relevant outcomes | * Type of cure assessed: microbiological (urine culture) * Population analysed (cure/failure): 60/9 * Timing of assessment: Day 2 OAT |
|  |  |
| ***Bakkaloglu*** |  |
|  |  |
| Methods | * Year of publication: 1996 * Study design: double-blind randomized clinical trial * Study period: 11/1991 - 04/1993 * Condition: pyelonephritis, upper UTI * Power calculation: NS |
| Participants | * Country: Turkey * Setting: tertiary care hospital * Inclusion Criteria: patients with complicated or uncomplicated pyelonephritis, pyelonephritis defined as the presence of two or more of the following signs or symptoms: fever, flank pain, pyuria, bacteriuria and urine culture showing >105 CFU/ml * Exclusion criteria: NS * Age group: mean age ± SD (years): treatment group 1 (8.1 ± 3.6); treatment group 2 (8.3 ± 2. * 9) * Gender (m/f): 22/78 * Numbers: Treatment group 1 (50), treatment group 2 (50), |
| Interventions | * ceftriaxone 50 mg/kg (once-daily) for 10 days * cefotaxime 50 mg/kg (twice-daily) for 10 days |
| Relevant outcomes | * Type of cure assessed: microbiological (persistent bacteriuria) * Population analysed (cure/failure): 100 (37/8) * Timing of assessment: 10 days after EOT |
|  |  |
| ***Benador*** |  |
|  |  |
| Methods | * Year of publication: 2001 * Study design: multi-centre, randomized controlled trial * Study period: 06/1995 - 04/1999 * Condition: pyelonephritis * Power calculation: 106 children per group to detect difference of 20% in the rate of renal scarring, with a power of 80% and a value of 0.05 (two tailed) |
| Participants | * Country: Switzerland * Setting: tertiary hospitals (inpatients) * Inclusion Criteria: children aged between 3 months and 16 years with probable acute pyelonephritis * Exclusion criteria: age less than 3 months, history of abnormalities of the urinary tract; and hypersensitivity to cephalosporins * Age group: 3 months – 16 years * Gender (m/f): 52/177 * Numbers: Treatment group 1 (111), treatment group 2 (118) |
| Interventions | * IV ceftriaxone (50 mg/kg once daily) for 10 days * IV ceftriaxone (50 mg/kg once daily) for 3 days followed by p.o. cefixime (4 mg/kg twice daily) to 15 days |
| Relevant outcomes | * Type of cure assessed: clinical (recurrence of UTI with fever) and microbiological (repeat urine culture) * Population analysed (cure/failure): 229 (205/15) * Timing of assessment: <14 days after EOT |
|  |  |
| ***Bocquet*** |  |
|  |  |
| Methods | * Year of publication: 2012 * Study design: multi-centre, prospective randomized trial * Study period: 08/2004 - 04/2008 * Condition: pyelonephritis * Power calculation: 349 per group to detect difference in rate of kidney scarring of 20% |
| Participants | * Country: France * Setting: hospital emergency departments (outpatients) * Inclusion Criteria: Children aged 1 month to 36 months, first febrile UTI, temperature ≥ 38.5ºC, positive urine for WBC and gram negative rods, pro-calcitonin ≥ 0.5 ng/mL, normal kidney ultrasound & pre-natal ultrasound and no known uropathy * Exclusion criteria: Primary exclusion criteria; allergy to study medications, severely ill children, vomiting and/or diarrhea precluding oral medication; uncertain adherence; received antibiotic therapy in 5 days before inclusion/ Secondary; normal DMSA, procalcitonin < 0.5 ng/mL, urine culture negative or > 1 organism or resistant to study drugs; recurrence of acute pyelonephritis before 2nd DMSA * Age group: 1 month to 36 months * Gender (m/f): 31/65 * Numbers: Treatment group 1 (85), treatment group 2 (86) |
| Interventions | * Oral group: cefixime for 10 days (initial double-dose (8 mg/kg) followed by 4 mg/kg twice daily) * Sequential group: IV ceftriaxone 50 mg/kg for 4 days followed by oral cefixime 4 mg/kg twice daily for 6 days |
| Relevant outcomes | * Type of cure assessed: clinical (apyrexia during treatment, recurrence at month 1) * Population analysed (cure/failure): 171 (NS/NS) * Timing of assessment: OAT, at 1 month |
|  |  |
| ***Bégué*** |  |
|  |  |
| Methods | * Year of publication: 1998 * Study design: prospective, multi-centric, parallel, randomised, open clinical trial * Study period: 09/1989 - 07/1990 * Condition: upper UTI * Power calculation: NS |
| Participants | * Country: France * Setting: inpatients/outpatients * Inclusion Criteria: neonates>31 gestation weeks - 15 years old, fever > 38.5 oC, C-reactive protein > 25 mg/l and positive urine culture * Exclusion criteria: allergy to study drug, patients treated previously with parenteral antibiotic therapy, resistance to study drugs, bacterial persistence, acquired resistance, relapse (one month after discharge), recurrence * Age group: Neonates (>31 weeks) - 15 years * Gender (m/f): not reported * Numbers: Treatment group (81), treatment group (50) |
| Interventions | * IV or IM ceftriaxone 50mg/kg/d once daily for 5-14 days * IV or IM cefotaxime 100-150 mg/kg/d in 3-4 injections for 5-14 days * In both groups, possibility to switch to oral therapy |
| Relevant outcomes | * Type of cure assessed: clinical (defervescence, recurrence of clinical signs or symptoms) and microbiological (urine culture) * Population analysed (cure/failure): 131 (data not reported separately for UTIs) * Timing of assessment: at day 5 to day 14 (EOT), 1 month after the EOT |
| ***Carapetis*** |  |
|  |  |
| Methods | * Year of publication: 2001 * Study design: prospective, randomized controlled, not blinded * Study period: 03/1994 - 01/1997 * Condition: pyelonephritis, UTI * Power calculation: 87 per group to show one day difference in fever duration |
| Participants | * Country: Australia * Setting: tertiary care hospital (inpatients) * Inclusion Criteria: Children aged 1 month to 12 years, ill, vomiting and unable to take orals   Reliably, urine culture: suprapubic aspirate specimens or a pure growth of ≥ 108 bacteria/L (= 105/mL)   * Exclusion criteria: allergy to aminoglycoside, renal, hearing, vestibular dysfunction, neutropenia/immunodeficiency * Age group: 1 months – 12 years * Gender (m/f): 57/122 * Numbers: Treatment group 1 (90), treatment group 2 (89) |
| Interventions | * gentamicin once daily 7.5 mg/kg (<5 years); 6.0 (5 to 10 years); and 4.5 (>10 years) * gentamicin three doses daily 7.5 mg/kg (<5 years); 6.0 (5 to 10 years); and 4.5 (>10 years)   For both groups, when subjects were afebrile for 24 h, gentamicin was discontinued for oral therapy |
| Relevant outcomes | * Type of cure assessed: clinical (resolution of clinical signs and symptoms resolved and no new clinical signs and symptoms without use of other antibiotics) and microbiological cure (eradication of the causative pathogen) * Population analysed (cure/failure): 179 (116/3) * Timing of assessment: day 2 of OAT |
|  |  |
| ***Cheng*** |  |
|  |  |
| Methods | * Year of publication: 2006 * Study design: parallel, randomized – controlled study * Study period: 01/2003 - 12/2004 * Condition: acute lobar nephronia * Power calculation: NS |
| Participants | * Country: Taiwan * Setting: tertiary care hospital (inpatients) * Inclusion Criteria: Children aged 0 months to 16 years; UTI plus CT findings of lobar nephronia following US showing nephromegaly and/or focal renal mass * Exclusion criteria: uncomplicated acute pyelonephritis * Age group: mean age ± SD (years): treatment group 1 (4.16 ± 4.22), treatment group 2 (3.72 * ± 4.14) * Gender (m/f): 30/50 * Numbers: Treatment group 1 (39), treatment group 2 (41) |
| Interventions | * 2-week antibiotic treatment * 3-week antibiotic treatment |
| Relevant outcomes | * Type of cure assessed: clinical (persistence or recurrence of symptoms of a UTI) and microbiological (urine culture- bacteriological persistence or relapse ) * Population analysed (cure/failure): 80 (73/7) * Timing of assessment: 3-7 days after EOT |
|  |  |
| ***Chong*** |  |
|  |  |
| Methods | * Year of publication: 2003 * Study design: parallel, randomized – controlled study * Study period: 01/2000-05/2001 * Condition: pyelonephritis, UTI * Power calculation: 220 patients in total to show 10% difference in UTI cure with 80% power |
| Participants | * Country: Singapore * Setting: tertiary care hospital (inpatients) * Inclusion Criteria: Children aged I month to 13 years; UTI confirmed on 2 clean catch urine samples (single organism > 100,000/mL) or 1 catheter specimen (single organism > 1,000/mL) * Exclusion criteria: known obstructive uropathy; aminoglycoside or other nephrotoxic agent in previous month; allergy to aminoglycoside; renal or hearing impairment (including abnormal baseline) * Age group: 1 month -13 years * Gender (m/f): 85/87 * Numbers: Treatment group 1 (84), treatment group 2 (88) |
| Interventions | * OD gentamicin 5 mg/kg d * TDS gentamicin 6 mg/kg d divided 8 hourly. For both groups, when afebrile and provided negative blood culture, switch to a suitable oral antibiotic (co-trimoxazole or cephalexin), total 14 days if abnormal imaging or 10 days if imaging are normal |
| Relevant outcomes | * Type of cure assessed: clinical (defervescence) and microbiological (urine culture) * Population analysed (cure/failure): 172 (172/0) * Timing of assessment: OAT and EOT |
|  |  |
| ***Dagan*** |  |
|  |  |
| Methods | * Year of publication: 1992 * Study design: multi-centre, open label, randomized, comparative study * Study period: 01/1989 - 06/1991 * Condition: UTI * Power calculation: NS |
| Participants | * Country: Israel * Setting: five medical centres (inpatients/outpatients) * Inclusion Criteria: patients 6 months to 13 years old, having symptoms suggestive of UTI for less than 2 weeks, urinalysis > 10/hpf in a SPA, catheter, bacteriuria, colonies > 1000 cfu/ml (suprapublic aspiration or catheter), > 100000 cfu/ml (clean-catch or 2 bag specimens), one single pathogen * Exclusion criteria: unable to take oral treatment due to frequent vomiting, unequivocal alternative source for fever, allergy to study drugs, UT abnormalities, chronic disease: underlying anomalies or chronic disease (gastrointestinal, liver, kidney, malignancy), concurrent antibiotics, negative urine culture or more than one type of bacteria, resistance to study antibiotics, poor compliance * Age group: 6 months -13 years * Gender (m/f): 9/67 * Numbers: Treatment group 1 (31), treatment group 2 (33) |
| Interventions | * cefixime 8 mg/kg/d once a day 7-10 days * co-trimoxazole 8/40mg/kg/d in 2 doses 7-10 days |
| Relevant outcomes | * Type of cure assessed: clinical (defervescence) and microbiological (urine culture) * Population analysed (cure/failure): 76 (61/3) * Timing of assessment: 72 hours OAT, 3-4 weeks after EOT |
|  |  |
| ***Francois*** |  |
|  |  |
| Methods | * Year of publication: 1997 * Study design: multi-centre, open, randomized, comparative, equivalence study * Study period: 11/1993 - 01/1995 * Condition: pyelonephritis * Power calculation: NS |
| Participants | * Country: France * Setting: tertiary care hospitals (inpatients) * Inclusion Criteria: children with fever ≥ 38 oC, signs of systematic infection, increased C-reactive protein and neutrophils, positive urinalysis (white blood cells ≥ 10000/ml and bacteriuria) and ≥ 100000 cfu/ml of a single pathogen in urine culture * Exclusion criteria: previous acute pyelonephritis, resistance to study antibiotics, allergy   to study drugs, known urinary tract pathology, need for IV treatment based on ultrasound, kidney failure, immunodeficiency, other concurrent infection   * Age group: > 6months - ≤ 10 years * Gender (m/f): 14/114 * Numbers: Treatment group 1 (63); treatment group 2 (65) |
| Interventions | All patients D1-D4: ceftriaxone 50mg/kg/d + netilmicin 6-7.5 mg/kg/d in 3 doses).  After randomisation:   * Group A outpatient oral cefixim 8mg/kg/d in 2 doses. * Group B Day 5-10: intpatient IM or IV ceftriaxone 50 mg/kg/d. * Control Day 5-10: IV ceftriaxone |
| Relevant outcomes | * Type of cure assessed: clinical (resolution of all signs and symptoms) and microbiological (urine culture) * Population analysed (cure/failure): 128 (127/1) * Timing of assessment: >2 days after EOT |
|  |  |
| ***Gok*** |  |
|  |  |
| Methods | * Year of publication: 2001 * Study design: randomized, prospective, single centre study * Study period: 11/1998 - 09/1999 * Condition: pyelonephritis * Power calculation: NS |
| Participants | * Country: Turkey * Setting: tertiary care hospital * Inclusion Criteria: symptoms consistent with UTI, urinalysis showing >5 leukocytes/high power field, urine culture was defined as >105 colonies of a single organism isolated from clean-catch urine * Exclusion criteria: none of the patients were on antibiotic prophylaxis * Age group: 1 month - 15 years * Gender (m/f): 10/44 * Numbers: Treatment group 1 (), control group 2 () |
| Interventions | * oral cefixime 8 mg/Kg/day for 10 days * im ceftizoxime 50 mg/Kg twice a day for 2 days followed by oral cefixime for 8 days |
| Relevant outcomes | * Type of cure assessed: clinical (resolution of all signs and symptoms of UTI) and microbiological (eradication of baseline pathogen) * Population analysed (cure/failure): 54 (48/6) * Timing of assessment: EOT and 3 weeks after EOT |
| ***Huang*** |  |
|  |  |
| Methods | * Year of publication: 2011 * Study design: double-blind, placebo-controlled, randomly assigned, prospective study * Study period: 01/2002 - 12/2004 * Condition: pyelonephritis * Power calculation: NS |
| Participants | * Country: Taiwan * Setting: tertiary referral center (inpatients) * Inclusion Criteria: between 1 week and 16 years of age, had evidence of UTI (core temperature of ≥38°C, positive urine culture, growth of microorganisms ≥ 105 colony-forming units per mL from a clean, voided midstream urine in older children or ≥ 103 colony-forming units per mL after bladder catheterization or any growth from a suprapubic puncture in younger children, and ≥5 leukocyte cells per high-power field), being at high risk of renal scar formation (see full-text) * Exclusion criteria: a history of UTI, previous treatment with either oral or intravenous antibiotics, there was concurrent urogenital uropathy (except vesicoureteral reflux [VUR]), DMSA was not performed within 72 hours of admission, and there was no photopenic finding or diffuse photopenic kidney on DMSA or space-occupying lesions on ultrasonography, except those progressing to abscess formation * Age group: 1 week -16 years * Gender (m/f): 44/40 * Numbers: Methylprednisolone group (19), placebo group 2 (65) |
| Interventions | * Group A IV cephalothin (100 mg/kg/d) every 6 hours + IV gentamicin (5 mg/kg/d) in 2 doses daily for a minimum of 3 days + oral Methylprednisolone for 3 days (1.6 mg/kg per day, maximum of 48 mg/day) in 4 divided doses. * Group B: same antimicrobial treatment, placebo instead of methylprednisolone   Both groups: IV antibiotics were changed to the oral form once patients had been afebrile for 48 hours, for approximately an additional 14 days. |
| Relevant outcomes | * Type of cure assessed: Clinical (defervescence) and microbiological (urine culture) * Population analysed (cure/failure): 84 (84/0) * Timing of assessment: 1, 3, and 6 months after hospital discharge |
|  |  |
| ***Kafetzis*** |  |
|  |  |
| Methods | * Year of publication: 2000 * Study design: parallel, randomized-controlled study * Study period: na * Condition: pyelonephritis * Power calculation: NS |
| Participants | * Country: Greece * Setting: tertiary care hospital (inpatients) * Inclusion Criteria: patients between 1 month and 12 years of age with acute pyelonephritis requiring intravenous antimicrobial treatment, fever > 38.0°C, signs/symptoms of UTI according to their age, pyuria, leukocytosis, increased C-reactive protein (>30 mg/ml) and increased erythrocyte sedimentation rate, isolation of a bacterial pathogen from two samples of clean catch urine at ]105 colony-forming units/ml or of ]103 CFU from a urine sample obtained by suprapubic aspiration or urethral catheterization before treatment * Exclusion criteria: any antibacterial treatment within four weeks prior to study initiation, a history of intolerance to any aminoglycoside, impaired baseline renal, hearing or vestibular function or were infected with a pathogen resistant to aminoglycosides * Age group: 1 month - 12 years * Gender (m/f): 6/10 * Numbers: Treatment group 1 (10), treatment group 2 (6) |
| Interventions | * isepamicin at 7.5 mg/kg twice daily * amikacin at 7.5 mg/kg twice daily for 10–14 days |
| Relevant outcomes | * Type of cure assessed: clinical (re-appearance of signs and symptoms) and microbiological (urine culture) * Population analysed (cure/failure): 16 (16/0) * Timing of assessment: 2–3 days OAT, EOT, and 7 and 30 days after EOT |
|  |  |
| ***Levtchenko*** |  |
|  |  |
| Methods | * Year of publication: 2001 * Study design: prospective randomized study * Study period: 12/1995 - 12/1998 * Condition: pyelonephritis * Power calculation: NS |
| Participants | * Country: Belgium * Setting: tertiary care hospital (inpatients) * Inclusion Criteria: Children aged 6 weeks to 15 years, severely ill, fever ≥ 38.3°C associated with variable combinations of clinical signs ; biological alterations (sedimentation rate > 30mm/h, increased CRP, leukocyte count > 15,000 with more than 50% neutrophils) and urinalysis revealing abnormal amounts of leukocytes (> 5 WBC/mm³) and/or bacteria, absence of other focal infection * Exclusion criteria: negative urine culture, resistant organisms, severe uropathies, fever > 38°C within 24 hours of randomisation * Age group: 6 weeks -15 years * Gender (m/f): NS * Numbers: Treatment group 1 (43), treatment group 2 (44) |
| Interventions | Temocillin 25 mg/kg within first few hours.  After 3 days of IV treatment the patients were randomized:   * group A: IV treatment continued for another 4 days * group B: oral treatment chosen according to the antibiogram   At the end of day 7, oral treatment was started in group A and continued until day 21 for both groups. |
| Relevant outcomes | * Type of cure assessed: microbiological (urine culture) * Population analysed (cure/failure): 87 (87/0) * Timing of assessment: Day 7 OAT and follow-up 3 weeks to 6 months after discharge |
|  |  |
| ***Marild*** |  |
|  |  |
| Methods | * Year of publication: 2009 * Study design: prospective, coordinated, randomized, open, multi-centre trial * Study period: 06/1996 - 02/2001 * Condition: febrile UTI * Power calculation: 256 and 128 required for each group for a difference in treatment response ≤ 8% |
| Participants | * Country: Sweden * Setting: tertiary care hospital (inpatients/outpatients) * Inclusion Criteria: aged between 1 month and 12 years, fever ≥38.5°C during the last 24 h, clinical manifestations (optional: abdominal pain, vomiting, flank pain or costo-vertebral angle tenderness), serum C-reactive protein of at least 20 mg/L, significant growth: ≥102 colony forming units (cfu)/mL for suprapubic aspirates, ≥104 cfu/mL for midstream samples and ≥105 cfu/mL for bag urines * Exclusion criteria: previous treatment for UTI, antibiotics in previous 7 days, needing IV therapy, known uropathy, hypersensitive to medications, growth of more than two bacterial species were considered to be contaminated * Age group: 1 month - 12 years * Gender (m/f): 106/277 * Numbers: Treatment group 1 (255), treatment group 2 (128) |
| Interventions | * ceftibuten (9 mg/kg/day) * TMP-SMX (3 mg + 15 mg)/kg given twice daily for 10 days |
| Relevant outcomes | * Type of cure assessed: Clinical (resolution of signs/symptoms) and microbiological (urine culture) * Population analysed (cure/failure): 383 (342/21) * Timing of assessment: 4–10 days after EOT |
|  |  |
| ***Montini*** |  |
|  |  |
| Methods | * Year of publication: 2007 * Study design: randomised controlled, multicentre, open labelled, parallel group, non-inferiority trial * Study period: 06/2000 - 07/2005 * Condition: pyelonephritis, febrile UTI * Power calculation: 220/group for 10% difference between groups |
| Participants | * Country: Italy * Setting: tertiary care hospitals (inpatients) * Inclusion Criteria: Children aged 1 month to < 7 years; first episode of APN, normal antenatal ultrasound, 2 concordant urinalyses (> 25 WBC/μL) and 2 concordant urine cultures (> 100,000 CFU/mL) collected in sterile bags, at least 2 of fever ≥ 38ºC, ESR ≥ 30mm, CRP ≥ 3 times upper limit of normal, neutrophil count > normal for age * Exclusion criteria: severe clinical sepsis, dehydration, vomiting, allergy to study drugs, creatinine clearance < 70 * Age group: 1 month - <7 years * Gender (m/f): 180/322 * Numbers: Treatment group 1 (255), treatment group 2 (128) |
| Interventions | * oral treatment with co-amoxiclav 50 mg/kg/d in 3 doses for 10 days * initial parenteral treatment with ceftriaxone 50 mg/kg/d in a single dose for 3 days, followed by oral co-amoxiclav 50 mg/kg/day in three doses for 7 days |
| Relevant outcomes | * Type of cure assessed: Clinical (time to defervescence) and microbiological (urine culture) * Population analysed (cure/failure): 502 (388/2) * Timing of assessment: Day 3 OAT |
|  |  |
| ***Neuhaus*** |  |
|  |  |
| Methods | * Year of publication: 2008 * Study design: prospective, randomized, controlled, multi-centre trial * Study period: 07/2001-04/2004 * Condition: pyelonephritis * Power calculation: 98/group for 20% difference in renal scarring between groups |
| Participants | * Country: Switzerland * Setting: tertiary care hospitals (inpatients/outpatients) * Inclusion Criteria: children aged 6 months to 16 years, fever > 38.5ºC, abnormal urinalysis, with/without abdominal or flank pain, irritability, vomiting, diarrhea, feeding difficulties * Exclusion criteria: age < 6 months, antibiotic pre-treatment of acute infection, other abnormalities of the urinary tract, known impaired renal function, patients on immunosuppressive therapy and known hypersensitivity to cephalosporins, if the clinical condition suggested septicaemia or if other reasons precluded oral treatment, patients subsequently found not to have UTI or APN on DMSA were excluded * Age group: 6 months - 16 years * Gender (m/f): 18/134 * Numbers: Treatment group 1 (255), treatment group 2 (128) |
| Interventions | * oral-only group: 9 mg/kg of ceftibuten orally twice on the first day and once daily thereafter for 14 days * intravenous/oral group: 50 mg/kg IV ceftriaxone once daily for 3 days and then 9 mg/kg of ceftibuten orally for 11 days |
| Relevant outcomes | * Type of cure assessed: clinical (defervescence) and microbiological (urine culture) * Population analysed (cure/failure): 152 (137/15) * Timing of assessment: Day 3 OAT |
|  |  |
| ***Noorbakhsh*** |  |
|  |  |
| Methods | * Year of publication: 2004 * Study design: prospective, randomized, clinical study * Study period: 02/2003 - 06/2003 * Condition: pyelonephritis * Power calculation: NS |
| Participants | * Country: Iran * Setting: tertiary care hospital (inpatients) * Inclusion Criteria: children aged 1 to 10 years, need for IV therapy, pathogen susceptible to study drug * Exclusion criteria: allergy to study drugs, kidney obstruction/abscess, severe underlying disease/immunosuppressive therapy, other antibiotics required; abnormal transaminases/full blood count, treated with IV antibiotics for 24 hours plus within 72 hours of baseline mid-stream urine, CKD stages 4, 5 * Age group: ≤ 10 years * Gender (m/f): NS * Numbers: Treatment group 1 (30), treatment group 2 (24) |
| Interventions | * Group A: IV amikacin (15 mg/Kg daily) or gentamicin (3 mg/Kg daily) + ampicillin (100 mg/Kg daily) for 7-10 days * Group B: IV ceftriaxone (50 mg/Kg daily) for the first 2 days and then switched to cefixime (8 mg/Kg daily) orally for 8 days |
| Relevant outcomes | * Type of cure assessed: clinical (clinical response) and microbiological (urine culture) * Population analysed (cure/failure): 54 (45/9) * Timing of assessment: 3 to 5 days, end of therapy, 5 to 9 days after EOT and 4 to 6 weeks |
|  |  |
| ***Peña*** |  |
|  |  |
| Methods | * Year of publication: 2009 * Study design: prospective, randomized study * Study period: 04/2003 - 04/2005 * Condition: febrile UTI * Power calculation: NS |
| Participants | * Country: Chile * Setting: tertiary care hospital (inpatients/outpatients) * Inclusion Criteria: fever ≥ 38oC, absence of other sources for fever, abnormal urine sample, catheter >10000 cfu/ml, responsible guardians, easy access to the hospitals * Exclusion criteria: severely ill: haemodynamic failure, history of UTI or UT abnormalities, chronic disease: immunodeficiency, chronic pathology, protocol violation: patients that received "mixed" antimicrobial treatment, no adherence to oral therapy due to poor tolerance * Age group: 2 months – 2 years * Gender (m/f): 42/70 * Numbers: Treatment group 1 (54), control group 2 (58) |
| Interventions | Amikacin or ceftriaxone according to urine culture result and randomized in:   * IV in the hospital * IV in outpatient facility then switched to oral cefadroxil or cefuroxime or nitrofurantoin or ciprofloxacin based on in vitro susceptibility completing 7 to 10 days of treatment |
| Relevant outcomes | * Type of cure assessed: clinical (resolution of signs and symptoms) and microbiological (urine culture) * Population analysed (cure/failure): 112 (80/3) * Timing of assessment: day 5 of OAT, 5 days after EOT |
| ***Schaad*** |  |
|  |  |
| Methods | * Year of publication: 1998 * Study design: randomized, open label (but third party-blinded), parallel group, multicenter trial * Study period: na * Condition: pyelonephritis * Power calculation: 150 patients/group to ensure difference in eradication rates < * 12.6% |
| Participants | * Country: Switzerland, Finland, Greece, France, Israel, Belgium, Hungary, Slovenia, Spain, Germany, Sweden, Netherlands, Czech Republic * Setting: (inpatients) * Inclusion Criteria: Children aged ≥1 month to 12 years,fever of at least 38.5°C; WBC > 15.000/mL, CRP > 30 μg/mL, evidence of pyuria, aged > 2 years to have one of the following: abdominal pain or tenderness, flank pain, or tenderness and dysuria, positive urinalysis (> 10/mm3 , 10/hpf,) and urine culture (SPA: any number; catheter: ≥ 10000 cfu/ml; clean-catch or bag: ≥ 100000 cfu/ml; at least one causative pathogen) * Exclusion criteria: weight < 3 kg, previous investigational drug, allergy to beta-lactams or arginine, kidney or liver dysfunction, immunodeficiency, severely ill: concurrent illness that obscuring the clinical outcome * Age group: 1 month - 12 years * Gender (m/f): 69/166 * Numbers: Treatment group 1 (115), treatment group 2 (120) |
| Interventions | • iv cefepime 50 mg/kg/8 h until child afebrile for at least 48 hours  • iv ceftazidime 50 mg/kg/8 h until child afebrile for at least 48 hours  Both groups: switch to TMP-SMZ orally until total duration of therapy 12-14 days (if resistance or intolerance, or was between 1 and 2 months old, other oral agent) |
| Relevant outcomes | * Type of cure assessed: clinical (improvement in signs and symptoms improved and no new) and microbiological (urine culture) * Population analysed (cure/failure): 235 (180/32) * Timing of assessment: EOT, 5-9 days after EOT and 4-6 weeks after EOT |
|  |  |
| ***Sobouti*** |  |
|  |  |
| Methods | * Year of publication: 2013 * Study design: simple non-blind open label randomized clinical trial * Study period: 09/2004-10/2006 * Condition: pyelonephritis * Power calculation: using Altman nomogram with a power of 80 %. |
| Participants | * Country: Iran * Setting: tertiary care hospital (inpatients) * Inclusion Criteria: high grade fever (>38.5 °C), with or without vomiting, malaise, loin pain, or tenderness of costovertebral angle, and the absence of other sources for fever on physical examination, positive urine culture was defined as the isolation of >105 colony forming units (cfu)/ml of a single bacterium from the midstream urine sample taken from a continent child, the isolation of bacteria (per ml) from a suprapubic urine sample, or the isolation of >1,000 colonies of a single organism from the catheter urine sample, positive DMSA (any photopenic lesion visible on the posterior view without volume loss) * Exclusion criteria: children with neurogenic bladder, systemic hypertension, obstructive uropathy, and high grade vesicoureteral (grade 4–5) * Age group: 1 months - 10 years * Gender (m/f): 2/59 * Numbers: Aminoglycoside group (25), aminoglycoside and vitamin A group (17), aminoglycoside and vitamin A group (19) |
| Interventions | * cephalothin or ampicillin (100 mg/kg/d four times daily) and amikacin (15 mg/kg/d three times daily) for 10 days +oral vitamin A (1,500 U/kg/d) * cephalothin or ampicillin (100 mg/kg/d four times daily) and amikacin (15 mg/kg/day three times daily) for 10 d + oral vitamin E (20 IU/day) * cephalothin or ampicillin (100 mg/kg/d four times daily) and amikacin (15 mg/kg/d three times daily) for 10 days |
| Relevant outcomes | * Type of cure assessed: clinical (defervescence) and microbiological (urine culture) * Population analysed (cure/failure): 54 (na/na) * Timing of assessment: day 3 OAT |
|  |  |
| ***Tapaneya-Olarn*** |  |
|  |  |
| Methods | * Year of publication: 1999 * Study design: double-blind randomized placebo-controlled * Study period: 09/1996 - 09/1997 * Condition: UTI * Power calculation: NS |
| Participants | * Country: Thailand * Setting: NS * Inclusion Criteria: patients with fever, signs and symptoms of UTI and urine culture obtained from cleaned catch urine or cleaned bag with more than 105 colonies/ml of a single organism * Exclusion criteria: known allergy to aminoglycosides, recently received aminoglycosides in the past 2 weeks, on high dose of diuretics or amphotericin B, underlying renal disease prior to studies, history of hearing loss or vestibular dysfunction, immunocompromised host, neutropenia, or renal impairment. * Age group: 6 months – 12 years * Gender (m/f): 12/12 * Numbers: Treatment group 1 (13), Treatment Group 2 (11) |
| Interventions | * IV gentamicin 4.5mg/kg/d once daily for 3 d followed by amoxicillin plus clavulanic acid 50 mg/kg/d (in 3 divided doses) oral for 7 days * IV gentamicin 4.5mg/kg/d in 3 divided doses for 3 d followed by amoxycillin plus clavulanic acid 50 mg/kg/d (in 3 divided doses) p.os for 7 days |
| Relevant outcomes | * Type of cure assessed: microbiological (urine culture) * Population analyzed (cure/failure): 24 (24/0) * Timing of assessment: Day 2 OAT and 10 days after EOT |
| ***Toporovski*** |  |
|  |  |
| Methods | * Year of publication: 1992 * Study design: open, prospective, multicentre, randomized comparative study * Study period: NS * Condition: pyelonephritis * Power calculation: NS |
| Participants | * Country: Brazil, Germany, Switzerland * Setting: tertiary care hospitals (inpatients/outpatients) * Inclusion Criteria: proven bacteriuria (> 105 colony forming units/ml cultured in a first void clean-catch, mid-stream specimen in two consecutive urine samples) and at least two suggestive symptoms: fever (≥37.5°C); dysuria; flank tenderness; urgency; and pyuria (> 25 leucocytes/high power field) * Exclusion criteria: resistance of the isolated, causative pathogen to the trial drugs, i.e, a zone diameter of ≤ 16mm and a minimal inhibitory concentration > 16 ug/rnl, as determined using standard methods; hypersensitivity of the patient to 13 beta-lactam antibiotics; renal impairment; and liver insufficiency * Age group: 2 years - 14 years * Gender (m/f): 13/24 * Numbers: Treatment group 1 (18), treatment group 2 (8), treatment group 3 (11) |
| Interventions | * group 1: 10 mg/kg of cefetamet pivoxil twice daily for 7 -10 days * group 2: 20 mg/kg of cefetamet pivoxil twice daily for 7-10 days * group 3: 30 - 50 mg /kg amoxycillin/clavulanic acid three times daily for 7 - 10 days |
| Relevant outcomes | * Type of cure assessed: clinical (clinical response) and microbiological (urine culture) * Population analysed (cure/failure): 37 (37/0) * Timing of assessment: EOT and 28 ± 7 days after start of treatment |
|  |  |
| ***Vigano*** |  |
|  |  |
| Methods | * Year of publication: 1992 * Study design: prospective, randomized trial * Study period: NS * Condition: pyelonephritis, complicated UTI, uncomplicated UTI * Power calculation: to detect 20% difference in effectiveness |
| Participants | * Country: Italy * Setting: tertiary hospital (inpatients) * Inclusion Criteria: age: 1 month to 12 years, two different urine samples collected by the clean-catch method or bladder catheterization containing ≥105 CFU of gram-negative bacteria per ml not resistant to the study agent) and signs of pyelonephritis (body temperature, ≥38.50C; erythrocyte sedimentation rate, >25 mm/l h; C-reactive protein, >20 ,ug/ml) * Exclusion criteria: (i) hypersensitivity to aminoglycosides; (ii) serum creatinine values abnormal for age; (iii) presence of ileostomies, ureterostomies, or neurogenic bladder; and (iv) a history or signs of deafness * Age group: 1 month – 12 years * Gender (m/f): 42/102 * Numbers: Treatment group 1 (74), treatment group 2 (70) |
| Interventions | * netilmicin 5 mg/kg four times daily intramuscularly for 10 days * netilmicin 2 mg/kg three times daily intramuscularly for 10 days |
| Relevant outcomes | * Type of cure assessed: microbiological (urine culture) * Population analysed (cure/failure): 144 (143/1) * Timing of assessment: 1 week after EOT |
|  |  |
| ***Vigano*** |  |
|  |  |
| Methods | * Year of publication: 1996 * Study design: multicentric randomized comparative study * Study period: na * Condition: UTI * Power calculation: NS |
| Participants | * Country: Italy, Greece, Netherlands, Colombia, Panama, Chile, Argentina, Mexico, Spain, Portugal, Guatemala, Venezuela * Setting: tertiary care hospitals (inpatients) * Inclusion Criteria: fever > 38 oC, WBC > 11000 (immature leukocytes >10%), positive urine culture, requiring hospitalization and IV treatment at least 5 days * Exclusion criteria: severely ill; high risk of death within 72h, allergy to study drugs, chronic disease such as renal failure, hearing disorder, severe prematurity, unacceptable concurrent therapy, negative urine culture, resistance to any usual treatment, poor compliance, requiring >14 days of treatment, insufficient data, incorrect initial diagnosis, incorrect inclusion criteria * Age group: 16 days - 16 years * Gender (m/f): NS * Numbers: Treatment group 1 (76), treatment group 2 (42) |
| Interventions | * IV or IM isepamicin at 7.5mg/kg twice daily for 4-14 days * IV or IM amikacin at 7.5mg/kg twice daily for 4-14 days |
| Relevant outcomes | * Type of cure assessed: clinical (resolution of all signs and symptoms of UTI) and microbiological (urine culture) * Population analysed (cure/failure): 118 (NS/NS) * Timing of assessment: daily, EOT and within 10-15 days by the end of EOT |
|  |  |
| ***Vilaichone*** |  |
|  |  |
| Methods | * Year of publication: 2001 * Study design: prospective randomized controlled trial * Study period: 01/1998 - 07/1999 * Condition: pyelonephritis * Power calculation: NS |
| Participants | * Country: Thailand * Setting: tertiary care hospital (inpatients) * Inclusion Criteria: Children aged 1 month to 15 years, fever ≥ 38oC, pyuria WBC ≥ 5/high power field and/or bacteriuria (≥ 1 gram negative rod per 10 oil immersion fields) , positive urine culture (> 105 cfus/ml of a single mathogen in midstream urine or bag), DMSA scan demonstrated cortical defect * Exclusion criteria: age < 1 month; previous UTI, known uropathy, allergic to study antibiotics, kidney failure, chronic disease, antibiotics in previous 48 hours * Age group: 1 month -15 years * Gender (m/f): 19/17 * Numbers: Treatment group 1 (18), control group 2 (18) |
| Interventions | • Study group: IV ceftriaxone 75 mg/kg/day switched on ceftibuten per OS 9 mg/Kg/day 24-48 hrs after defervescence  • Control group: IV ceftriaxone 75 mg/Kg/day for 10 days |
| Relevant outcomes | * Type of cure assessed: clinical (symptoms/signs) and microbiological (urine culture) * Population analysed (cure/failure): 36 (36/0) * Timing of assessment: 14 days after EOT, at 1 ,3 and 6 months |
|  |  |
| ***Yosefichaijan*** |  |
|  |  |
| Methods | * Year of publication: 2016 * Study design: randomised clinical trial * Study period: 07/2011-07/2012 * Condition: febrile UTI * Power calculation: NS |
| Participants | * Country: Iran * Setting: tertiary care hospital * Inclusion Criteria: girls aged 3 to 12 with UTI * Exclusion criteria: NS * Age group: 3 years - 12 years * Gender (m/f): NS * Numbers: NS |
| Interventions | * IV Ceftriaxone 50-75mg/kg/d and oral Cefixime 8mg/kg/d for 14 days + 250 mg vitamin C daily * IV Ceftriaxone 50-75mg/kg/day and oral Cefixime 8mg/kg/day for 14 days |
| Relevant outcomes | * Type of cure assessed: clinical (resolution of fever) and microbiological (urine culture) * Population analysed (cure/failure): NS * Timing of assessment: NS |
|  |  |
| ***Yousefichaijan*** |  |
|  |  |
| Methods | * Year of publication: 2015 * Study design: double-blinded, randomized, controlled trial * Study period: 04/2012 - 11/2013 * Condition: pyelonephritis * Power calculation: considering the prevalence of UTI, sample size was determined at 152 |
| Participants | * Country: Iran * Setting: (inpatients) * Inclusion Criteria: female, aged 5 to 12 years old, had a medical history and symptoms of UTI and diagnosed with acute pyelonephritis based on fever (without any source other than UTI) and evidence of renal inflammation on DMSA scan, and had positive urinalysis and culture results only for E coli sensitive to ceftriaxone and cefixime * Exclusion criteria: diagnosis of renal scarring based on the results of DMSA scan; history of any form of UTI; vesicoureteral reflux, symptoms of renal abscess, renal and urinary tract calculus, urinary tract obstruction, emphysematous pyelonephritis, renal hypoplasia, ectopic kidney, and any unilateral or bilateral renal anomaly based on ultrasonography, CT scan, and voiding cystourethrography findings; neurogenic bladder; history of voiding dysfunctions; anatomical problems of the genitalia such as labial adhesion, due to trauma, surgery, and congenital anomalies; history of allergy to vitamin E or its intolerance; history of diabetes mellitus, immunodeficiency, and organ transplantation; administration of antibiotics or vitamin E at least 5 days before the start of the study; severe sepsis and bacteremia; severe dehydration * Age group: 5 years - 12 years * Gender (m/f): 0/152 * Numbers: Treatment group 1 (76), treatment group 2 (76) |
| Interventions | * IV ceftriaxone 50 -75 mg/kg/d in 2 divided doses during hospitalization and 8 mg/kg/d of oral cefixime in 2 divided doses after discharge + 100 IU of oral vitamin E on a daily basis * IV ceftriaxone 50 -75 mg/kg/d in 2 divided doses during hospitalization and 8 mg/kg/d of oral cefixime in 2 divided doses after discharge + placebo 14 days |
| Relevant outcomes | * Type of cure assessed: clinical (resolution of fever and UT-related symptoms and signs) and microbiological (urine culture) * Population analysed (cure/failure): 152 (151/1) * Timing of assessment: day 3-4 OAT, 7 to 10 days after EOT |
|  |  |
| ***Yousefichaijan*** |  |
|  |  |
| Methods | * Year of publication: 2016 * Study design: randomized trial * Study period: na * Condition: febrile UTI * Power calculation: NS |
| Participants | * Country: Iran * Setting: tertiary care hospital (inpatients) * Inclusion Criteria: existence of UTI, an age of 3 to 12 years old, and indications for hospitalization to receive IV medication absence of a previous UTI history, dehydration (moderate to severe), inability to drink fluids and medications (oral drug intolerance), vomiting and suspected bacteraemic UTI * Exclusion criteria: patients who were not willing to participate or to take medication, diagnosis of renal scarring based on the results of DMSA scan; history of any form of UTI; vesicoureteral reflux, symptoms of renal abscess, renal and urinary tract calculus, urinary tract obstruction, emphysematous pyelonephritis, renal hypoplasia, ectopic kidney, and any unilateral or bilateral renal anomaly based on ultrasonography, CT scan, and voiding cystourethrography findings; neurogenic bladder; history of voiding dysfunctions; anatomical problems of the genitalia such as labial adhesion, due to trauma, surgery, and congenital anomalies; history of allergy to vitamin E or its intolerance; history of diabetes mellitus, immunodeficiency, and organ transplantation; severe sepsis and bacteremia * Age group: 3 years - 12 years * Gender (m/f): NS * Numbers: Treatment group 1 (100), control group 2 (100) |
| Interventions | * IV ceftriaxone at 50-75 mg/kg/d, + Zinc syrup (1 mg/kg/d) for 14 days * IV ceftriaxone at 50-75 mg/kg/d   Both groups: treatment was continued after discharge using cefixime suspension for a total of 14 days |
| Relevant outcomes | * Type of cure assessed: clinical (resolution of signs/symptoms) and microbiological (urine culture) * Population analysed (cure/failure): 200 (197/3) * Timing of assessment: 48 hours and 7 to 10 days after the start of * the treatment, and monthly after EOT for 3 months |
|  |  |

NS, not specified; na, not applicable; UTI, urinary tract infection; UT, urinary tract; OAT, on-antibiotic therapy; EOT, end of treatment; IV, intravenous; im, intramuscular; DMSA, dimercaptosuccinic acid

**Supplementary Table 2. Risk of bias in included studies**

|  |  |  |
| --- | --- | --- |
| ***Allameh 2015*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Low | Block-randomization |
| Allocation concealment (selection bias) | High | Children were allocated to the intervention according to their weight |
| Blinding of participants and personnel (performance bias) | Low | Incomplete blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken |
| Blinding of outcome assessment (detection bias) | Low | "The prescriber, and the examiner who measured and recorded outcomes were blinded to the allocations." |
| Incomplete outcome data (attrition bias) | Unclear | No cure/failure rates provided |
| Selective reporting (reporting bias) | Unclear | No cure/failure rates provided |
| Other bias | High | No limitations mentioned in the study. |
|  |  |  |
| ***Baker 2001*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Low | Opaque sealed envelopes |
| Allocation concealment (selection bias) | Low | Opaque sealed envelopes |
| Blinding of participants and personnel (performance bias) | High | No blinding. No placebo injection given. |
| Blinding of outcome assessment (detection bias) | Low | “Physician caring for patient at follow-up usually was not the physician who cared for the patient at ﬁrst visit”. All children had bandage on thigh (IM injection) |
| Incomplete outcome data (attrition bias) | Low | Only 4 (5.5%) patients lost in follow-up. Unlikely to influence results. |
| Selective reporting (reporting bias) | Low | Relevant outcomes reported |
| Other bias | High | Study supported by pharmaceutical company |
|  |  |  |
| ***Bakkaloglu 1996*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear | No information |
| Allocation concealment (selection bias) | Unclear | No information |
| Blinding of participants and personnel (performance bias) | High | Said to be “double-blind, randomized clinical trial” but no placebo injection given to ceftriaxone group |
| Blinding of outcome assessment (detection bias) | High | No blinding |
| Incomplete outcome data (attrition bias) | Low | All patients completed follow-up |
| Selective reporting (reporting bias) | Low | Relevant outcomes reported |
| Other bias | High | Study supported by pharmaceutical company |
|  |  |  |
| ***Bégué 1998*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear | Mentioned as "randomised", but no information on how patients were randomised is provided. |
| Allocation concealment (selection bias) | Unclear | No information |
| Blinding of participants and personnel (performance bias) | High | Open label study |
| Blinding of outcome assessment (detection bias) | High | Open label study. Clinical efficacy may have been affected by the lack of blinding. Laboratory outcomes (C-reactive protein normalisation and urine culture) unlikely to have been influenced by the lack of blinding. |
| Incomplete outcome data (attrition bias) | Unclear | No cure/failure rates provided separately for upper urinary tract infection. |
| Selective reporting (reporting bias) | Unclear | No cure/failure rates provided separately for upper urinary tract infection. |
| Other bias | Unclear | No information |
|  |  |  |
| ***Benador 2001*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Low | Opaque sealed envelopes |
| Allocation concealment (selection bias) | Low | Opaque sealed envelopes |
| Blinding of participants and personnel (performance bias) | High | No blinding |
| Blinding of outcome assessment (detection bias) | Low | Outcome (microbiological recurrence- repeat urine culture) was laboratory based and unlikely to be inﬂuenced by blinding. |
| Incomplete outcome data (attrition bias) | Low | 9 of 229 (4.4%) were excluded from results. Unlikely to inﬂuence results |
| Selective reporting (reporting bias) | Low | Relevant outcomes reported |
| Other bias | Unclear | No information |
|  |  |  |
| ***Bocquet 2012*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Low | Computer generated code |
| Allocation concealment (selection bias) | Unclear | No information |
| Blinding of participants and personnel (performance bias) | High | No blinding |
| Blinding of outcome assessment (detection bias) | Low | The determination of the day of defervescence cannot be influenced by the personnel's judgement. |
| Incomplete outcome data (attrition bias) | Unclear | No cure/failure rates provided |
| Selective reporting (reporting bias) | Unclear | No cure/failure rates provided |
| Other bias | Low | Grant supported |
|  |  |  |
| ***Carapetis 2001*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Low | Block-randomisation |
| Allocation concealment (selection bias) | Unclear | No information |
| Blinding of participants and personnel (performance bias) | High | Open label study |
| Blinding of outcome assessment (detection bias) | High | Open label study |
| Incomplete outcome data (attrition bias) | Low | None of 179 excluded from primary outcome of clinical cure. |
| Selective reporting (reporting bias) | Low | Relevant outcomes reported |
| Other bias | Unclear | No information |
|  |  |  |
| ***Cheng 2006*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | High | “Randomly allocated with serial entry” |
| Allocation concealment (selection bias) | High | Patients allocated alternately to each group (information from the authors)\* |
| Blinding of participants and personnel (performance bias) | High | No blinding |
| Blinding of outcome assessment (detection bias) | High | No blinding |
| Incomplete outcome data (attrition bias) | Low | No loss in follow-up. |
| Selective reporting (reporting bias) | High | Incomplete data on clinical symptom resolution |
| Other bias | Unclear | No information |
|  |  |  |
| ***Chong 2003*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear | No information |
| Allocation concealment (selection bias) | Unclear | No information |
| Blinding of participants and personnel (performance bias) | High | No blinding |
| Blinding of outcome assessment (detection bias) | Low | No blinding . Primary outcome was a laboratory result (negative urine culture) and unlikely to inﬂuenced by lack of blinding. |
| Incomplete outcome data (attrition bias) | Low | 15 (8%, excluding patients without UTI) were excluded from analysis. This is unlikely to inﬂuence results |
| Selective reporting (reporting bias) | Low | Relevant outcomes reported |
| Other bias | Low | Grant supported |
|  |  |  |
| ***Dagan 1992*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Low | "Sealed tables for randomisation" |
| Allocation concealment (selection bias) | Low | "Sealed tables for randomisation". Labels were not opened prior to enrolment. |
| Blinding of participants and personnel (performance bias) | High | No blinding |
| Blinding of outcome assessment (detection bias) | Low | "Clinical failure was defined as no or minimal alleviation of fever or persistence of positive urine culture after 72 hours of treatment, or recurrence of fever or positive urine culture during treatment." The measurement of fever or the urine culture result cannot be influenced by individual judgement. |
| Incomplete outcome data (attrition bias) | High | Among 85 patients who received treatment successfully, 21 (24.7%) were missed (9 did not present for follow-up while 12 did not have evaluable outcomes). This may have influenced the results. |
| Selective reporting (reporting bias) | Low | Relevant outcomes reported |
| Other bias | High | Supported by pharmaceutical company |
|  |  |  |
| ***Francois 1997*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Low | Computer generated list |
| Allocation concealment (selection bias) | Unclear | No information |
| Blinding of participants and personnel (performance bias) | High | No blinding |
| Blinding of outcome assessment (detection bias) | Low | No blinding. Clinical and microbiological outcomes evaluated by a scientiﬁc committee so unlikely to be inﬂuenced by the lack of blinding. Bacteriological outcomes not affected by the lack of blinding. |
| Incomplete outcome data (attrition bias) | Low | All patients with positive urine-cultures were evaluated for efficacy |
| Selective reporting (reporting bias) | Low | Relevant outcomes reported |
| Other bias | Unclear | No information |
|  |  |  |
| ***Gok 2001*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear | Mentioned as "randomised", but no information on how patients were randomised is provided. |
| Allocation concealment (selection bias) | Unclear | No information |
| Blinding of participants and personnel (performance bias) | High | No blinding (not possible due to different routes of administration) |
| Blinding of outcome assessment (detection bias) | Unclear | Laboratory based outcome (sterilisation of urine) unlikely to be inﬂuenced by lack of blinding. Interpretation of resolution of signs/symptoms could have been influenced by the lack of blinding. |
| Incomplete outcome data (attrition bias) | Low | All patients completed follow-up |
| Selective reporting (reporting bias) | Low | Relevant outcomes reported |
| Other bias | High | No limitations mentioned in the study. |
|  |  |  |
| ***Huang 2011*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Low | A computer generated list of random therapy assignments was used, and the code was not broken until the completion of the study. |
| Allocation concealment (selection bias) | Low | A computer generated list of random therapy assignments was used, and the code was not broken until the completion of the study. |
| Blinding of participants and personnel (performance bias) | Low | Patients and personnel blinded to the main outcome (DMSA scan). Unknown if blinded for the microbiological outcome but laboratory-based outcome unlikely to be influenced. |
| Blinding of outcome assessment (detection bias) | Low | Patients and personnel blinded to the main outcome (DMSA scan). Unknown if blinded for the microbiological outcome but laboratory-based outcome unlikely to be influenced. |
| Incomplete outcome data (attrition bias) | Low | All patients completed follow-up |
| Selective reporting (reporting bias) | Low | Relevant outcomes reported |
| Other bias | Low | Grant supported |
|  |  |  |
| ***Kafetzis 2000*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear | No clear information |
| Allocation concealment (selection bias) | Unclear | No clear information |
| Blinding of participants and personnel (performance bias) | High | No blinding |
| Blinding of outcome assessment (detection bias) | Low | Primary efﬁcacy outcome was laboratory based and unlikely to be inﬂuenced by blinding |
| Incomplete outcome data (attrition bias) | Low | All patients completed follow-up |
| Selective reporting (reporting bias) | Low | Relevant outcomes reported |
| Other bias | High | Study supported by pharmaceutical company |
|  |  |  |
| ***Levtchenko 2001*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear | No information |
| Allocation concealment (selection bias) | Unclear | No information |
| Blinding of participants and personnel (performance bias) | High | No blinding |
| Blinding of outcome assessment (detection bias) | Low | No blinding but primary outcome of urine culture: laboratory based and unlikely to affected by blinding |
| Incomplete outcome data (attrition bias) | Low | 5 (5.4%) of patients did not complete follow-up. Unlikely to inﬂuence outcome |
| Selective reporting (reporting bias) | High | No detailed information on clinical response or adverse effects |
| Other bias | Unclear | No information |
|  |  |  |
| ***Marild 2009*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Low | Computer generated block randomisation |
| Allocation concealment (selection bias) | Low | Sealed envelopes assigned treatment and randomisation number, opened in numeric order |
| Blinding of participants and personnel (performance bias) | High | No blinding |
| Blinding of outcome assessment (detection bias) | High | No blinding |
| Incomplete outcome data (attrition bias) | Low | 37/420 (8.8%) patients excluded: unlikely to inﬂuence results |
| Selective reporting (reporting bias) | Low | Relevant outcomes reported |
| Other bias | High | Study supported by pharmaceutical company |
|  |  |  |
| ***Montini 2007*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Low | Computer generated block randomisation |
| Allocation concealment (selection bias) | Low | centres received allocation codes in sealed and numbered opaque envelopes, sequence concealed until interventions assigned, children allocated in numeric order |
| Blinding of participants and personnel (performance bias) | High | No blinding (not possible due to different routes of administration) |
| Blinding of outcome assessment (detection bias) | Low | Time to defervescence and laboratory-based outcomes (inflammatory markers and urine culture) were objective outcome measures and unlikely to be influenced by the lack of blinding |
| Incomplete outcome data (attrition bias) | High | Loss to follow-up was 22.3% (112/502) and could have inﬂuenced results |
| Selective reporting (reporting bias) | Low | Relevant outcomes reported |
| Other bias | Low | Grant supported |
|  |  |  |
| ***Neuhaus 2008*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Low | Computer generated code |
| Allocation concealment (selection bias) | Low | Blocks of opaque sealed envelopes provided to centres |
| Blinding of participants and personnel (performance bias) | High | No blinding |
| Blinding of outcome assessment (detection bias) | Low | Microbiological cure: laboratory based outcome and unlikely to be influenced by the lack of blinding |
| Incomplete outcome data (attrition bias) | High | 67/219 (30%) excluded from analysis as they could not be assessed for the primary outcome. This could have inﬂuenced the results as cure rates are not reported for those patients. |
| Selective reporting (reporting bias) | High | No report on microbiological cure for the patients that were not evaluable for the primary outcome. |
| Other bias | High | Study supported by pharmaceutical company |
|  |  |  |
| ***Noorbakhsh 2004*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | High | "Children were allocated alternately to each group" |
| Allocation concealment (selection bias) | High | "Children were allocated alternately to each group" |
| Blinding of participants and personnel (performance bias) | High | No blinding. Unclear switching patterns for interventional drugs. |
| Blinding of outcome assessment (detection bias) | High | No blinding. |
| Incomplete outcome data (attrition bias) | Low | All patients completed follow-up |
| Selective reporting (reporting bias) | High | No report on adverse effects |
| Other bias | High | Author employed by pharmaceutical company |
|  |  |  |
| ***Peña 2009*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear | Mentioned as "randomised", but no information on how patients were randomised is provided. |
| Allocation concealment (selection bias) | Unclear | No information |
| Blinding of participants and personnel (performance bias) | High | No blinding |
| Blinding of outcome assessment (detection bias) | High | No blinding |
| Incomplete outcome data (attrition bias) | High | 29/112 (25.9%) patients did not have a complete follow-up, which may have influenced the results |
| Selective reporting (reporting bias) | Low | Relevant outcomes reported |
| Other bias | High | No limitations mentioned in the study. |
|  |  |  |
| ***Schaad 1998*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear | Stratiﬁed by age (1 month to 2 years; > 2 years) |
| Allocation concealment (selection bias) | Unclear | No information |
| Blinding of participants and personnel (performance bias) | High | No blinding. |
| Blinding of outcome assessment (detection bias) | Low | “Individual results were evaluated by blinded committee of experts” |
| Incomplete outcome data (attrition bias) | High | 40/299 excluded for no pathogen; 47/259 (18.1%) not assessed for cure. This may introduce bias in the study. |
| Selective reporting (reporting bias) | Low | Relevant outcomes reported |
| Other bias | High | Study supported by pharmaceutical company. Statistics and data management by the pharmaceutical company. |
|  |  |  |
| ***Sobouti 2013*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | High | "Based on the file number, children were assigned in parallel and randomized to three groups sequentially" |
| Allocation concealment (selection bias) | High | "Based on the file number, children were assigned in parallel and randomized to three groups sequentially" |
| Blinding of participants and personnel (performance bias) | High | No blinding |
| Blinding of outcome assessment (detection bias) | High | No blinding |
| Incomplete outcome data (attrition bias) | Unclear | No cure/failure rates provided |
| Selective reporting (reporting bias) | Unclear | No cure/failure rates provided |
| Other bias | High | "Low power of the study" |
|  |  |  |
| ***Tapaneya-Olarn 1999*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear | Mentioned as "randomised", but no information on how patients were randomised is provided. |
| Allocation concealment (selection bias) | Unclear | No information |
| Blinding of participants and personnel (performance bias) | High | No blinding (not possible due to different regimens - once daily versus thrice daily) |
| Blinding of outcome assessment (detection bias) | High | No blinding |
| Incomplete outcome data (attrition bias) | Low | 49 patients enrolled. 25 patients excluded as unclear diagnosis (negative urine culture or mixed growth). Among the 24 patients assessed for cure, no loss in follow-up. |
| Selective reporting (reporting bias) | Low | Relevant outcomes reported |
| Other bias | High | No limitations mentioned in the study. |
|  |  |  |
| ***Toporovski 1992*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Low | Computer-generated randomisation list |
| Allocation concealment (selection bias) | Unclear | No information |
| Blinding of participants and personnel (performance bias) | High | No blinding |
| Blinding of outcome assessment (detection bias) | High | No blinding |
| Incomplete outcome data (attrition bias) | Low | All patients completed follow-up |
| Selective reporting (reporting bias) | Low | Relevant outcomes reported |
| Other bias | High | Author supported by pharmaceutical company |
|  |  |  |
| ***Vigano 1992*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear | "patients were randomly allocated" |
| Allocation concealment (selection bias) | Unclear | "patients were randomly allocated" |
| Blinding of participants and personnel (performance bias) | High | No blinding |
| Blinding of outcome assessment (detection bias) | Low | No blinding but primary outcome of urine culture: laboratory based and unlikely to affected by blinding |
| Incomplete outcome data (attrition bias) | Low | 6/150 (4%) excluded from analysis: unlikely to inﬂuence results |
| Selective reporting (reporting bias) | High | No clinical outcomes reported |
| Other bias | Unclear | No information |
|  |  |  |
| ***Vigano 1996*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | High | Randomisation was "open" |
| Allocation concealment (selection bias) | High | Patients were allocated in an open fashion. |
| Blinding of participants and personnel (performance bias) | High | No blinding |
| Blinding of outcome assessment (detection bias) | High | No blinding |
| Incomplete outcome data (attrition bias) | Unclear | No cure/failure rates provided |
| Selective reporting (reporting bias) | Unclear | No cure/failure rates provided |
| Other bias | Unclear | No information |
|  |  |  |
| ***Vilaichone 2001*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear | “Randomized by blocks of four” |
| Allocation concealment (selection bias) | Unclear | “prospective randomized trial" |
| Blinding of participants and personnel (performance bias) | High | No blinding |
| Blinding of outcome assessment (detection bias) | Low | No blinding but microbiological cure laboratory based and unlikely to be inﬂuenced by the lack of blinding |
| Incomplete outcome data (attrition bias) | Low | All patients completed follow-up |
| Selective reporting (reporting bias) | Low | Relevant outcomes reported |
| Other bias | High | No limitations mentioned in the study. |
|  |  |  |
| ***Yosefichaijan 2016 (Vitamin C)*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Low | Block-randomization |
| Allocation concealment (selection bias) | Unclear | No information |
| Blinding of participants and personnel (performance bias) | High | No blinding |
| Blinding of outcome assessment (detection bias) | High | No blinding |
| Incomplete outcome data (attrition bias) | Unclear | No cure/failure rates provided |
| Selective reporting (reporting bias) | Unclear | No cure/failure rates provided |
| Other bias | Unclear | No information |
|  |  |  |
| ***Yousefichaijan 2015*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear | Mentioned as "randomised", but no information on how patients were randomised is provided. |
| Allocation concealment (selection bias) | Unclear | Allocation unclear |
| Blinding of participants and personnel (performance bias) | Low | "Placebos were similar to vitamin E regarding their shape, color, and size. Vitamin E and the placebo were administered in unnamed capped containers with a label containing the code of each medicine by a group other than the groups who examined and followed up the patients. The participants were unaware of the type of administered medicine." |
| Blinding of outcome assessment (detection bias) | Low | "The assessment of clinical response and the follow-up of patients were conducted by research assistant who was unaware of the type of medicine administered to patients for 14 days." |
| Incomplete outcome data (attrition bias) | High | 68/152 (44.7%) were not evaluable for the main outcomes. 21/152 (13.8%) were known to have a recurrent UTI, however, they were not taken into account in final analysis. |
| Selective reporting (reporting bias) | Low | Expected outcomes reported. |
| Other bias | High | Study's flowchart states that dropouts were replaced with "matching cases". No further information is being given in the text. |
|  |  |  |
| ***Yousefichaijan 2016*** |  |  |
| Bias | Authors’ judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear | Mentioned as "randomised", but no information on how patients were randomised is provided. |
| Allocation concealment (selection bias) | Unclear | Allocation unclear |
| Blinding of participants and personnel (performance bias) | High | The one group received the tested supplemental study drug (zinc) while the other group did not receive any placebo. |
| Blinding of outcome assessment (detection bias) | High | No blinding |
| Incomplete outcome data (attrition bias) | Low | All patients assessed for the outcome of interest (microbiological cure), although lack of adherence to treatment and follow-up is mentioned in the limitations. |
| Selective reporting (reporting bias) | Low | Relevant outcomes reported |
| Other bias | High | Low power of sample, self-reporting of clinical outcomes from children, special patterns of hospitalisation and discharge |

**Supplementary Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies**



**Supplementary Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study**

