Treatment of UTIs in Infants <2 Months: A Living Systematic Review

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ABSTRACT

CONTEXT: Urinary tract infections (UTIs) are the most common bacterial infections in infants <2 months of age. However, there are no clear guidelines on the appropriate duration of antibiotics in this age group.

OBJECTIVE: In this living systematic review, we compared different durations of parenteral antibiotics (≤3 vs >3 days) in neonates and young infants (<2 months) with UTIs. The secondary objective was to compare different durations of total antibiotic courses (≤10 vs >10 days).


STUDY SELECTION: Citations were screened in triplicate by using a crowdsourcing methodology, to identify randomized controlled trials and observational studies.

DATA EXTRACTION: Data were extracted by 2 crowd members and verified by an expert investigator. Outcomes were pooled via random-effects models.

RESULTS: A total of 10 334 citations were screened, and 12 eligible studies were identified. A total of 59 of 3480 (1.7% [95% confidence interval (CI): 1.3% to 2.2%]) infants had a UTI recurrence within 30 days after short parenteral treatment (≤3 days), and 47 of 1971 (2.4% [95% CI: 1.8% to 3.2%]) after longer courses. The pooled adjusted odds ratio for UTI recurrence with a short versus long duration of parenteral antibiotics was 1.02 (95% CI: 0.64 to 1.61; P = .95; n = 5451). A total of 5 studies assessed the risk of recurrence on the basis of the total duration of antibiotics (≤10 vs >10 days) with no significant differences (pooled odds ratio: 1.29 [95% CI: 0.45 to 3.66; P = .63; n = 491).

CONCLUSIONS: On the basis of retrospective studies and Grading of Recommendations, Assessment, Development, and Evaluation level low evidence, short and long duration of parenteral antibiotics were associated with a similar risk of UTI recurrence in infants <2 months.
Urinary tract infections (UTIs) are a major burden of pediatric disease, being the most common bacterial infections in infants ≤2 months of age. However, high-quality evidence on the treatment of UTIs in this age group is lacking. Commonly encountered questions include the appropriate time to switch from parenteral to oral (PO) treatment and the total duration of antibiotics required. Young infants are typically treated for 10 to 14 days, with a parenteral course consisting of 2 days or up to the total duration. Clinicians’ main concerns are inadequate treatment with shorter antibiotic duration or a premature switch to PO therapy, which may increase the risk of UTI recurrence. Over the last decade, in several studies, researchers have targeted these questions. Most studies to date have been retrospective, small, and underpowered to detect small but potentially important changes in clinical outcomes with different durations of antibiotics.

With an active research field and ongoing primary studies regarding this topic, it is important to incorporate the most up-to-date evidence in clinical practice. We conducted a living systematic review of existing literature for the management of UTIs in infants ≤2 months of age and meta-analysis, summarizing the results of available studies. The primary objective was a comparison of different duration of parenteral antibiotics (≤ 3 vs >3 days), with regards to UTI recurrence. Our secondary objective was to compare different durations of total antibiotic courses (≤ 10 vs >10 days).

METHODS

This is a living systematic review and meta-analysis, prospectively registered (International Prospective Register of Systematic Reviews: CRD42020167098) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Search Strategy and Selection Criteria

We searched for citations relevant to neonatal and infantile UTI, pyelonephritis, and/or bacteriuria, with no filtering of language or study design (Supplemental Information 1). The searched databases were the following: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Web of Science, Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), and Google Scholar. In addition, a comprehensive gray literature search was undertaken: clinicaltrials.gov, World Health Organization International Clinical Trials Registry Platform, Papers First (via WorldCat), Proceedings (via WorldCat), Networked Digital Library of Theses and Dissertations, ProQuest Dissertations and Theses Global, and OAster (narrowing to theses and dissertations; via WorldCat). The search was completed on February 25, 2020, and updated on March 2, 2021. The reference list of any included study or relevant systematic review was searched for other potentially eligible studies.

Studies were included if they were randomized controlled trials (RCTs), quasi-RCTs, observational cohorts, or case-control studies. Studied populations were patients <2 months of age with a UTI. The studies had to compare different durations of parenteral antibiotics (intravenous [IV] or intramuscular [IM]) and/or compare different total durations of antibiotic therapy.

Studies were excluded if they had no patient <2 months of age or were limited to the following populations: preterm infants, those with immunodeficiency disorders, and/or those with hospital-acquired UTIs. Patients with an abnormal genitourinary tract have a different risk of recurrence and UTI etiologies. As such, we have excluded studies that were focused solely on infants with urologic abnormalities (a full list of excluded urologic abnormalities is available in Supplemental Information 2). However, studies were retained if the researchers had a portion of patients who had undiagnosed urologic abnormalities at the time of first UTI presentation. Case reports or series of ≤5 patients and studies evaluating prophylactic antibiotics were also excluded. When studies included eligible patients <2 months as well as older ones, studies were included if the data for the eligible age group were presented separately. If studies included data specific to <1 year of age, authors were contacted to obtain the data for our population of interest. Both hospitalized patients and those treated in an outpatient setting were included.

Crowdsourcing of Study Selection

A selection of potentially relevant citations (citation screening) was completed on insightScope, a platform designed for crowdsourcing systematic reviews. Crowdsourcing has been employed in other medical fields, with growing use in systematic reviews.

Mounting evidence reveals significant work saved to the investigative team, whereas the higher quality and robust methodology of a systematic review is maintained.

For crowd recruitment, an e-mail was sent to all registered crowd members. The crowd is mostly composed of students with postsecondary training (undergraduate, medical, and graduate students). Additional crowd recruitment was conducted by disseminating details regarding this review through pediatric interest groups, research interest groups, and undergraduate societies at medical schools and universities across Canada and on the Cochrane task exchange platform. Before citation screening was initiated, the study leads created a qualification set of 50 abstracts. The qualification set contained 4 eligible studies. Each interested crowd member was then required to complete the qualification set and demonstrate acceptable performance (sensitivity ≥80% and specificity ≥70%). The first author contacted crowd members with a sensitivity between 80% to 90% and discussed the reasons behind missing eligible citations and explained the eligibility criteria in more detail.

To improve sensitivity during citation screening, each abstract was screened independently in triplicate, with the first author resolving conflicts.
Fig 4). At the full-text stage, the crowd uploaded the full-text documents for all citations retained at the title and abstract level, and full citations were screened by 3 independent reviewers. Citations were removed from the pool visible to the crowd once reviewed by 3 crowd members. The final list of citations retained by the crowd was reviewed by the first author to confirm eligibility. Thirty-one crowd members joined the review from 13 countries and screened citations in 18 languages (Supplemental Figs 5 and 6). Crowd members had a median sensitivity of 100.0%, specificity of 91.1%, and moderate interrater reliability with a $\kappa$ of 0.51 (Supplemental Table 3). Among identified citations, 98.0% ($n = 10131$ of 10334) were screened within 17 days (Supplemental Fig 8).

Crowdsourcing of Data Extraction

Data were extracted independently by 2 crowd members and verified by the first author. Corresponding authors of eligible studies were contacted to (1) obtain relevant data not reported in the publication and (2) confirm whether they were aware of any additional published or ongoing studies. To assess the risk of bias, we used the Newcastle-Ottawa Scale (NOS) for observational studies. Cohort studies were judged as having a low risk of bias if they scored $\geq 7$ on the NOS scale and as having a moderate risk of bias if they scored $\geq 5$. A sensitivity analysis was conducted for the primary outcome by using unadjusted effect estimates (Supplemental Fig 9). By using R packages meta (version 4.15.1) and metafor (version 2.4.0), studies were pooled in a meta-analysis via random-effects model (DerSimonian and Laird inverse variance). Studies were not included in the meta-analysis if clinical heterogeneity was observed. The heterogeneity of treatment effects was explored visually by using a forest plot and statistically by using $I^2$. The potential for publication bias was investigated visually by using a funnel plot. In a subgroup analysis, patients were stratified by month of age as well as by the presence of bacteremia associated with the UTI. We considered stratification by presence of genitourinary abnormalities and the severity of illness; however, data were only available in a small number of studies. Initially, the registered study protocol aimed to assess patients $<3$ months of age. This was modified to 2 months to specifically address the age group not currently covered by national guidelines. The originally planned analysis including patients $\geq 3$ months of age was conducted and is presented in Supplemental Fig 10. Grading of

Outcomes of Interest

The primary outcome of the study was UTI recurrence within 30 days of treatment. The secondary outcomes were UTI recurrence with the same organism, length of hospital stay, hospital readmission for UTI, and all-cause hospital readmission. If a study presented other outcomes, these were assessed in an exploratory analysis. The duration of monitoring for UTI recurrence or readmission was defined as 30 days to capture any potential treatment failure. If, in the studies, researchers monitored for a longer duration, the authors were asked to provide data on the outcomes of interest up to 30 days.

Data Analysis

Data analysis was done in R version 4.0.2. Crowdsourcing of Data Extraction was assessed on the basis of sensitivity and specificity. These were defined as the percentage of eligible citations retained and ineligible citations excluded by the crowd member, respectively. Interrater reliability was measured by using a Fleiss’ $\kappa$. For the effect measure in the meta-analysis, odds ratio (OR) and mean difference (MD) were used for binary and continuous outcomes, respectively. When calculating ORs and no events occurred in one of the arms, a continuity correction of 0.5 was added. When available, estimates adjusted for covariates were used to minimize the risk of bias due to confounding factors. A sensitivity analysis was conducted for the primary outcome by using unadjusted effect estimates (Supplemental Fig 9). By using R packages meta (version 4.15.1) and metafor (version 2.4.0), studies were pooled in a meta-analysis via random-effects model (DerSimonian and Laird inverse variance). Studies were not included in the meta-analysis if clinical heterogeneity was observed. The heterogeneity of treatment effects was explored visually by using a forest plot and statistically by using $I^2$. The potential for publication bias was investigated visually by using a funnel plot. In a subgroup analysis, patients were stratified by month of age as well as by the presence of bacteremia associated with the UTI. We considered stratification by presence of genitourinary abnormalities and the severity of illness; however, data were only available in a small number of studies. Initially, the registered study protocol aimed to assess patients $<3$ months of age. This was modified to 2 months to specifically address the age group not currently covered by national guidelines. The originally planned analysis including patients $\geq 3$ months of age was conducted and is presented in Supplemental Fig 10. Grading of

Living Systematic Review

In general, most published reviews are out of date by 5 years. Living reviews have evolved over the last decade as an approach to update systematic reviews. They aim to provide a living synthesis of evidence that is updated shortly after the publication of new studies and trials. This methodology has been previously employed in pediatrics to target the use of hypertonic saline in bronchiolitis. Eligible citations and available results were uploaded to an online database, hosted on Open Science Framework (https://www.bccr.ca/nama-lab/projects/UTI). New citations will be screened and extracted, similar to the original review. The database will be updated at least every 4 months. The synthesis of available evidence will also be updated by the first author to reflect the most up-to-date estimates of the measured outcomes. The crowdsourcing platform (insightScope) offers a large database of crowd members. Similar to other living systematic reviews, reviewers’ attention is anticipated. However, the platform would allow recruitment of additional crowd members, who will undergo the same rigor of quality control as employed in the original publication. New crowd members will have to demonstrate acceptable performance on the qualification set, and each citation will be screened in triplicate. No compensation will be offered for participating in the review update. However, crowd members will be acknowledged on the online database.

RESULTS

Characteristics of Included Studies

Overall, 10334 citations were screened (Fig 1). A total of 22 citations covered the population of interest, including 17 different studies. A total of 4 studies contained older children, and authors were unable to provide data specific to those $<2$ months of age. Finally, 1 study was only published as an abstract without any outcome data. Studies were published between 1978 and 2020 (Table
1) and reported on a median sample size of 143.5 (range: 12–3973) participants per study. A total of 11 studies were retrospective observational cohorts,8,9,11–13,34–39 and 1 was a retrospective case-control study.40 A positive urine culture result was required to confirm the diagnosis in 10 studies, whereas a positive urinalysis result was required in only 5 studies (Supplemental Table 4). Some studies had multiple requirements for patient’s selection. UTI cases were selected on the basis of discharge diagnosis in 6 studies. In 5 studies, researchers selected only UTI patients with fever or systemic signs. A total of 2 studies targeted patients with bacteremia specifically, whereas 3 excluded any patient with bacteremia. A total of 6 studies exclusively targeted hospitalized patients, whereas 2 studies also included those managed on an outpatient basis. Patients’ characteristics were compared depending on the duration of parenteral antibiotics (Supplemental Table 5). The risk of bias assessment of observational studies revealed a median study score of 7 (range: 5–8) on the NOS (Table 1). Details on each domain are provided in Supplemental Table 6. A total of 7 retrospective studies were determined to be at a low risk of bias (NOS ≥7). The remaining studies were at a moderate risk of bias.

**Primary Outcome: UTI Recurrence**

One study by Amodio et al34 was not included in the meta-analysis because of clinical heterogeneity because it was conducted in 1978 with a different antimicrobial resistance profile, compared with the more recent studies. In their study, Kantamalee et al36 included 21 patients <2 months of age. All patients received a short duration of parenteral antibiotics, and the study was not included in the primary meta-analysis (only included for the secondary comparison of short versus long duration of total antibiotics).
| Study                      | Study Design        | Country | Age               | Eligible Patients, n<sup>a</sup> | Population                                                                 | Treatment Protocol                                                                 | Outcomes                                                                                     | Risk of Bias<sup>b</sup> |
|----------------------------|---------------------|---------|-------------------|----------------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Amodio et al<sup>34</sup> | Retrospective cohort| Italy   | 0–7 mo            | 12                               | Infants (&lt;7 mo) with culture-positive UTIs sensitive to tobramycin       | Different durations of IM tobramycin                                                          | Clearance of bacteriuria at the end of therapy                                              | Moderate risk               |
| Díaz-Álvarez et al<sup>39</sup> | Retrospective cohort | Cuba    | 0–30 d            | 188                              | Healthy nontoxic and nonbacteremic newborns with pyelonephritis and no genitourinary malformations. | Parenteral antibiotics for 3 or 5 d, followed by PO to complete at least 10 d. | UTI clearance, recurrence within 3 mo, and evidence of renal scarring                      | Low risk                   |
| Magín et al<sup>13</sup> | Retrospective cohort | Spain   | 0–31 d            | 172                              | Neonates (&lt;31 d) hospitalized for UTIs                                 | IV antibiotics for 3–5 d or until afebrile for 24 h, followed by PO to complete 10 d.      | Treatment failure or recurrence with the same organism                                       | Moderate risk               |
| Schroeder et al<sup>8</sup> | Retrospective cohort | United States | 0–3 mo           | 198                              | Infants (&lt;3 mo) with bacteremic UTIs                                    | Compares different durations of parenteral (IV and IM) antibiotic therapy.                 | Recurrence of UTI (with or without bacteremia, with same or different organism), readmission for UTI, all-cause readmission, clinical deterioration, and/or length of stay. | Moderate risk               |
| Lewis-de los Angeles et al<sup>9</sup> | Retrospective cohort | United States | 0–60 d           | 3973                             | Healthy term infants (&lt;60 d) admitted for IV antibiotics with a primary discharge diagnosis of a UTI | Short-duration IV antibiotics (&lt;3 d) compared with longer.                                | Readmission for UTIs or other causes, within 30 d of discharge                              | Low risk                   |
| Desai et al<sup>11</sup> | Retrospective cohort | United States | 0–60 d           | 115                              | Infants (&lt;60 d) hospitalized for bacteremic UTI                        | Short-duration IV and IM antibiotics (&lt;7 d) compared with longer.                        | Recurrence of UTI, hospital length of stay, all-cause reutilization, and adverse events within 30 d of discharge | Low risk                   |
| Lessard et al<sup>12</sup> | Retrospective cohort | Canada  | 0–60 d            | 108                              | Infants (&lt;60 d) with pyelonephritis, diagnosed on the basis of systemic symptoms and positive urine culture result | Short-duration IV antibiotics (&lt;3 d) compared with longer; before switching to PO to complete 10 or 14 d | Recurrence of pyelonephritis within 2 mo                                                   | Low risk                   |
| Swartz et al<sup>35</sup> | Retrospective cohort | United States | 0–60 d           | 183                              | Infants (&lt;60 d) hospitalized for UTI                                   | Different durations of parenteral and total antibiotic courses                             | Length of stay and hospital readmission within 30 d                                       | Low risk                   |
| Fernandez et al<sup>14</sup> | Retrospective cohort | United States | 0–60 d           | 322                              | Infants (&lt;60 d) with febrile UTI caused by *Escherichia coli* or *Klebsiella pneumoniae* | Narrow versus broad spectrum oral antibiotic                                           | Readmission for true relapse within 30 d, readmission or return to emergency department, and length of stay | Moderate risk               |
| Marsh et al<sup>37</sup>  | Retrospective cohort | United States | 0–28 d           | 112                              | Term neonates (&lt;28 d) hospitalized for UTI                             | Short-duration IV antibiotics (&lt; 2 d) compared with longer.                              | Return to ED and readmissions within 30 d, and UTI treatment failure                      | Moderate risk               |
In the remaining 10 studies, UTI recurrence within 30 days was 1.9% (95% confidence interval [CI]: 1.6% to 2.3%; n = 106 of 5451). This ranged between 0.0% and 10.2% in individual studies (Fig 2). A total of 50 of 3480 (1.7%; 95% CI: 1.3% to 2.2%) infants had a UTI recurrence within 30 days after short parenteral treatment (≤3 days), and 47 of 1971 (2.4%; 95% CI: 1.8% to 3.2%) had a UTI recurrence within 30 days after longer courses. Infants who received ≤3 days of parenteral antibiotics had a similar odds of recurrence as those who received >3 days (pooled adjusted OR: 1.02 [95% CI: 0.64 to 1.61]; P = .95; GRADE level: low; Table 2). There was no significant heterogeneity of treatment effects noted between studies (I² = 0%; P = .99; Fig 2). A funnel plot did not reveal visual evidence of asymmetry (Supplemental Fig 11).

In a subgroup analysis (Fig 3), UTI recurrence was 2.2% (95% CI: 1.7% to 2.9%; n = 51 of 2275) in neonates (≤1 month) and 1.5% (95% CI: 1.1% to 2.1%; n = 42 of 2715) among infants between 1 and 2 months of age. There was no statistically significant difference in the recurrence according to the duration of parenteral treatment in either of the age groups. Similarly, there was no significant difference in UTI recurrence with an IV duration ≤3 days, as compared with >3 days in bacteremic patients (pooled OR: 0.91 [95% CI: 0.22 to 3.80; P = .89; 4 observational studies; n = 358; GRADE level: very low) and in nonbacteremic infants (pooled OR: 1.07 [95% CI: 0.66 to 1.73; P = .79; 7 observational studies; n = 4731; GRADE level: low).

Secondary Outcomes

Infants with a shorter duration of parenteral antibiotics were not more likely to experience (Supplemental Fig 12) recurrence with the same organism (pooled OR: 1.18 [95% CI: 0.33 to 4.18]), hospital readmission for UTI (pooled OR: 1.04 [95% CI: 0.60 to 1.82]), or readmission for all-causes (pooled OR: 0.89 [95% CI: 0.64 to 1.23]). A shorter parenteral course was associated with a shorter length of stay (MD: −3.48 [95% CI: −5.03 to −1.93]). The total duration of antibiotics was compared only in 6 observational studies (Supplemental Table 7; Supplemental Fig 13), and, in 5 studies, researchers provided data on the primary outcome. Infants that received ≤10 vs >10 total days of antibiotics had similar odds of recurrence (pooled OR: 1.29 [95% CI: 0.43 to 3.86]; P = .63; 5 observational studies; n = 491).

DISCUSSION

This meta-analysis reveals no difference in clinical outcomes with a shorter duration of parenteral antibiotics (≤3 days) in infants <2 months of age with UTIs. The current evidence is of low quality and based on retrospective studies. The duration of parenteral treatment has shortened over the years, and a high-quality prospective trial can be used to provide further support to this change in clinical practice. With this living systematic review of observational studies, we offer the first meta-analysis in this area of research. Future studies, preferably RCTs can be incorporated shortly after publication to maintain the most up-to-date summary of evidence.

The duration of parenteral antibiotics in the age group of interest is widely variable and depends on physician preference and local practices. This duration has shortened over the years, with an increasing emphasis on antimicrobial stewardship. The hesitancy regarding this early transition stems from concerns regarding enteral absorption of antibiotics in ill newborns and drug bioavailability. The results of this meta-analysis did not reveal a difference in clinical outcomes between patients who

### TABLE 1 Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Country</th>
<th>Age</th>
<th>Eligible Patients, n</th>
<th>Population</th>
<th>Treatment Protocol</th>
<th>Outcomes</th>
<th>Risk of Biasb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kantamalee et al46</td>
<td>Retrospective cohort</td>
<td>Thailand</td>
<td>0–15 d</td>
<td>21</td>
<td>Children (&lt;15 y) with UTI caused by E coli, K pneumoniae, or Proteus</td>
<td>Comparison of patients treated with empirical antibiotic covering the etiologic organism to those that were not</td>
<td>Clearance of UTI symptoms at 72 h, clearance of urine culture at 48 h, readmission for UTI within 30 d, time to deferescence, and length of stay</td>
<td>Low risk</td>
</tr>
<tr>
<td>Goeller et al46</td>
<td>Retrospective case control</td>
<td>France</td>
<td>0–11 y</td>
<td>64</td>
<td>Children (&lt;11 y) with bacteremic and nonbacteremic febrile UTI</td>
<td>Compare the parenteral antibiotic treatment duration among children with bacteremic and nonbacteremic febrile UTIs</td>
<td>Parenteral antibiotic treatment duration, total antibiotic treatment duration, hospital length of stay, clinical and microbiologic features, and imaging and clinical evolution</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

a No. patients <2 mo of age.

b Risk of bias assessment by using the NOS for retrospective studies.
received ≤3 days of parenteral antibiotics and those that received longer courses. This finding was congruent with the results of the 10 included studies, in which no significant difference in UTI recurrence was noted in any study. Meanwhile, the potential risks associated with longer duration of parenteral antibiotics are well documented. Shorter parenteral antibiotic courses were associated with a mean of 3.5 hospitalization days less, when compared with long parenteral treatment. Considering hospital charges of $10,489 for an average hospital stay for pediatric UTI,41 this decrease in length of stay could represent a substantial cost saving. Additionally, prolonged hospital stays are associated with increased exposure to nosocomial infections,42 and maintaining a child on parenteral antibiotics for the majority of the treatment course leads to potential complications from IV catheters.43,44 Physicians need to balance the risks and benefits of antibiotic administration and length of treatment.

### TABLE 2 Summary of Findings Table

<table>
<thead>
<tr>
<th>Outcomes, Follow-up</th>
<th>No. Participants (No. Observational Studies)</th>
<th>Certainty of the Evidence, GRADE</th>
<th>Relative Effect, OR (95% CI)</th>
<th>Risk With Long Parenteral Antibiotics (&gt;3 d)</th>
<th>Risk Difference With Short Parenteral Antibiotics (≤3 d)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI recurrence follow-up, range: 14–90 d</td>
<td>5451 (10)</td>
<td>★★★ LOW</td>
<td>1.02 (0.64 to 1.61)</td>
<td>24 per 1000</td>
<td>0 fewer per 1000 (8 fewer to 14 more)</td>
</tr>
<tr>
<td>Subgroup Analyses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UTI recurrence (0–1 mo) follow-up, range 14–90 d</td>
<td>2275 (7)b</td>
<td>★★★ LOW</td>
<td>1.17 (0.66 to 2.08)</td>
<td>19 per 1000</td>
<td>3 more per 1000 (6 fewer to 20 more)</td>
</tr>
<tr>
<td>UTI recurrence (1–2 mo) follow-up, range 30 d</td>
<td>2715 (5)c</td>
<td>★★★ LOW</td>
<td>0.90 (0.44 to 1.88)</td>
<td>26 per 1000</td>
<td>3 fewer per 1000 (14 fewer to 22 more)</td>
</tr>
<tr>
<td>UTI recurrence (bacteremic) follow-up, range: 14–30 d</td>
<td>358 (4)d</td>
<td>★★★★★ LOW</td>
<td>0.91 (0.22 to 3.80)</td>
<td>49 per 1000</td>
<td>4 fewer per 1000 (38 fewer to 115 more)</td>
</tr>
<tr>
<td>UTI recurrence (nonbacteremic) follow-up, range: 14–90 d</td>
<td>4731 (7)d</td>
<td>★★★ LOW</td>
<td>1.07 (0.66 to 1.73)</td>
<td>18 per 1000</td>
<td>1 more per 1000 (6 fewer to 12 more)</td>
</tr>
</tbody>
</table>

a The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and relative effect of the intervention (and its 95% CI).

b Two additional studies contained patients in this age group but did not provide data separately. In 1 study (Goeller et al40), all patients in this age group received long parenteral antibiotics, and the study was not included in this subgroup analysis.

c A total of 2 additional studies contained patients in this age group but did not provide data separately.

d A total of 1 additional study contained patients with and without bacteremia but did not provide data separately (Fernández et al38). In 2 studies (Goeller et al40 and Lessard et al12), all bacteremic patients received long parenteral antibiotics, and the study was not included in this subgroup analysis.

e The studies were small, and the pooled estimate had wide CIs.
FIGURE 3  Subgroup analyses of primary outcome (UTI recurrence) according to age group and presence or absence of bacteremia. UTI recurrence (event) was compared between patients who received ≤3 days of parenteral antibiotics and longer courses. ORs from individual studies were pooled by using a random-effects model. Outcomes were missing for 4 patients from Díaz-Alvarez et al. A, Age: 0 to 1 months. B, Age: 1 to 2 months. C, Blood culture = nonbacteremia. D, Blood culture = bacteremia.
benefits of prolonging the parenteral course. Nonetheless, it is important to recognize that our findings were only on the basis of low-grade evidence from retrospective studies. In some observational studies, researchers provided measures adjusted for potential confounders; however, most were not able to control for severity of illness. Shorter courses were likely administered to patients with milder presentations, who were at low risk of UTI recurrence.

Beyond the timing of switching to oral therapy, the appropriate total duration of antibiotic treatment in this age group is uncertain. Currently, the American Academy of Pediatrics recommends between 7 and 14 days of treatment of children >2 months of age. In this systematic review, we identified 6 observational studies that targeted this question. Similarly, no difference in recurrence was noted when comparing ≤10 to >10 days.

Systematic reviews are placed at the top of the evidence pyramid; however, they are challenging to complete and are often out of date soon after publication. In the field of UTI management for young infants, most studies have been completed over the last decade, and 6 have been published in the past year. Shortly after the publication of further studies, we will be able to incorporate them in the online living review and update the meta-analysis results and conclusions. This is facilitated by the novel crowdsourcing methodology, which allowed a more extensive search strategy and the screening of >10,000 citations within a short time period.

Our study had some limitations. First, the number of studies was low, and all were retrospective, with a strong potential for confounding. The value of additional retrospective studies is limited. A large prospective randomized trial can be used to provide further support regarding the optimal duration of parenteral antibiotics. Considering the risk of recurrence observed here (1.7% and 2.4% for ≤3 and >3 days of parenteral antibiotics, respectively), a total sample size of 154 is required to provide a power of 80% with a significance level of 5% and noninferiority margin of 5%. Second, in 2 of the included studies, researchers selected patients on the basis of diagnostic codes. The American Academy of Pediatrics recommends having a positive urine culture result and urinalysis to diagnose UTIs in patients >2 months of age; hence, these cohorts might include patients without a true UTI. Third, studies focused solely on patients with urologic abnormalities were excluded. In eligible studies, researchers did not provide data separated by the presence or type of urologic abnormalities. Physicians should exercise caution if extrapolating this study’s findings to patients with abnormal genitourinary tracts. Similarly, in the studies, researchers did not provide data separated for patients with hospital-acquired UTIs, which have higher rates of antibiotics resistance and might require longer therapy. Finally, using individual participant data in reviews allows the investigation of the role of covariates and their impact on treatment. However, individual participant data reviews require substantial time and expertise to complete, and this would not be sustainable with our current living model.

CONCLUSIONS

With this meta-analysis, we are the first to summarize studies that were specifically targeted the treatment of UTIs in infants (<2 months). Evidence based on retrospective observational studies did not reveal a significant change in clinical outcomes with early transition to oral antibiotics (<3 days) in this age group. Prospective trials may be used to provide further support. Given the living nature of this systematic review, any new studies will be incorporated rapidly in the evidence synthesis, by using a novel crowdsourcing approach.

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Dr Nama conceptualized and designed the study, designed the data collection instruments, coordinated and supervised data collection, completed data analysis, drafted the initial manuscript, and critically reviewed and revised the manuscript; Dr Donken conceptualized and designed the study, collected data, reviewed data analysis, and critically reviewed and revised the manuscript; Mrs Pawliuk conceptualized and designed the study, designed the search strategy, and critically reviewed and revised the manuscript; Dr Leach collected data, and critically reviewed and revised the manuscript; Drs Sadarangani and Barwana conceptualized and designed the study, and critically reviewed and revised the manuscript; The insightScope team screened citations, collected data, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data are available on request from the corresponding author.
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