Antibiotic Prophylaxis for Urinary Tract Infections in Antenatal Hydronephrosis

BACKGROUND AND OBJECTIVE: Continuous antibiotic prophylaxis (CAP) is recommended to prevent urinary tract infections (UTIs) in newborns with antenatal hydronephrosis (HN). However, there is a paucity of high-level evidence supporting this practice. The goal of this study was to conduct a systematic evaluation to determine the value of CAP in reducing the rate of UTIs in this patient population.

METHODS: Pertinent articles and abstracts from 4 electronic databases and gray literature, spanning publication dates between 1990 and 2010, were included. Eligibility criteria included studies of children <2 years old with antenatal HN, receiving either CAP or not, and reporting on development of UTIs, capturing information on voiding cystourethrogram (VCUG) result and HN grade. Full-text screening and quality appraisal were conducted by 2 independent reviewers.

RESULTS: Of 1681 citations, 21 were included in the final analysis (N = 3876 infants). Of these, 76% were of moderate or low quality. Pooled UTI rates in patients with low-grade HN were similar regardless of CAP status: 2.2% on prophylaxis versus 2.8% not receiving prophylaxis. In children with high-grade HN, patients receiving CAP had a significantly lower UTI rate versus those not receiving CAP (14.6% [95% confidence interval: 9.3–22.0] vs 28.9% [95% confidence interval: 24.6–33.6], P < .01). The estimated number needed to treat to prevent 1 UTI in patients with high-grade HN was 7.

CONCLUSIONS: This systematic review suggests value in offering CAP to infants with high-grade HN, however the impact of important variables (eg, gender, reflux, circumcision status) could not be assessed. The overall level of evidence of available data is unfortunately moderate to low. Pediatrics 2013;131:e251–e261

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KEY WORDS
antibiotic, hydronephrosis, prophylaxis or prevention, urinary tract infection

ABBREVIATIONS
APD—anteroposterior diameter
CAP—continuous antibiotic prophylaxis
CI—confidence interval
HN—hydronephrosis
OR—odds ratio
SFU—Society for Fetal Urology
UTI—urinary tract infection
VCUG—voiding cystourethrogram
VUR—vesicoureteral reflux

Dr Braga conceptualized and designed the study, interpreted the data, and drafted and revised the initial manuscript; Dr Mijovic carried out initial analyses and drafted the initial manuscript; Dr Farrokhyar carried out final analyses and critically reviewed the manuscript; Ms Pemberton designed the data collection instruments, coordinated and supervised data collection, and revised the manuscript; Dr DeMaria conceptualized the study and critically reviewed the manuscript; and Dr Lorenzo interpreted the data and critically reviewed the manuscript. All authors approved the final manuscript as submitted.

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Antenatal hydronephrosis (HN) is one of the most common congenital anomalies, occurring in 1% to 5% of all pregnancies. Continuous antibiotic prophylaxis (CAP) has been empirically recommended for newborns who have antenatal HN in an attempt to reduce the rate of urinary tract infections (UTIs) during the first 2 years of life. Given the 2009 American Urological Association update and the 2010 Society for Fetal Urology (SFU) consensus statement on HN, it seems prudent to consider use of CAP in “high-risk” populations, such as those with higher grades of HN. Nevertheless, this practice is admittedly based on limited data and heavily reflects expert opinion.

Previous reports have suggested that infants who have moderate to severe HN are at a higher risk of developing UTIs, infants who have moderate to severe HN are at a higher risk of developing UTIs, and/or possible impact on UTI prevention clearly stated?

Methods

Eligibility Criteria

Studies fulfilling the following eligibility criteria were included: (1) primary diagnosis of antenatal HN; (2) all subjects aged <2 years; (3) intervention arms include CAP, no treatment, or both; (4) reported rate of UTI; (5) reported number of patients who underwent voiding cystourethrogram (VCUG); (6) HN grade according to the SFU classification and/or anteroposterior diameter (APD) of the renal pelvis; and (7) publication date between 1990 and 2010. Exclusion criteria included case reports, case series with <5 subjects, and review articles. No language restrictions were imposed.

Identification of Studies

A comprehensive and systematic search of 4 databases (Medline, Embase, CINAHL, and CENTRAL) was conducted in duplicate. When possible, the search used MeSH terms, and the strategy was devised with an information specialist at our institution. Gray literature was searched by using key words in PapersFirst and ProceedingsFirst databases, along with a hand search of Dialogues in Pediatric Urology. The reference list of prominent review articles was cross-referenced to minimize omissions. Lastly, a content expert review of the final list of included studies was conducted.

Screening and Assessing for Eligibility

Two reviewers screened titles and abstracts of the identified studies from the electronic search to select all citations that might contain the comparisons of interest. Subsequently, 2 independent reviewers conducted full-text screening of identified pertinent articles as well as those obtained by hand-search review of reference lists. All screening results were reviewed for concordance, and all disagreements were resolved by a third reviewer and content expert. The following languages were included: English, French, Italian, Dutch, Portuguese, Spanish, German, Chinese, and Arabic. Study selection was not blinded; concealment has been shown to have no significant effect on the final results of systematic reviews.

Assessment of Methodologic Quality

Critical appraisal and assignment of a level of evidence for the included studies was conducted by 2 independent reviewers by using a quality assessment instrument adopted from Elyas et al, modified to fit the objectives of this study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Unclear (%)</th>
<th>NA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nature of the research question (was question regarding CAP on antenatal HN, and/or possible impact on UTI prevention clearly stated?)</td>
<td>13 (62)</td>
<td>5 (24)</td>
<td>3 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Standard quality items</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was the study design reported?</td>
<td>18 (86)</td>
<td>0 (0)</td>
<td>3 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Was a follow-up schedule reported?</td>
<td>14 (67)</td>
<td>7 (33)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Was the number of patients who were lost to follow-up adequately described?</td>
<td>10 (48)</td>
<td>11 (52)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Were the reasons for loss to follow-up adequately described?</td>
<td>4 (19)</td>
<td>15 (71)</td>
<td>0 (0)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Was statistical tests reported?</td>
<td>15 (71)</td>
<td>6 (29)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Was P value reported for primary research study question?</td>
<td>11 (52)</td>
<td>9 (43)</td>
<td>1 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Were 95% CIs reported?</td>
<td>7 (33)</td>
<td>13 (62)</td>
<td>1 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Were eligibility criteria reported (inclusion and exclusion)?</td>
<td>20 (95)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Specific quality items</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was antibiotic administration adequately described?</td>
<td>11 (52)</td>
<td>8 (38)</td>
<td>1 (5)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Was there a comparative group (control)?</td>
<td>5 (24)</td>
<td>16 (76)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Were the criteria for febrile UTI reported?</td>
<td>11 (52)</td>
<td>10 (48)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Was the method of urine collection reported?</td>
<td>9 (43)</td>
<td>12 (57)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Were any complications reported?</td>
<td>10 (47)</td>
<td>9 (43)</td>
<td>1 (5)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

NA, not applicable.
study (Table 1). All discrepancies were resolved through third-party review of the methodology.

Study rating was determined by dividing the number of criteria met (indicated as “Yes”) by the total number of quality assurance criteria in the instrument \((n = 13)\), obtaining a percentage result. For scoring purposes, we have assumed equal weight for all questions. The data were then segregated into studies that met <25% of the quality criteria (very low methodologic quality), between 25% and 49% (low quality), between 50% and 74% (moderate quality), and >75% of the criteria (high quality).

**Extraction of Data**

Data extraction was completed in duplicate and reviewed for accuracy and quality. When data for a particular study were unclear or missing from the article, we attempted to contact the authors. Unfortunately, in cases of missing information, we were unable to obtain any additional information.

**Assessment of Agreement**

The \(\kappa\) statistic was used to examine the extent of agreement between individuals who determined study eligibility and to evaluate interobserver agreement in methodologic quality scores. A priori, we chose a criterion of \(\kappa \geq .65\) to indicate adequate agreement.

**Outcome Measures**

The SFU system was used to grade postnatally confirmed HN. For the purpose of this review, we considered SFU grades I and II and/or corresponding transverse renal pelvis APD ranging between 4.0 and 14.9 mm on postnatal ultrasound as low-grade HN. Whenever possible, we excluded patients with no HN when these were reported within a category (i.e., SFU 0–II). If not enough information was provided to conduct this segregation, these children were analyzed with the lowest grade of HN (SFU I). SFU grades III and IV and/or a transverse APD of the renal pelvis \(\geq 15.0\) mm on postnatal ultrasound were grouped into high-grade HN.

The primary outcome was development of UTI in infants with low-grade HN compared with those with high-grade HN, as previously defined and based on the information extracted from the included studies. This was analyzed in the context of prophylaxis administration, with comparisons made between infants receiving CAP versus those not receiving CAP at the time of the UTI. We accepted that the protocol for administration, type of antibiotic, and duration of prophylaxis would vary between studies. Nevertheless, CAP does not refer to antibiotics provided for surgical prophylaxis or before completing imaging studies (VCUG). For the purpose of this review, we focused on administration of antibiotics beyond that period.

Secondary analyses chosen a priori were as follows: occurrence of a UTI in patients with concomitant vesicoureteral reflux (VUR) versus no VUR, and occurrence of a UTI in females compared with males. Although we initially planned on assessing UTI rates in circumcised versus uncircumcised boys, data from the available studies were insufficient to allow for this particular comparison.

**Statistical Analyses**

We anticipated that the search results would yield case series (single group retrospective or prospective studies) reporting the overall proportion of UTI and some comparative data reporting the proportion of UTI for CAP status (yes versus no) or HN grade (high versus low). Therefore, due to the inherent heterogeneity of the case series and observational designs, we planned a priori to use random effects models to account for between-study heterogeneity.

Odds ratios (OR) and 95% confidence intervals (CIs) for the primary outcome...
were calculated whenever frequency data were available. We included in our primary meta-analyses any study that reported a rate of UTI, obtaining pooled estimates for infants with low- and high-grade HN, patients on CAP versus not, infants with and without VUR, and girls compared with boys. We applied the random effects model by using the DerSimonian-Laird method due to the inherent heterogeneity of case series to estimate the pooled weighted UTI proportion of the included studies in these meta-analyses. The pooled weighted proportion was calculated as the back-transformation of the weighted mean of the transformed proportions, using DerSimonian-Laird (1986) weights for the random effects model. StatsDirect software version 2.7.8 (www.statsdirect.com) was used to calculate the pooled weighted proportions.

When deemed appropriate, we conducted a secondary meta-analysis of any study that reported a direct comparison of UTI rates for infants with low- and high-grade HN, patients on CAP versus not, and girls compared with boys. We performed a random effects model by using an inverse variance method to calculate the OR with 95% CIs for the primary outcome (UTI) for CAP status (yes versus no), HN grade (high versus low), and gender (girls versus boys). StatsDirect software version 2.7.8 (www.statsdirect.com) was used to calculate the pooled weighted proportions.

**TABLE 2 Characteristics of Included Studies**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study Type</th>
<th>N</th>
<th>Girls (%)</th>
<th>Boys (%)</th>
<th>Boys Circ</th>
<th>SFU I–II Patients N (%)</th>
<th>SFU III–IV Patients N (%)</th>
<th>CAP N (%)</th>
<th>VUR N (%)</th>
<th>UTI N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dacher et al</td>
<td>1992</td>
<td>US</td>
<td>Prospective</td>
<td>413</td>
<td>3</td>
<td>10</td>
<td>3</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>47 (11%)</td>
<td>13 (3.1%)</td>
</tr>
<tr>
<td>Blachar et al</td>
<td>1994</td>
<td>Israel</td>
<td>Prospective</td>
<td>99</td>
<td>NS</td>
<td>NS</td>
<td>101</td>
<td>15*</td>
<td>NS</td>
<td>14 (14.1%)</td>
<td>7 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>Misra et al</td>
<td>1999</td>
<td>UK</td>
<td>Prospective</td>
<td>42</td>
<td>17</td>
<td>25</td>
<td>NS</td>
<td>22*</td>
<td>18*</td>
<td>12 (28.8%)</td>
<td>5 (11.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Herndon et al</td>
<td>1999</td>
<td>US</td>
<td>Retrospective</td>
<td>71</td>
<td>15</td>
<td>56</td>
<td>37</td>
<td>NS</td>
<td>NS</td>
<td>71 (100%)</td>
<td>18 (25.4%)</td>
<td></td>
</tr>
<tr>
<td>Yerkes et al</td>
<td>1999</td>
<td>US</td>
<td>Prospective</td>
<td>60</td>
<td>17</td>
<td>43</td>
<td>NS</td>
<td>60 (100%)</td>
<td>NS</td>
<td>NS</td>
<td>6 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>Farhat et al</td>
<td>2000</td>
<td>Canada</td>
<td>Retrospective</td>
<td>31</td>
<td>7</td>
<td>24</td>
<td>NS</td>
<td>31*</td>
<td>9*</td>
<td>31 (100%)</td>
<td>31 (100%)</td>
<td>8 (25.8%)</td>
</tr>
<tr>
<td>Molloy et al</td>
<td>2000</td>
<td>New Zealand</td>
<td>Retrospective</td>
<td>69</td>
<td>37</td>
<td>32</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>88 (100%)</td>
<td>8 (11.6%)</td>
</tr>
<tr>
<td>Brophy et al</td>
<td>2002</td>
<td>US</td>
<td>Retrospective</td>
<td>234</td>
<td>60</td>
<td>174</td>
<td>NS</td>
<td>141 (60.3%)</td>
<td>80 (34.2%)</td>
<td>97 (41.3%)</td>
<td>10 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>Mc Lellan et al</td>
<td>2002</td>
<td>US</td>
<td>Retrospective</td>
<td>54</td>
<td>18</td>
<td>36</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>54 (100%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Shukla et al</td>
<td>2005</td>
<td>US</td>
<td>Retrospective</td>
<td>40</td>
<td>8</td>
<td>32</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>12 (30.0%)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Wellenberg et al</td>
<td>2005</td>
<td>Switzerland</td>
<td>Retrospective</td>
<td>78</td>
<td>NS</td>
<td>NS</td>
<td>42 (53.8%)</td>
<td>36 (48.2%)</td>
<td>41 (52.6%)</td>
<td>9 (11.5%)</td>
<td>15 (19.2%)</td>
<td></td>
</tr>
<tr>
<td>Mears et al</td>
<td>2007</td>
<td>UK</td>
<td>Prospective</td>
<td>55</td>
<td>16</td>
<td>39</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>8 (14.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Song et al</td>
<td>2007</td>
<td>South Korea</td>
<td>Retrospective</td>
<td>105</td>
<td>23</td>
<td>82</td>
<td>0</td>
<td>0</td>
<td>105 (100%)</td>
<td>0</td>
<td>0</td>
<td>38 (38.2%)</td>
</tr>
<tr>
<td>Coelho et al</td>
<td>2008</td>
<td>Brazil</td>
<td>Prospective</td>
<td>192</td>
<td>52</td>
<td>140</td>
<td>0</td>
<td>139 (72.4%)</td>
<td>53 (27.6%)</td>
<td>119 (62.0%)</td>
<td>16 (8.3%)</td>
<td>27 (14.1%)</td>
</tr>
<tr>
<td>deKort et al</td>
<td>2008</td>
<td>Netherlands</td>
<td>Retrospective</td>
<td>125</td>
<td>26</td>
<td>99</td>
<td>NS</td>
<td>106 (84.8%)</td>
<td>19 (15.2%)</td>
<td>125 (100%)</td>
<td>11 (8.8%)</td>
<td>9 (7.2%)</td>
</tr>
<tr>
<td>Lee et al</td>
<td>2008</td>
<td>South Korea</td>
<td>Retrospective</td>
<td>430</td>
<td>79</td>
<td>351</td>
<td>0</td>
<td>255 (59.5%)</td>
<td>175 (40.7%)</td>
<td>0</td>
<td>0</td>
<td>83 (19.3%)</td>
</tr>
<tr>
<td>Liedfelt et al</td>
<td>2008</td>
<td>Sweden</td>
<td>Retrospective</td>
<td>103</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>1514 (100%)</td>
<td>NS</td>
<td>NS</td>
<td>50 (48.5%)</td>
<td>9 (8.7%)</td>
</tr>
<tr>
<td>Estrada et al</td>
<td>2009</td>
<td>US</td>
<td>Retrospective</td>
<td>1514</td>
<td>NS</td>
<td>NS</td>
<td>1514</td>
<td>322 (21.3%)</td>
<td>322 (21.3%)</td>
<td>21 (1.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mami et al</td>
<td>2009</td>
<td>Italy</td>
<td>Prospective</td>
<td>223</td>
<td>NS</td>
<td>NS</td>
<td>223</td>
<td>0</td>
<td>4 (1.8%)</td>
<td>8 (3.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roth et al</td>
<td>2009</td>
<td>US</td>
<td>Retrospective</td>
<td>92</td>
<td>20</td>
<td>72</td>
<td>NS</td>
<td>92 (100%)</td>
<td>0</td>
<td>0</td>
<td>4 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>Yakasan et al</td>
<td>2010</td>
<td>Turkey</td>
<td>Prospective</td>
<td>246</td>
<td>63</td>
<td>183</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>246 (100%)</td>
<td>32 (13.0%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Circ, circumcised; NS, not stated; UK, United Kingdom; US, United States.

* In renal units. Some studies did not specify criteria.
that is due to heterogeneity rather than chance. Publication bias was graphically assessed by constructing funnel plots depicting precision (measured according to sample size) against the logit of the event rate.

Secondary meta-analyses were selectively conducted for studies that reported a direct comparison between UTI rates according to the grade of HN (low versus high) and CAP use (yes versus no) to reduce clinical heterogeneity. Methodologic heterogeneity was explored by conducting sensitivity analyses comparing low- versus high-quality articles according to our quality appraisal criteria.

RESULTS

Included Studies

Our literature search identified 1681 potentially relevant citations. After screening, a total of 309 articles underwent full-text review, and 21 of these citations proved eligible for inclusion and final analysis (Fig 1). The weighted $\kappa$ for overall agreement between reviewers for the final eligibility decision was 0.85 (95% CI: 0.57–1.00). None of the included studies was a randomized clinical trial, and thus all were observational. Thirteen studies had a retrospective design and 8 were prospective.

Patient Characteristics

Patient characteristics for the included studies are summarized in Tables 2 and 3. The total number of infants in these studies was 3876. Given the inconsistencies in available data provided by each study, we conducted analyses including only complete relevant information to obtain pooled estimates that would specifically address the objectives of our review.

Study Quality

Five studies were judged to be of high methodologic quality. Eight studies were prospective.

Overall Methodologic Quality

TABLE 4 Overall Methodologic Quality Rating of Included Studies

<table>
<thead>
<tr>
<th>Methodologic Quality</th>
<th>Stated</th>
<th>Not Stated</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (75%)</td>
<td>5 (24)</td>
<td></td>
</tr>
<tr>
<td>Moderate (50–74%)</td>
<td>8 (38)</td>
<td></td>
</tr>
<tr>
<td>Low (25–49%)</td>
<td>5 (24)</td>
<td></td>
</tr>
<tr>
<td>Very low (&lt;25%)</td>
<td>3 (14)</td>
<td></td>
</tr>
</tbody>
</table>

CAP and Rates of UTI

UTI rates for infants receiving CAP were reported in 8 (23,25,26,28,29) of 21 studies, for a total of 851 patients; UTI rates for those not receiving CAP were reported in 8 (23,25,26,28,29) of 21 studies, for a total of 2370 infants. The pooled UTI rate for antenatal HN patients receiving CAP was similar to that of infants not receiving CAP (9.9% [95% CI: 4.6–17.1] vs 3.3% [95% CI: 2.9–16.0], $P = .21$) (Figs 3 A and B, respectively).

High-Grade Versus Low-Grade HN and Rates of UTI

A stratified analysis was conducted by using individual patient data available from eligible studies to determine UTI rates in infants with low-grade and high-grade HN according to their CAP status. The pooled UTI rates in patients with low-grade HN were similar regardless of CAP status (2.2% [95% CI: 1.3–4.0] for infants on CAP vs 2.8% [95% CI: 2.1–3.7] for those not on CAP, $P = .52$) (Table 5, $n = 2181$ patients). In the high-grade HN group, infants on CAP had a significantly lower UTI rate versus those not on CAP (14.8% [95% CI: 9.3–22.0] vs 28.9% [95% CI: 24.6–33.6], $P < .01$) (Table 6, $n = 507$ infants). The estimated number needed to treat to prevent UTIs in infants with high-grade HN receiving CAP was 7, which represents a measure of benefit (ie, that prescribing CAP to 7 infants with high-grade HN translates into preventing 1 UTI).

VUR and Rates of UTI

The pooled UTI rate for infants with VUR was 22.8% (95% CI: 9.7–39.4) compared with the pooled rate of 9.3% (95% CI: 3.1–18.5) for patients without VUR ($P = .31$) (Figs 4 A and B). We could not extract sufficient data to examine the association between VUR and UTI stratified according to HN grade or use of CAP.

Gender and Rates of UTI

A total of 8 studies reported on UTI rates according to gender: UTI rates were similar in boys and girls with antenatal HN (15% vs 18.9%; $P = .21$) (Fig 5). We could not extract
sufficient data to compare UTI rates between girls and boys based on HN grade or addressing circumcision status.

**Heterogeneity and Publication Bias**

To reduce heterogeneity, a random effects model was followed when conducting the current meta-analysis, limited to studies reporting a direct comparison between low- versus high-grade HN (Fig 6). The pooled OR was 5.8 (95% CI: 3.9–8.7), suggesting that high-grade HN was significantly associated with a higher rate of UTI. To adjust for potential confounding effects of VUR and CAP on UTI, we have chosen to display the percentage of VUR and CAP patients in Fig 6. To further validate these findings, a sensitivity analysis was conducted, comparing moderate versus high methodologic quality articles. The pooled OR for high-quality studies (6.3 [95% CI: 3.9–9.5]) also suggests that high-grade HN was significantly associated with higher UTI rates (Fig 7).

When we conducted a separate meta-analysis including only studies that compared CAP use versus no use of CAP, we obtained a pooled OR of 1.7 (95% CI: 1.1–2.8), indicating that patients receiving CAP had significantly lower UTI rates (Fig 8).

A funnel plot was created, involving 17 studies that reported UTI rates. The distribution of studies is scattered over the 4 quadrants of the graph, suggesting a lack of publication bias (Fig 9).

**DISCUSSION**

With the widespread practice of routine prenatal ultrasound, the number of fetuses with detected HN has increased commensurately. Management of the many patients who have persistent HN...
TABLE 5 Rates of UTI in Infants With SFU Grades I and II HN

<table>
<thead>
<tr>
<th>CAP Status</th>
<th>UTI</th>
<th>No UTI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
<td>2.2%</td>
<td>449</td>
</tr>
<tr>
<td>No</td>
<td>49</td>
<td>2.8%</td>
<td>1673</td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
<td>2.7%</td>
<td>2122</td>
</tr>
</tbody>
</table>

Data were stratified according to CAP status based on available data from the following studies included in the analysis: 6, 20, 25, 28, and 29 (VUR was an exclusion criterion in studies 6 and 23). * P ≤ .05.
* 95% CI for CAP use: 1.5 to 4.0.
* 95% CI for no CAP use: 2.1 to 3.7; 348 (16%) of 2181 patients had VUR.

TABLE 6 Rates of UTI in Infants With SFU Grades III and IV HN

<table>
<thead>
<tr>
<th>CAP Status</th>
<th>UTI</th>
<th>No UTI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Yes</td>
<td>18</td>
<td>14.6%</td>
<td>105</td>
</tr>
<tr>
<td>No</td>
<td>111</td>
<td>28.9%</td>
<td>273</td>
</tr>
<tr>
<td>Total</td>
<td>129</td>
<td>25.4%</td>
<td>378</td>
</tr>
</tbody>
</table>

Data were stratified according to CAP status based on available data from the following studies included in the analysis: 4, 6, 7, 20, 23, and 25 (VUR was an exclusion criterion in studies 4, 6, 7, and 23). * P ≤ .01.
* 95% CI for CAP use: 9.3 to 22.
* 95% CI for no CAP use: 24.6 to 33.6; 28 (5.5%) of 507 patients had VUR.

After birth remains controversial and devoid of guidance based on high levels of evidence. Among contentious topics, the routine prescription of CAP has gained attention due to the perceived lack of clinically significant benefit in VUR trials, as well as concerns for bacterial resistance and long-term adverse effects. Highlighting these issues, the 2009 Canadian Urological Association guidelines on antenatal HN stated that the role of CAP is indeed controversial and provided a grade D recommendation (based on case series and clinical experts’ opinion) for this specific topic.50 More recently, the 2009 American Urological Association Update Series on Prenatal Diagnosis of Urological Disease stated that although CAP is generally recommended for severe (grades III and IV) HN, the practice is not evidence based.1 Not surprisingly, the lack of consensus has translated into noticeable differences between individual health care providers and specialties.1,51–53 Ismaili et al31 conducted a study among French-speaking pediatric nephrologists and urologists and found a significant variation in CAP prescribing patterns for antenatal HN within and across the 2 groups. Similarly, a survey of pediatric urologists from Europe and the United States concluded that there is also a considerable variation in CAP use for antenatal HN between the 2 continents, as well as among pediatric urologists from the same country.32

In general, physicians prescribe CAP to reduce the risk of UTI in infants who have antenatal HN and to prevent UTI-associated morbidity as well as long-term complications of renal damage.34 Nevertheless, the ultimate decision to start an infant on CAP currently centers on parental acceptance aligning with individual health care provider and/or institution protocols. Due to the paucity of published data, treatment philosophy plays an important role. Thus, the decision is based on partially defined risks and benefits, heavily affected by the perception of what is more valuable: potentially preventing pyelonephritis and sepsis or accepting the administration of a drug that may provide little benefit but can be associated with adverse effects and bacterial resistance. Conceptually, it would make sense to tailor the prescription of CAP based on specific patient characteristics that affect the odds of experiencing the outcome of interest. However, consensus on what constitutes a risk factor for UTI warranting CAP in this population has yet to be determined. To date, there is limited information on the topic.

All of the reviewed publications have recognized important shortcomings in terms of study design, number of patients evaluated, inclusion and exclusion criteria, definition of events, and monitoring and assessment of compliance. Thus, the information gathered from each of them on an individual basis is difficult to bring into clinical practice. In addition, the findings from relevant series are at times inconsistent. Coelho et al55 found that girls with VUR or urinary tract obstruction had a higher risk of UTI during follow-up and recommended CAP and close clinical monitoring. Estrada et al28 observed that in patients with postnatal persistent grade II HN, identification of VUR through a VCUG and use of CAP significantly reduced the risk of febrile UTI. Conversely, some authors have argued that CAP does not change the risk of UTI in specific patient populations. Roth et al56 conducted a retrospective study of patients with SFU grade III/IV HN and, based on an overall low baseline rate of UTI (4%), recommended against widespread use of CAP for all infants with antenatal HN. Similarly, in a recent prospective study, Islek et al57 concluded that CAP use is not indicated in infants with ureteropelvic junction obstruction, regardless of its severity, as the risk of UTI was minimal in this group.

Given these discrepancies, our goal was to conduct a systematic review, aiming to summarize the current evidence regarding the use of CAP in antenatal HN patients. In addition, this exercise sought to further analyze direction and magnitude of potential treatment effects while highlighting deficiencies in knowledge that should be considered for future studies. To our knowledge, no similar reviews have been published on this particular topic thus far. Our strict eligibility criteria for included studies have allowed us to gather a rather homogeneous patient population, summarizing information on a relatively large number of infants identified antenatally and followed up for a minimum of 12 months after birth.
Aggregate evaluation by using meta-analysis demonstrated that UTI rates are significantly higher in infants with high-grade HN even when restricted to selected articles that reported a direct comparison of UTI rates between patients with low- versus high-grade HN within the same study. CAP in the high-grade HN group was associated with significant reduction of UTI rates when compared with no treatment (14.6% vs 28.9%, *P* < .01). In contrast, UTI rates in infants with low-grade HN were similar regardless of CAP use. This core finding supports the notion of selective use of CAP for patients with high-grade HN. Nevertheless, it should also be noted that due to limitations of the reported data in the studies included, the effect of important variables (eg, VUR, gender) could not be properly evaluated.

As with most meta-analyses, the current report has important limitations. The
most notable is the unavoidable restriction to observational studies because we could not identify any randomized controlled trials examining the relationship between CAP and UTIs in infants with antenatal HN. This finding reflects the state of current evidence on the topic of CAP and antenatal HN. Methodologic and analytical issues related to observational studies of different quality have to be carefully considered and kept present when aggregating data and placing these outputs in perspective. Even if all the included nonexperimental studies were of high methodologic quality, the resultant level of evidence would be moderate. In addition, it is possible that our estimates of UTI rates were biased due to restricted analysis of the 6 studies with data on direct comparison of UTI rates between infants with low- and high-grade HN. Nevertheless, the followed strategy allowed for optimizing statistical power (by virtue of a larger sample size) within a more homogeneous patient population, ultimately combining results and providing a common measure of effect size. Moreover, the format in which data were presented varied widely between studies. We elected to group infants based on SFU grade to be able to make meaningful comparisons between the studies. However, inconsistent grading of HN (a situation that was more notable in older studies) made it difficult to compare all patient populations. As previously indicated, some studies were excluded from the final analysis because the provided measurements could not be translated into SFU grading. Similarly, although most articles reported on occurrence of antenatal HN in individual patients, some articles reported their results in renal units without correlating these data to the number of patients affected (as shown in Table 2). Due to the paucity of data, we were unable to comment on the association between antenatal HN concurrent with VUR and UTI, and gender effect on UTI, adjusted according to HN grade. Associations between the primary outcome and isolated HN (ureteropelvic junction obstruction–like) or hydronephrosis (primary megaureter) were often difficult to analyze because the included articles had not

<table>
<thead>
<tr>
<th>SFU-3-4 HN</th>
<th>VUR (%)</th>
<th>Study or Subgroup</th>
<th>Antibiotic prophylaxis</th>
<th>no prophylaxis</th>
<th>OR H, Random, 95% CI</th>
<th>OR H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>34.2</td>
<td>17.1</td>
<td>Brophy et al.</td>
<td>6</td>
<td>97</td>
<td>4</td>
<td>137</td>
</tr>
<tr>
<td>27.6</td>
<td>8.3</td>
<td>Coelho et al.</td>
<td>20</td>
<td>119</td>
<td>7</td>
<td>73</td>
</tr>
<tr>
<td>0.0</td>
<td>21.3</td>
<td>Estrada et al.</td>
<td>5</td>
<td>322</td>
<td>16</td>
<td>1192</td>
</tr>
<tr>
<td>NS</td>
<td>0.7</td>
<td>Litteret et al.</td>
<td>7</td>
<td>50</td>
<td>2</td>
<td>53</td>
</tr>
<tr>
<td>NS</td>
<td>0.0</td>
<td>Shulks et al.</td>
<td>2</td>
<td>12</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>46.2</td>
<td>11.5</td>
<td>Wollenberg et al.</td>
<td>8</td>
<td>41</td>
<td>7</td>
<td>37</td>
</tr>
<tr>
<td>Total (H)</td>
<td></td>
<td></td>
<td>641</td>
<td>1520</td>
<td>100.0%</td>
<td>1.73 (1.05–2.85)</td>
</tr>
</tbody>
</table>

| Total events | 48 | 36 |

Heterogeneity: $t^2 = 0.00; f^2 = 0.00; P = 0.00$; Test for overall effect: $Z = 2.17 (P = 0.03)$

FIGURE 7
Sensitivity analysis comparing high-quality versus moderate-quality studies. AHN, antenatal HN.

FIGURE 8
Meta-analysis on UTI rate in CAP use versus no CAP use.
consistently provided UTI rates discriminated according to etiology. In an attempt to assess UTI rates solely in patients with hydroureteronephrosis without VUR (primary megaureter), we obtained data from 4 pertinent studies \(^4\)–\(^7\) as displayed in Fig 10. The pooled UTI rate was 34% (95% CI: 14–58), significantly higher than the rate of all patients with high-grade HN (23.3% [95% CI: 3.7–12]), suggesting that these patients might be at an even higher risk of developing UTI and could benefit from administration of CAP.

Finally, in the same way, we were unable to draw conclusions about the impact of circumcision on UTI rates; UTI data on circumcised males were only available for 10 boys in 2 studies.

Despite those limitations, we believe there is value in the current report. We present compelling evidence to suggest that infants who have high-grade HN who are not receiving CAP are at a significantly higher risk of UTI when compared with infants who have high-grade HN who are receiving prophylaxis. This information is a first step toward tailoring our approach for patients with antenatal HN, which could be selectively favored in cases of high-grade HN. This systematic review corroborates the presence of clinical equipoise regarding the postnatal management of infants with antenatal HN due to the lack of sound evidence supporting or disproving the effectiveness of CAP to prevent UTIs in this patient population.

**CONCLUSIONS**

This systematic review implies that offering CAP to 7 infants who have high-grade HN would prevent 1 UTI, suggesting value in this subgroup of patients. Given the existing data, the effect of VUR, gender, and circumcision on UTI could not be determined. Current lack of best practice guidelines in the pediatric urology community, coupled with the controversial literature surrounding this topic, calls for prospective, randomized placebo-controlled trials to investigate the effect of CAP in reducing UTI rates in infants with antenatal HN.

**ACKNOWLEDGMENTS**

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/content/early/2012/12/12/peds.2012-1870