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Review Article

Role of antibiotic prophylaxis in antenatal hydronephrosis: A systematic review from the European Association of Urology/European Society for Paediatric Urology Guidelines Panel

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Summary

Background
The benefits and harms of continuous antibiotic prophylaxis (CAP) versus observation in patients with antenatal hydronephrosis (ANH) are controversial.

Objective
The aim was to determine the effectiveness of CAP for ANH, and if beneficial to determine the best type and regimen of antibiotic and the most harmful to provide guidance for clinical practice.

Methods
A systematic literature search was performed in databases including Medline, Embase, and Cochrane in June 2015. The protocol was prospectively registered to PROSPERO (CRD42015024775). The search started from 1980, when maternal ultrasound was first introduced into clinical practice. Eligible studies were critically evaluated for risk of bias using Revman software. The outcomes included reduction in urinary tract infections (UTI), drug-related adverse events and kidney functions.

Results
Of 797 articles identified, 57 full text articles and six abstracts were eligible for inclusion (2 randomized controlled trials, 11 non-randomized comparative studies, and 50 case series). It remains unclear whether CAP is superior to observation in decreasing UTIs. No conclusion could be drawn for drug-related adverse events and kidney function because of lack of data. Children who were not circumcised, with ureteral dilatation, and high-grade hydronephrosis may be more likely to develop UTI, and CAP may be warranted for these subgroups of patients. A majority of the studies had low-to-moderate quality of evidence and with high risk of bias.

Conclusions
The benefits of CAP in a heterogeneous group of children with ANH involving different etiologies remains unproven. However, the evidence in the form of prospective and retrospective observational studies has shown that it reduces febrile UTI in particular subgroups.

Introduction

Antenatal hydronephrosis (ANH) is one of the most common birth abnormalities with an overall incidence between 1% and 5% [1]. The widespread use of ultrasonography during pregnancy has resulted in a higher detection rate for ANH. Owing to the increased risk of urinary tract infections (UTIs) and upper urinary tract (UUT) deterioration, the use of continuous antibiotic prophylaxis (CAP) is recommended [2,3]. However, the evidence-based data for this practice are lacking and the use of CAP is generally based on expert opinion. Prophylactic policies seem extremely variable, and UTI rates vary widely with comparable rates reported between patients followed on and off antibiotics [4]. Nevertheless, infants who are potentially at increased risk of UTI are recommended to receive CAP in many reports.

Observation is another option in those children which eliminates the side effects of the antibiotics and reduces the cost. However, the risk of developing UTI during observation is also unclear. Therefore, the benefits and harms of CAP versus observation in patients with ANH still remains controversial.

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In a previous systematic review by Braga et al. [4], no benefit of CAP could be demonstrated in ANH. Infants with high-grade hydronephrosis (HN) were at increased risk of developing UTI. However, the other important variables such as ureteral dilatation, circumcision status, and vesicoureteral reflux (VUR) could not be assessed.

The challenge in the management of ANH is to decide whether CAP should be used or not, and if decided, in whom, how, and when should it be started.

This systematic review was performed by the European Association of Urology (EAU) Pediatric Urology Guideline Panel as part of its update for 2017 and aimed to determine the effectiveness of CAP in infants with ANH, and, if beneficial, to determine the best type and regime of antibiotic and the most harmful to provide guidance for clinical practice.

Methods

Search strategy

The protocol of this review was published in PROSPERO website (www.crd.york.ac.uk) with the registration number CRD42015024775. The search strategy is provided in the Electronic Supplement 1. In summary, databases, including Embase, Medline, and Cochrane, were systematically searched in June 2015. All abstracts and full texts of the articles were evaluated by two independent reviewers (M.S.S., S.U.) for eligibility. Disagreements were resolved by interactive discussion or by consulting an independent third reviewer. Only studies published after 1980 were included since maternal ultrasound was popularized afterwards. No language restrictions were applied. The search was supported by additional sources including pediatric urology congress abstracts and a panel of experts (EAU-ESPU Paediatric Urology Guideline Panel).

Types of study design

All study types, including randomized controlled trials (RCTs), non-randomized comparative studies (NRSs), and single-arm case series of no treatment or antibiotic prophylaxis for ANH. Systematic or narrative reviews were excluded but retained as a source for discussion.

Types of participants

Children (<18 years old) with HN diagnosed prenatally and confirmed postnatally or diagnosed postnatally within the first year of life (for postnatal diagnosis, it has to be made 3 days or more after delivery) were included. Only asymptomatic patients at diagnosis with bilateral or unilateral HN were included in this review. The definition of HN included all grades (1–4) of the Society for Foetal Urology (SFU), anteroposterior renal pelvis diameter, and severity (mild-moderate and severe) of HN. If grade or severity was not specified, all types of descriptions and severity of HN were included. The presence/absence of vesicoureteric reflux (VUR) was not an exclusion criterion, but data on this were to be analyzed as a subgroup. The cause of HN was also considered as a subgroup (e.g., ureteropelvic junction obstruction [UPJO], megaureter, VUR, duplicated systems, etc.). Children with solitary kidney, posterior urethral valves, bladder exstrophy, and neurological abnormality (e.g., spina bifida) were excluded. The other subgroups analyzed were gender (girls versus boys), circumcision versus non-circumcision for boys, grade of HN (low grade versus high grade), and ureteral dilation (HN versus hydroureteronephrosis [HUN]).

Types of interventions

The experimental intervention was administration of antibiotic prophylaxis in asymptomatic patients only, including (but not restricted to) trimethoprim, Macrodantin, cephalosporin, amoxycillin, sulphometoxazole, with trimethoprim, and any others as specified by the trialist and judged relevant by reviewer. The control intervention was observation or no treatment in asymptomatic patients with ANH.

Types of outcome measures

The primary benefit outcome was the reduction in UTIs; there was no restriction on the definition of UTI (i.e., as defined by trialists, including standardized or non-standardized definitions), measured within the first 2 years of life. The primary harm outcomes were drug-related adverse effects (e.g., allergies, diarrhea, antimicrobial resistance, constipation, etc.) and any other adverse events as defined and reported by trialists.

The secondary outcomes were reduction in UTI measured after 2 years of life, febrile and non-febrile infections, and function of kidney, defined in the following ways: (1) renography (i.e., split renal function; delayed drainage from renal pelvis; etc.); (2) renal scarring (as determined by DMSA only); (3) anatomical or morphological changes (as determined by ultrasound; e.g., changes to HN, anteroposterior diameter, etc.), measured at any time point. The other secondary outcomes were pain (as defined by trialist) and severity or grade of HN at the end of follow-up.

Assessment of risk of bias

The "risk of bias" (RoB) of each included study was assessed by two independent reviewers and any disagreement was resolved by discussion or by consulting a third review author. RoB of the eligible RCTs were assessed by using the recommended tool in the Cochrane Handbook for Systematic Reviews of Interventions [5].

RoB in NRSs was assessed using all the domains used for RCTs plus assessing the risk of confounding. This was a pragmatic approach informed by methodological literature for the assessment of RoB in NRSs. Four potential confounders were identified and developed a priori by the EAU Paediatric Urology Guideline Panel: severity or grade of HN, cause of HN, gender, and circumcision status for boys. The

judgment of each confounder depended on whether it was measured, balanced between the groups, or if it was statistically adjusted.

RoB in case series were assessed again with a pragmatic approach informed by methodological literature. In this case, the judgment was based on whether the study included consecutive patients, if there was a priori protocol, attrition bias (patients lost to follow up accounted for) and if the outcome measurements were addressed.

Data analysis

The number of UTIs and other outcomes measured including antibiotic type, dosage, and side effects were extracted from the eligible studies where available. The progress of HN and renal function at the end of follow-up were also extracted where available. Meta-analyses was intended for the data retrieved from RCTs, but because of the lack of this evidence data have been represented in Forest plots without meta-analysis (because of methodological heterogeneity and the high RoB). For binary/dichotomous/categorical benefit or harm outcomes, risk ratios (RR) or odds ratios (OR) were used where available. Mean difference (MD) or standardized mean difference (SMD) with corresponding 95% confidence intervals (CIs) were used to report the continuous outcomes.

If there were sufficient data, to elucidate the potential impact of clinical heterogeneity on outcomes, subgroup analyses were planned for factors, including presence of VUR, bladder pathology, distal ureteric dilatation, surgical intervention, antibiotic regime, circumcision status, gender, and febrile UTIs (see protocol for the review http://www.crd.york.ac.uk/PROSPERO; registration number CRD42015024775).

Results

Quantity of evidence identified

The selection process of the studies is demonstrated in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram (Fig. 1). A total of 811 abstracts and titles were screened and 97 were retrieved for full text screening. Finally, 63 studies were found eligible for the systematic review, recruiting a total of 10,019 children (RCTs, 85; NRSs, 4027; case series, 5907). This included two RCTs [7,11] (1 as an abstract only), 11 NRSs [6,8—10,12—18] (one as an abstract), and 50 case series [19—68] with four of them published as an abstract.

Characteristics of the included studies

The baseline characteristics of the 13 comparative studies and 50 case series are presented in Supplementary Tables 1 and 2, respectively.

Characteristics of comparative studies

Although all patients recruited had ANH, the etiology was variable between the studies. Two studies included only patients with primary obstructive megaureter (POM) (1 published as an abstract only) [6,16]. Three studies excluded children with VUR from their study cohort [6,7,16] while two studies included only patients with VUR [11,12].

The SFU grade or severity of HN was not stated in three studies [11,14,16]. In one study, only patients with mild HN were included [15], whereas in another only patients with SFU G2 HN were recruited [12].

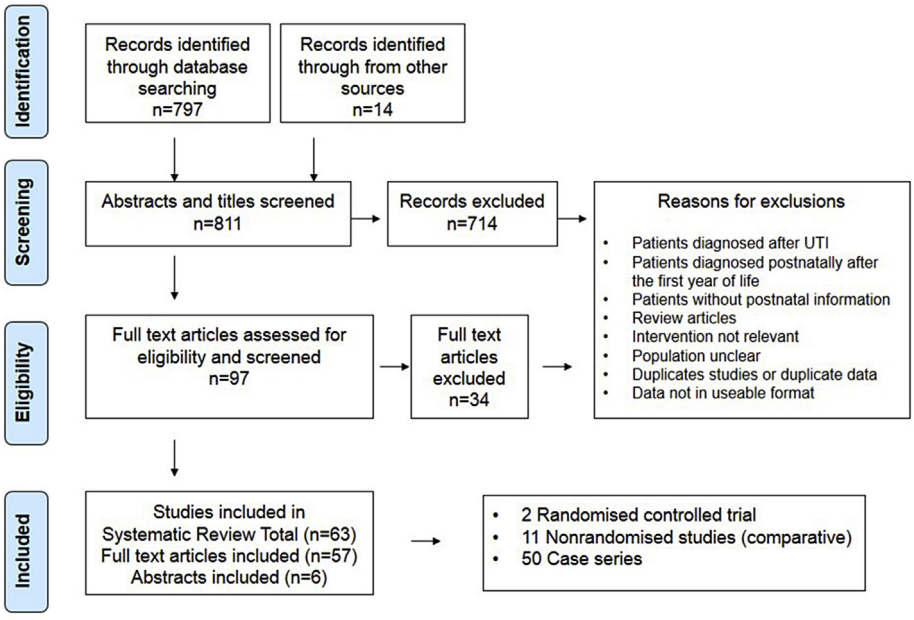

Figure 1 Prisma flow diagram.

In six studies, the numbers of circumcised boys were either not stated or unclear [9,11,12,14,16,17]. In one study all boys were non-circumcised [10].

Development of UTI during follow-up was reported in all comparative studies. However, the standardized definition of UTI was made in six of them [7,8,13,15,17,18]. Antibiotic side effects were not reported in any of the studies except one RCT [7].

Characteristics of case series

A total of 50 case series were included in this review. Of the 50 case series, 10 included patients with ANH plus VUR [31–33,37,42,43,49,58,61,63], three included ANH plus UPJO [20,47,66], five included ANH plus POM [21,23,34,50,67], and three included ANH plus ureterocele [27,28,30]. The rest of the case series included various subgroups.

The reported outcomes were variable in between the series but mainly included UTI rates, prognostic factors for UTI, necessity for surgery, efficacy of surgery, and the process of HN. Antibiotic type and dosage, side effects, progress of HN, and renal functions at the end of follow-up were rarely reported.

Risk of bias and confounding assessment of the included studies

Fig. 2A demonstrates the RoB summary and confounding assessments for the two RCTs and 11 NRSs. NRSs had high risk of selection, performance, and detection biases. There was also a high risk of attrition bias (incomplete outcome data) in the majority of the comparative studies. In addition, reporting bias was also either high risk or unclear in most studies. Severity of HN, cause of HN, and gender as the confounding factors were measured and corrected in most of the studies. However, circumcision status for boys was not considered in five studies and was unclear in two of them.

Fig. 2B demonstrates the RoB summary for the 50 case series. In general, these studies were at high risk of selection bias and selective outcome reporting. More than half of the studies had low RoB for loss to follow-up. Finally, 21 out of 50 studies had an a priori protocol.

Comparisons of intervention results

Data from comparative studies

The outcome results of two RCTs and 11 NRSs are summarized and demonstrated in Supplementary Table 3.

Clinical effectiveness of CAP on UTI rates. UTI rates in patients who received CAP ($n = 1307$) and no CAP ($n = 2692$) were reported in 12 comparative studies. It is unclear whether CAP makes any difference from the data available as ORs varied from 0.17 (95% CI 0.01–3.82) to 13.57 (95% CI 0.60–306.64), with a large variation in direction of effect between studies and wide confidence intervals throughout. This is demonstrated clearly in Fig. 3.

In the only RCT with full text available [7], 46 patients were enrolled into the study but only 29 completed the trial. In the end, the number of patients who received CAP was unclear and no conclusion could be drawn by the investigators regarding the clinical effectiveness of CAP.

In the prospective longitudinal study by Braga et al. [8], lack of CAP ($p < 0.01$) was found to be an independent risk factor for fUTI.

Coelho and coworkers [10] prospectively followed 192 children with ANH with a median period of 2 years. Antibiotic prophylaxis was discontinued in children without VUR and with renal pelvis diameter <10 mm. Twenty patients presented with UTI while on CAP and seven after discontinuation of CAP.

Herz et al. [13] retrospectively compared the UTI rates among 401 children who received CAP versus no CAP. The incidence of fUTI was significantly lower in children on CAP (7.9%) than no CAP (18.7%), ($p = 0.02$).

Zareba et al. [18] found no benefit of CAP on decreasing the risk of UTI (OR 0.93, CI 0.45–1.94, $p = 0.85$). CAP was also not beneficial in any high-risk group including females, uncircumcised males and high grade HN.

Antibiotic regimen and adverse events of CAP. In the majority of the comparative trials, the type and dosage of the antibiotic was not provided. In the rest of them, the most common antibiotic used for CAP was trimethoprim with 1 mg/kg dosage [7,10,14,18]. In one study trimethoprim/sulfamethoxazole (TMP/SMX) combination with 2 mg/kg dosage was preferred by the trialists [11].

The only report for side effects was from the RCT by Braga et al. [7] found a total of six side effects (5 gastroenteritis, 1 choking). The other comparative studies did not report whether a side effect was observed or not in their study population.

Circumcision status and rates of UTI. UTI rates in patients who were circumcised ($n = 674$) and non-circumcised CAP ($n = 484$) were reported in FOUR comparative studies. Data on this outcome seemed to be more consistent, with direction and size of effect broadly similar across studies (Fig. 4). OR varied from 0.12 (95% CI 0.04–0.37) to 0.30 (95% CI 0.10–0.91). Sencan et al. [15] found that 10 of the 15 males with UTI were non-circumcised and boys who were uncircumcised were at a 7.8-fold increased risk of UTI ($p < 0.01$).

Gender and rates of UTI. UTI rates of females ($n = 639$) versus males (1390) were reported and compared in seven comparative studies. Again, direction and magnitude of effects were variable and no definite conclusions could be drawn (Fig. 5).

In three comparative studies, female gender was reported as an independent predictor of developing UTI [8,10,18].

Low-grade versus high-grade HN and rates of UTI. The comparison of the UTI rates between patients with low-grade and high-grade HN was provided in five studies [6,8–10,18]. There appears to be a trend towards less UTI occurring in low-grade HN, particularly in the studies with larger sample sizes (Fig. 6).

Zareba et al. [18] reported that high-grade HN was an independent predictor of UTI (OR 2.40; 95% CI 1.26–4.56).

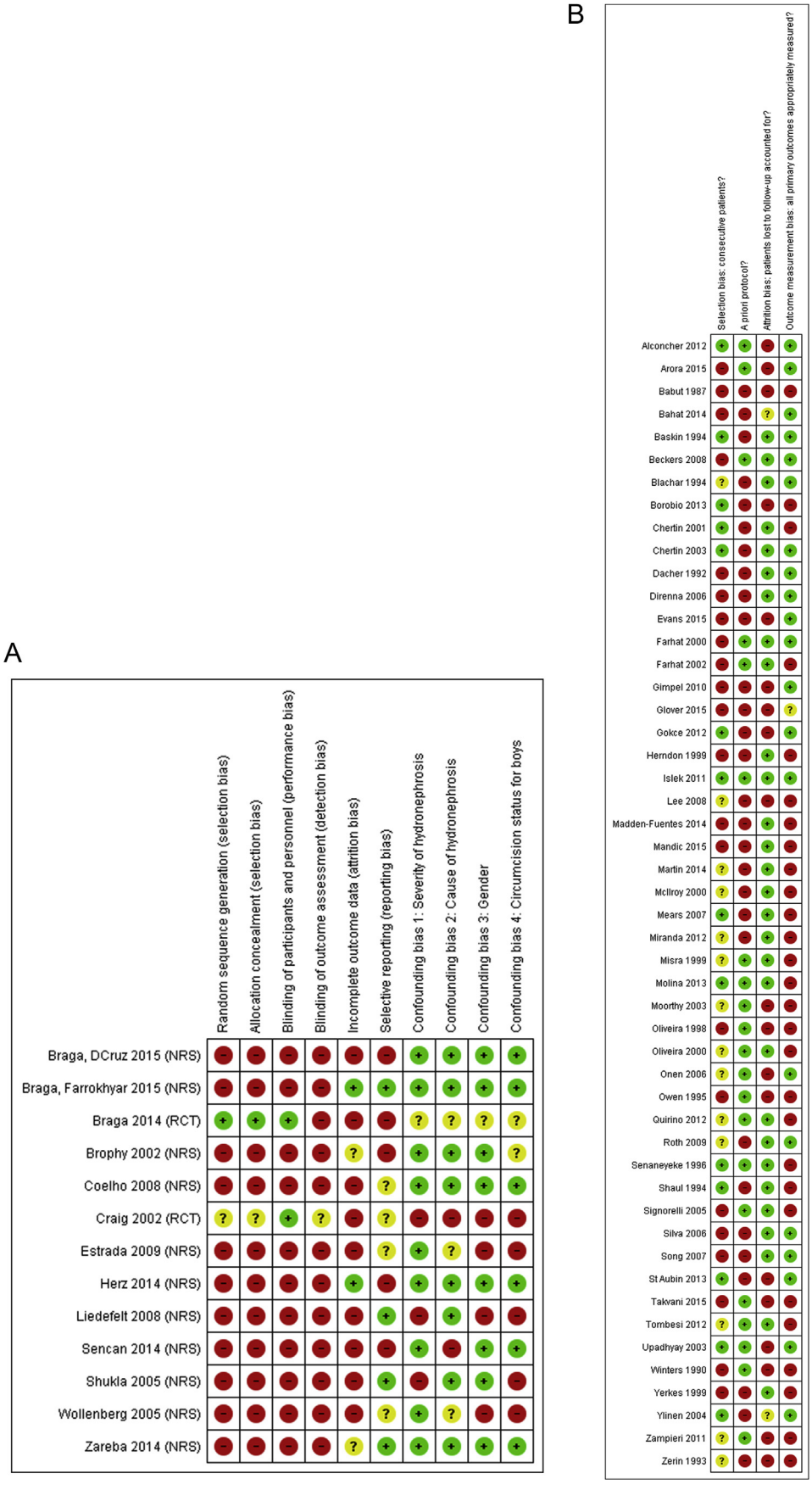

Figure 2 A. Risk of bias (RoB) summary and confounding assessments for comparative studies including the two RCTs and 11 NRSs. B. Risk of bias (RoB) summary and confounding assessments for case series.

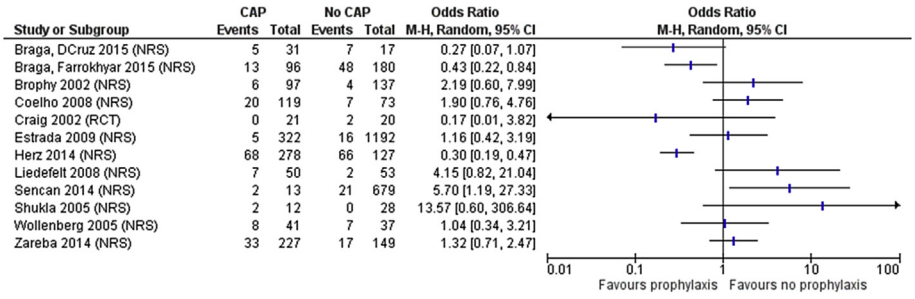

Figure 3 Forest plot demonstrating the development of urinary tract infection (UTI) in children receiving continuous antibiotic prophylaxis (CAP) versus no CAP.

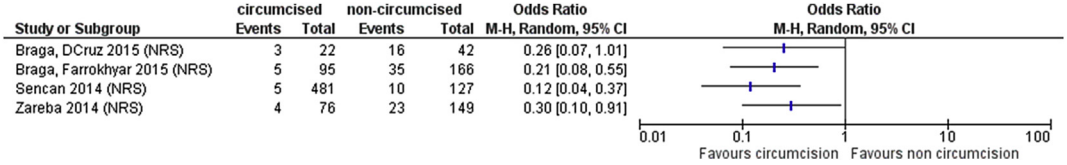

Figure 4 Forest plot demonstrating the development of urinary tract infection (UTI) in male patients who were circumcised versus non-circumcised.

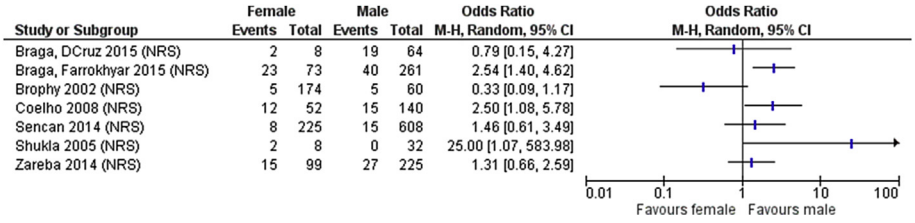

Figure 5 Forest plot demonstrating the development of urinary tract infection (UTI) in males versus females.

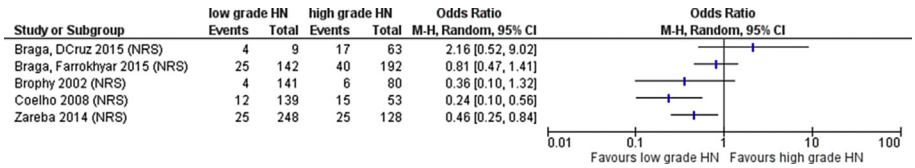

Figure 6 Forest plot demonstrating the development of urinary tract infection (UTI) in children with low grade versus high-grade hydronephrosis (HN).

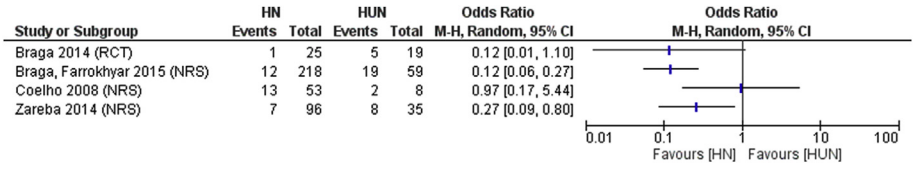

Figure 7 Forest plot demonstrating the development of urinary tract infection (UTI) in children with hydronephrosis (HN) versus hydroureteronephrosis (HUN).

In this study the fUTI rates were 10.1% (25/248) and 19.5% (25/128) for low-grade and high-grade HN respectively.

Ureteral dilatation and rates of UTI. UTI rates between patients with HN and HUN was compared and reported in four comparative studies. The studies seem to consistently suggest less UTI occurring with HN compared to HUN (Fig. 7).

Herz et al. demonstrated that in infants with ureteral dilatation >11 mm and not maintained on CAP had a 5.5-fold increased risk of developing fUTI (OR 5.54, 95% CI 3.15—7.42, $p = 0.001$). In a RCT by Braga et al. [7], a total of six UTIs were reported in 44 patients. Five of the six UTIs developed in children with HUN and one developed in a child with HN.

VUR and rates of UTI. The impact of VUR on UTI rates in infants with ANH could not be estimated because of a lack of reporting studies and heterogeneity of the subgroups.

In an RCT which was published as a congress abstract by Craig et al. [11], 46 infants with ANH and VUR were randomly assigned to 3 years of TMP/SMX 2 mg/kg daily

dose treatment or matching placebo. At the end of follow-up, two children with placebo and no children with CAP developed UTI ($p = 0.02$). Moreover, none of the children in either group developed new scar on DMSA scintigraphy.

Estrada et al. [12] focused on follow up outcomes of 1514 infants with G2 HN. The patients were divided into two groups, either screened or non-screened. In 322 patients with VUR who were screened, 1.6% had a rate of UTI under CAP. In the non-screened group who did not receive CAP and with 101 estimated patients with VUR, 11.8% developed UTI. Those results suggested the benefit of CAP in decreasing UTI rates among patients with VUR and ANH.

Kidney status at the end of follow-up. The kidney functions assessed by scintigraphy (DMSA) at the end of the follow-up was provided only in two studies [11,16]. In an RCT in children with VUR and ANH, none of the 41 children developed new scarring on DMSA at the end of 3 years [11]. Shukla et al. [16] reported a series of 40 patients with POM, and four patients required surgery because diminished renal function on scintigraphy.

The changes in the status of HN was also provided in two different studies [15,16]. The creatinine and glomerular filtration rate (GFR) was not provided in any of the studies.

Data from case series

The outcome results of 50 case series are summarized and demonstrated in Supplementary Table 4 [19—68].

Clinical effectiveness of CAP on UTI rates. The effect of CAP on UTI rates was demonstrated in some of the studies and the results were highly variable. Islek et al. [38] reported a case series including 84 infants with UPJO. After a median follow-up of 18 months without CAP none of the patients developed UTI, and CAP was not recommended in UPJO. Madden-Fuentes et al. [40] reported similar results in a cohort of isolated low-grade HN within the first year of life. In contrast, Song et al. [59] reported high UTI rates in neonates with UPJO (30.7%) and UVJO (50%) who did not receive CAP and recommended antibiotic prophylaxis in those subgroup of patients.

Antibiotic regimen and adverse events of CAP. CAP was administered in the majority of the case series. However, in general, antibiotic type and dosage was rarely reported. In addition, the side effects of antibiotics was not reported in any of the eligible studies.

Other prognostic factors on UTI rates. Lee et al. [39] investigated a total of 430 patients with ANH and without VUR. UTI rates were increased in infants with high grade HN, HUN, and with obstructive uropathy ($p < 0.001$ for all). Bahat et al. [22] reported a significant increased risk of developing UTI in female neonates with ANH (HR 3.3, $p = 0.04$).

Evans et al. [31] found increased risk of UTI in ANH neonates with congenital reflux nephropathy, non-circumcision, and with bladder dysfunction.

Kidney status during follow-up. The vast majority of the case series did not report long-term follow-up of kidney function, changes in the status of HN, and creatinine and GFR levels.

Upadhyay et al. [63] reported a case series including 25 neonates with ANH and VUR. In two patients the renal functions were decreased after 4 years of follow-up.

In the case series by Madden-Fuentes et al. [40] including neonates with low-grade HN, the HN resolved in 373, improved in 69, remained stable in 165, and worsened in 16 within the first year of life.

Discussion

Principal findings

Conflicting results regarding the effectiveness of CAP in infants with ANH were found. This may be attributed to the heterogeneity of the patient populations and different subgroups of ANH in the eligible trials. Some studies reported beneficial effect of CAP on UTI rates, such as the study by Braga et al. [8]. In that prospective longitudinal study, independent risk factors for fUTI was investigated in a total of 334 patients with ANH. Female gender ($p = 0.02$), uncircumcised males ($p = 0.02$), lack of CAP ($p < 0.01$), HUN ($p < 0.01$), and VUR ($p < 0.01$) were found to be the independent predictors. The subgroup analysis by excluding patients with VUR revealed that high-grade HN ($p = 0.04$) was also a significant predictor for fUTI.

Some other studies did not find any beneficial effect of CAP on UTI rates including the RCT by Craig et al. [11]. This study was mainly focused on patients with ANH and VUR, and the lack of the full text of this trial was a pitfall in terms of determining the details of the study population. However, there were some other reports clearly stating that no benefit of CAP was achieved regarding the UTI rates even in the high risk groups [18].

The results of the forest plot tables demonstrate five important findings. First, it is not possible to establish whether CAP was superior to no CAP in terms of decreasing UTI (Fig. 3). Second, non-circumcised infants, high-grade HN, and HUN may be at higher risk of developing UTI (Figs. 4, 6 and 7). Finally, there was no significant difference in UTI risk between males and females (Fig. 5). No conclusion could be drawn for the impact of VUR and no VUR and comparison of the different degrees of VUR because of lack of data in the available literature. It is indeed difficult to assess risk of UTI because different thresholds exist to screen for VUR in the available literature.

The best type of the antibiotic regimen and the adverse effects of the antibiotics could not be assessed either. The only thing that can be said is the most commonly chosen antibiotic in infants with ANH is trimethoprim, and, except in one pilot RCT [7], no side effect was reported in any of the eligible comparative studies or case series. The recently published paper which is a completion of the pilot RCT confirmed the same outcomes [69].

Implications for clinical practice

The benefit of CAP in infants with ANH is not proven. Based on the lack of clinical effectiveness and unreported side

effects, we are not able to recommend routine use of CAP in neonates with ANH. However, infants with ANH constitute a highly heterogeneous group of patients. Individual risk stratification is warranted taking patient factors (ureteral dilatation, circumcision status, high-grade HN) into account during decision-making. If CAP is favored by the clinician, no recommendations can be made on the type and optimal dose of antibiotic regimen.

Further research

Undoubtedly, RCTs are required to elucidate whether infants with ANH might benefit from CAP. There were only two RCTs included in this systematic review, and both of them had significant drawbacks [7,11]. One of them is a pilot study and no recommendation was provided by the authors, but multicenter collaborative trials were encouraged [7]. The other is a congress abstract lacking significant information in terms of methods and findings [11].

Another important area for future research is the subgroup of ANH, which carries different risks for developing UTI. Separate subgroup analyses should be conducted with the subgroups (HUN, VUR, high-grade HN, POM, etc.).

Finally, there is a need for optimization of the antibiotic regime and meticulous work to demonstrate the side effects in the future studies.

Limitations and strengths

The main limitation was the heterogeneity of the patient populations in the available literature which made meta-analysis inappropriate for this particular review. Overall, the data obtained from the eligible studies represent moderate quality of evidence. Another limitation was the varied definitions of different clinical entities. The severity of HN was reported in different ways including SFU grade, AP diameter, and other descriptions such as mild, moderate, and severe and needs to be standardized. In patients with HN without ureteral dilatation, the definitions including UPJO, isolated HN, and UPJO-like HN are used by the investigators and need standardization as well. The standardization in the definition of UTI and fUTI is another point that needs to be considered. Unfortunately, only a small number of the studies discriminated UTIs as febrile or non-febrile.

In the end, although we could not demonstrate the benefits and harms of CAP in ANH, we were able to identify some potential risk factors for developing UTI which may affect the treatment strategy of the clinicians. This systematic review was performed by a group of experts including clinicians and methodologists (EAU Pediatric Urology Guideline Panel) according to PRISMA guidelines, and the results will be incorporated into the 2017 practice guidelines.

Conclusions

The benefits of CAP in a heterogeneous group of children with ANH involving different etiologies remains unproven. However, the evidence in the form of prospective and retrospective observational studies has shown that it reduces fUTI in particular subgroups. Uncircumcised infants, HUN, and high-grade HN may be more likely to develop UTI. CAP may be reserved for this subgroup of patients who are proven to be at high risk. No conclusion could be drawn for patients with VUR and ANH.

Conflict of interest

None.

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None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpurol.2017.02.023.

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