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ORIGINAL ARTICLE

Antibiotic prophylaxis for prevention of urinary tract infections in the first year of life in children with vesicoureteral reflux diagnosed in the workup of antenatal hydronephrosis: a systematic review

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Abstract

Background Children with antenatal hydronephrosis (ANH) diagnosed with postnatal asymptomatic vesicoureteral reflux (VUR) are thought to be at higher risk of urinary tract infection (UTI). As such, continuous antibiotic prophylaxis (CAP) is empirically recommended until age of toilet training; however, there are limited data to support this. The objective of this systematic review was to summarize the existing data and compare UTI rates in infants with asymptomatic VUR on CAP during the first year of life, to those not on CAP. Secondary objectives were to determine associated risk factors with UTI development.

Methods A systematic search of all relevant studies and abstracts was conducted using 4 electronic databases by utilizing appropriate key words by an expert hospital librarian. Eligible studies included children with prenatal hydronephrosis, asymptomatic VUR with or without CAP, and reported on development of UTI in the first year.

Results Of 6903 citations screened, 18 were selected, giving a total population of 829 (69.4% male, median age 57 days) who met the inclusion criteria. Most studies were retrospective and of low-quality evidence. Overall, 15.4% of patients developed at least one breakthrough UTI and females had a higher risk of UTI (odds ratio (OR) 2.3, 95% CI 1.1–4.7). Comparison with children not taking CAP was not readily reported, and meta-analysis could not be completed.

Conclusions Randomized controlled trials and standardized reporting of clinical variables are required to understand the protective effect of antibiotic prophylaxis in this cohort.

Keywords Vesicoureteral reflux (VUR) · Antenatal hydronephrosis (ANH) · Continuous antibiotic prophylaxis (CAP) · Urinary tract infection (UTI) · Vesicocystourethrogram (VCUG)

Introduction

Antenatal hydronephrosis (ANH) is a common finding on prenatal ultrasound (US), affecting up to 5% of all pregnancies with several potential etiologies [1, 2]. The majority of persistent postnatal hydronephrosis is transient and self-limiting with spontaneous resolution [3, 4]. However, in some infants, hydronephrosis may be due to an obstructive process, urinary tract abnormalities, or due to vesicoureteral reflux (VUR). Infants with ANH may be investigated with a voiding cystourethrogram (VCUG) as a part of their diagnostic workup when attempting to determine etiology depending on the severity, laterality, and presence of ureteral dilatation [5–7]. Approximately one-third of these infants will be found to have VUR (asymptomatic VUR) [8, 9]. Patients with prenatal hydronephrosis and asymptomatic VUR have been shown to be at a higher risk for the development of urinary tract infection (UTI) [10] resulting in the use of continuous antibiotic

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prophylaxis (CAP). However, due to concerns about bacterial resistance and potential long-term side effects associated with the use of antibiotics, decisions about CAP use should be based on high-quality evidence.

CAP is often empirically recommended for infants with asymptomatic VUR with the aim of reducing the rate of UTI in the first year of life [11] with the presumption that VUR is a risk factor for UTI [12]. While this practice has been shown to be beneficial for infants with symptomatic VUR (i.e., VUR found after presentation with UTI) [13], there have been no trials evaluating this intervention in the asymptomatic VUR population. As such, our systematic review was conducted in order to summarize the existing data and compare the overall UTI rate in infants with asymptomatic VUR diagnosed in the setting of prenatal hydronephrosis on CAP and those not on CAP during the first year of life. We hypothesized that use of CAP would decrease the rate of UTI in patients overall. Furthermore, we hypothesized that females would develop more UTIs than compared to males due to anatomy, and that those with higher grade VUR would also have more infections.

Methods

Protocol

This systematic review was written in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidance (http://www.prisma-statement.org).

Eligibility criteria

Studies which fulfilled the following eligibility criteria were included in this systematic review: (1) diagnosis of antenatal hydronephrosis; (2) diagnosis of asymptomatic VUR in the routine workup of ANH; (3) report on UTI rates during first year of life; and (4) included group of patients placed on antibiotics during first year of life. All grades of ANH and VUR were included as were studies involving all types of antibiotics. The studies included had to have patients diagnosed with UTI by a physician. We accepted UTI definition as reported by the authors of the included studies. We excluded studies solely reporting on infants with VUR diagnosed after UTI, or infants found to have other uropathies (i.e., posterior urethral valves or duplication anomalies), as well as case series with less than 5 patients, conference abstracts, and review articles. The references of prominent review articles were screened to ensure no studies were overlooked. All completed single- and multi-center retrospective and prospective studies that focused on the use of CAP for infants with asymptomatic VUR were identified. We also evaluated all studies previously included in a systematic review of this topic [8].

Information sources and search

A systematic search of 4 electronic databases (Medline, Embase, CINAHL, and CENTRAL) of all relevant studies from January 1985 and May 2017 was conducted using appropriate key words (Online Resource 1) by an expert health sciences librarian. Gray literature was searched by using key words. The reference list of review articles was cross-referenced to decrease risk of omission. We performed a content expert review of the final list of included studies. Search strategy can be seen in Online Resource 2.

Study selection

Title and abstract screening were carried out independently by 2 content experts (JL and MR). Studies appropriate for full-text review identified as per the eligibility criteria were flagged using Covidence Systematic Review Software (www.covidence.org). Conflicts were resolved by review with a third content expert (RC) and full-text papers were obtained for the selected studies. Full-text papers were reviewed again by 2 content experts (JL and MR), and final studies for inclusion were selected based on eligibility criteria (Fig. 1). Study selection was not blinded.

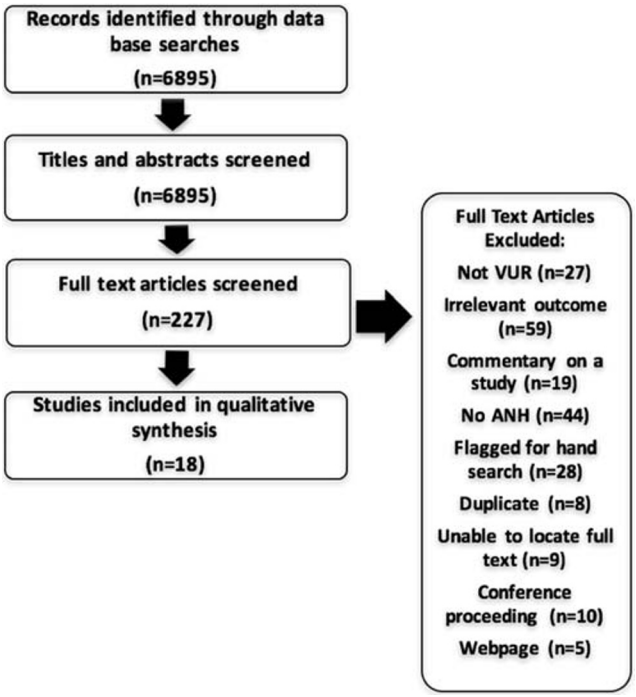

Fig. 1 Search strategy for studies included in the systematic review (Prisma Flow Diagram). Included studies can be found in supplementary data

Assessment of methodologic quality

Study quality was assessed using the Newcastle-Ottawa Scale [14]. Methodological quality was assessed using three categories: patient selection, comparability, and outcomes, as outlined in the Newcastle-Ottawa Scale (Table 1). Scores for each category were then added, and based on the total score, a study was determined to be either high or low methodological quality.

Extraction of data

Data was independently extracted and stored on a standardized data collection form. The following variables were extracted: sex, age at study inclusion, UTI rate (CAP vs. no CAP), type of antibiotic use, circumcision status (in males), and grade of VUR. All data was reviewed for accuracy and quality. Missing or unpublished data was noted. An attempt was made to contact authors in an effort to obtain unpublished data from the four studies which compared UTI rates in children on CAP vs. those who were not. In these cases, information was only obtained from one study. No studies were excluded due to being unable to contact the author.

Outcome measures

The primary outcome of the systematic review was to summarize the existing data, as well as compare the rate of UTI among infants with prenatal hydronephrosis and asymptomatic VUR taking CAP vs. those who were not, in the first year of life. It was accepted that the type of antibiotic may be different in each study. Secondary analyses included rates of UTI stratified by gender, VUR grade, and circumcision status in males.

Statistical analysis

Data synthesis was completed using Review Manager 5 (RevMan5) provided by the Cochrane Collaboration (www.cochrane.org). Continuous data were presented as median and interquartile range, and dichotomous data were presented as frequency and percentage. Odds ratios (OR) with a 95% confidence interval were reported and p value < 0.05 were considered as statistically significant. A sensitivity analysis for publication bias was completed.

Results

Search strategy

The initial search strategy resulted in 6895 articles. After title and abstract screening, 227 articles were selected for full review. After full-text review and application of eligibility criteria, a total of 209 studies were excluded, resulting in 18 included studies in our systematic review (Fig. 1). Of these, 11 were retrospective and 7 were

Table 1 Summary of quality assessment scores using Newcastle Ottawa Scale. Included studies can be found in supplementary data [12, 15–31]

First author	Selection (max 4 stars)	Comparability (max 2 stars)	Outcome (max 3 stars)	Methodological quality (high > 7 stars)
Yeunug et al.	***	–	*	Low
Stock et al.	*	–	*	Low
Polito et al.	***	–	**	Low
Lama et al.	***	–	**	Low
McIlroy et al.	***	–	**	Low
Upadhyay et al.	***	–	*	Low
Chen et al.	***	*	***	High
Farhat et al.	***	–	**	Low
Ylinen et al.	***	–	***	Low
Penido Silva et al.	***	–	**	Low
Lidefelt et al.	***	–	***	Low
Szymanski et al.	***	–	**	Low
Mohammadjafari et al.	***	–	***	Low
Zareba et al.	***	*	***	High
Herz et al.	***	*	***	High
Braga et al.	***	**	**	High
Zee et al.	***	–	***	Low
Visuri et al.	***	–	*	Low

prospective cohort studies. Study quality was assessed using the Newcastle-Ottawa Quality Assessment Scale [14]. Four studies (22.2%) were of high methodological quality and fourteen (77.8%) were of low quality (Table 1). Characteristics of the studies included in our systematic review are outlined in Table 2 (Online Resource 2). The majority of the studies were conducted in North America.

Patient characteristics

A total number of 3969 infants were included as part of these studies [10, 12, 15–30]. Of these patients, 829 (20.9%) had a diagnosis of asymptomatic VUR and received CAP, thus satisfying our inclusion criteria. It is these 829 patients who have been included in our current systematic review. There is an additional population of 30 children who had asymptomatic VUR and did not receive CAP, who have been included only in the section comparing patients on CAP vs. those not on CAP, as seen in Table 3. While some studies ($n = 4$) did not report on the gender breakdown of their populations, of those that did, 473 (69.4%) were males, and median age at study inclusion was 57 days (min 1, max 180 days), which was defined as the date of diagnosis by VCUG. We included all grades of VUR in the present review, and of those studies ($n = 12$) reporting VUR severity, 48.7% were high grade (VUR grades IV–V) (Table 2).

Table 2 Characteristics of studies included in the systematic review

First author	Year	Country	Type	Patients (*n*) on CAP	Patients (*n*) not on CAP	Male (*n*)	Age (days)	Number of patients with UTI (%)	VUR grades I–III (%)	VUR grade IV–V (%)
Yeunug et al.	1997	UK	Prospective cohort	155	0	117	66	6 (3.9)	101 (65)	54 (35)
Stock et al.	1998	USA	Retrospective cohort	12	0	9	1	7 (58)	0 (0)	12 (100)
Polito et al.	1999	Italy	Retrospective cohort	32	0	21	30	17 (53)	NR	NR
Lama et al.	2000	Italy	Retrospective cohort	34	0	25	12	7 (21)	NR	NR
McIlroy et al.	2000	New Zealand	Retrospective cohort	69	0	32	42	2 (2.9)	45 (65)	24 (35)
Farhat et al.	2000	Canada	Prospective cohort	31	0	24	NR	8 (26)	16 (52)	15 (48)
Chen et al.	2003	USA	Retrospective cohort	56	0	35	180	15 (27)	36 (64)	20 (36)
Upadhyay et al.	2003	Canada	Prospective cohort	31	0	24	NR	2 (7.7)	16 (52)	15 (48)
Ylinen et al.	2003	Finland	Prospective cohort	21	0	13	35	8 (38)	NR	NR
Penido Silva et al.	2005	Brazil	Retrospective cohort	47	0	41	60	12 (25)	NR	NR
Lidefelt et al.	2008	Sweden	Prospective cohort	6	0	NR	49	4 (67)	2 (33)	4 (67)
*Szymanski et al.	2012	Canada	Retrospective cohort	15	2	10	14	1 (6.7)	8 (53)	7 (47)
Mohammadjafari et al.	2013	Iran	Prospective cohort	67	0	45	42	4 (6.0)	41 (61)	26 (39)
*Zareba et al.	2014	Canada	Retrospective cohort	76	3	49	NR	14 (18)	58 (76)	18 (24)
*Herz et al.	2014	USA	Retrospective cohort	62	22	NR	21	NR	NR	NR
Braga et al.	2015	Canada	Prospective cohort	57	0	NR	115	4 (8.0)	NR	NR
*Zee et al.	2016	USA	Retrospective cohort	22	3	NR	NR	2 (9.0)	NR	NR
*Visuri et al.	2017	Finland	Retrospective cohort	36	Not specified	28	132	15 (42)	12 (33)	24 (67)

This table outlines the characteristics of the various studies included in the review, as well as the absolute number and percentage of patients with VUR and ANH who developed breakthrough UTI while on CAP. Included studies can be found in supplementary data. Studies with (*) beside the first author name denote those that included patients both on CAP and not on CAP [12, 15–31]

NR not reported

Table 3 Studies that examined UTI rates in patients on CAP vs. those not on CAP

First author	Patients on CAP (*n*)	Patients not on CAP (*n*)	Number of UTI on CAP (%)	Number of UTI not on CAP (%)
Zareba et al	76	3	14 (18)	2 (67)
Szymanski et al	15	2	1 (6.7)	0 (0)

Absolute number and percent of UTI development in patients with asymptomatic VUR on CAP was only compared to patients not on CAP in two studies [28, 30]

UTI rates

In the studies that reported number of patients with UTI, 128 out of 767 (15.4%) developed at least one breakthrough UTI despite initiation of CAP from birth (Table 2). The study by Herz et al. was excluded from this calculation as the authors reported an overall rate of UTIs and not among the children with VUR [16]. Five of the included studies reported on patients receiving CAP as well as patients who were not; however, only two provided us with data directly comparing UTI rates between these 2 cohorts [28, 30] (Table 3). The total population in these two studies was 96 patients. Of these, 94.8% were on CAP ($n = 91$). The combined percentage UTI on CAP was 12.6% as compared to 33.4% in patients not on CAP. An attempt was made to obtain the data from all studies which included both patients with or without CAP; however, no further information could be obtained. No studies were excluded if attempts at contacting authors were not successful. Detailed statistical analysis could not be conducted in these studies due to small sample sizes. Additionally, the effect of VUR grade or circumcision status on UTI rates could not be analyzed due to insufficient data.

UTI rates: based on gender

Of the included studies, 4 (24%) stratified the development of breakthrough UTI in patients with asymptomatic VUR by sex. Of the 157 patients included in these studies that met our inclusion criteria, 112 (71%) were male. In analysis of pooled data, 44% of females developed UTI while on CAP, vs. 26% of males (OR 2.3, 95% CI 1.1–4.7).

Discussion

Antibiotic prophylaxis is a widespread practice for several urinary tract conditions known to be associated with UTI development [31, 32]. Because UTI in infants has the potential to cause significant morbidity, many providers prescribe CAP with the intention of preventing UTI while waiting for these children to demonstrate spontaneous resolution or proceed to surgical intervention. Our systematic review was aimed at summarizing the existing data, as well as comparing the rate of UTI among infants with prenatal hydronephrosis and asymptomatic VUR taking CAP vs. those who were not, in the first year of life. The limited data available showed no conclusive benefit of CAP, primarily due to lack of a strong comparator cohort. Only two studies directly compared UTI rates on CAP vs. no CAP, one of which showed that the rate of UTI was lower in CAP patients and the other which had no significant difference between the two groups [28, 30]. We also showed that females with VUR were at 2 times higher risk of UTI compared to males despite being on CAP. Further pooled analysis was unable to be completed due to lack of pertinent variables in published studies. This review highlights the sparse evidence evaluating prophylactic antibiotic use in this particular patient population. The absence of evidence could be partly explained by the lack of high-quality studies in this cohort. Moreover, existing expertise-based guidelines recommend CAP use for primary or symptomatic VUR (i.e., those presenting with UTI) [2, 33–35]. Hence, in absence of any strong evidence of prophylactic use among those with VUR diagnosed in the setting of prenatal hydronephrosis, clinicians tend to err on the side of caution and extrapolate the findings on symptomatic VUR to these patients and prescribe CAP to them as well [13]. As such, it is challenging to establish the clinical equipoise required to conduct clinical trials on this population.

Analysis of the included studies demonstrated much variation in the reported UTI rates in children with VUR on CAP (2.90–66.7%). The most likely explanations for these differences are the lack of standardized reporting of important patient characteristics which may contribute to UTI. Several other studies have shown that variables such as circumcision status, presence, and degree of HN may contribute to UTI development in infants with urinary tract abnormalities including VUR [36–39]. Moreover, studies failing to report their diagnostic criteria for UTI may also result in over-reporting of outcomes if strict diagnostic criteria are not followed. For example, including urine specimens obtained by bag or considering non-febrile episodes to be infections may inflate the number of reported UTIs. Missing data are intrinsic limitations to retrospective and observational studies which contribute to the overall low quality of the included studies and provide rationale for standardized reporting and strict diagnostic criteria for UTI.

A systematic review conducted by Braga et al. evaluated CAP use in children with ANH and included patients with all

anatomic anomalies that could result in hydronephrosis [8]. They reported that the pooled UTI rate for ANH patients who received CAP was similar to those who did not (9.9% vs. 8.3%). Their overall UTI rate was 22.8% in children with VUR on CAP compared to 15.4% in our review. This was primarily due to the fact that the review by Braga et al. included both CAP and non-CAP ANH patients with UTI. They reported similar challenges with insufficient data extraction to determine the association between VUR and UTI stratified by HN grade due to inconsistent reporting.

The controversy of using CAP is not just limited to children with asymptomatic VUR but also among children with primary or symptomatic VUR. There have been 8 randomized controlled trials in this cohort between 2006 and 2014 evaluating the use of CAP, and have shown conflicting results. A recent systematic review and meta-analysis by Wang et al. [40] showed that CAP significantly reduced UTIs when compared to observation. The review included 1594 children enrolled in 8 randomized controlled trials and showed that CAP significantly reduced the risk of recurrent febrile or symptomatic UTI (pooled OR 0.63, 95% CI 0.42–0.96). Of note, the use of CAP also increased the risk of infection due to antibiotic-resistant bacteria. The main limitation of that review was the presence of significant heterogeneity and the presence of bias in included studies. It should be noted, however, that the results of that systematic review are not applicable to children who were diagnosed with VUR in the setting of prenatal hydronephrosis. Interestingly, there is another recent Cochrane Review by Williams et al., which looked at treatment options for children with VUR. The authors included all randomized studies ($n = 34$) comparing different treatment options in children with vesicoureteric reflux ($n = 4001$) and concluded that low-dose, long-term prophylaxis compared to no treatment makes little or no difference (RR 0.77, 95% CI 0.54–1.09) in the risk of repeat UTI [41]. Hence, in the absence of any strong evidence to support or refute the prophylactic use of antibiotics among those with VUR, it is difficult to come to a consensus on best practice with regard to antibiotic prophylaxis.

Previous studies have shown that female sex has widely been demonstrated to be a significant risk factor for development of UTI [12, 42], including among those with VUR [43]. Our findings are consistent with the published literature and further confirm the importance of considering sex when determining UTI risk in this patient population.

The present review has a number of important limitations. The most apparent would be the lack of a comparator cohort (i.e., VUR infants not on CAP) and thus inability to draw conclusions on the benefits/risks of CAP in this population. Further investigation with well-powered trials would be beneficial for this reason. As the goal of this systematic review was to summarize the current data regarding the use of CAP in patients with asymptomatic VUR and UTI rates, we have highlighted the need for stronger evidence related to this practice. To our knowledge, much of the current available evidence focuses on the use of CAP in infants with prenatally detected urinary tract abnormalities, but none focus solely on children with VUR.

Conclusions and future directions

To our knowledge, this is the only systematic review evaluating the effect of prophylactic antibiotics in preventing UTI in the first year of life in children with asymptomatic VUR. We focused on this population because there is a lot of published evidence on the use of CAP for infants with symptomatic reflux. However, it was not clear whether infants with asymptomatic VUR follow a similar or different disease process. Overall, the current available literature is of low quality and lacks standardized reporting of important clinical and patient variables. This resulted in our inability to carry out a meta-analysis and draw any reasonable cause and effect conclusions. Randomized controlled trials and standardized reporting of clinical and patient variables and outcomes are required for the development of future treatment guidelines.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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