Impact of antibiotic prophylaxis on urinary tract infection recurrence in children: Rapid review

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ABSTRACT

Introduction: Given the potential consequences associated with urinary tract infections (UTI), it has become standard practice to use continuous antibiotic prophylaxis (CAP) in children, even if controversial. We reviewed the effectiveness of CAP on recurrent UTI in a pediatric population to determine if equipoise remains and allow for a placebo control group to study the effectiveness of the vaccine MV140.

Method: We completed a rapid review. We searched Medline, Embase and the Cochrane Library and data extraction was completed by a single reviewer.

Our search criteria were 2005–2022, English and French language, randomized controlled trials (RCTs) and systematic reviews only. The population was 19 years and younger, including: vesicoureteral reflux (VUR), congenital anomalies of the kidneys and urinary tracts (CAKUT), and bladder and bowel dysfunction (BBD).

Results: Three RCTs and three systematic reviews found a benefit for CAP, mostly for a population with VUR, and those with severe VUR have more benefit. Most studies were not able

KEY MESSAGES

- The use of continuous antibiotic prophylaxis to prevent UTI in children is still debatable.
- No clear benefits can be found when considering major recent meta-analysis.
- The impact of preventing UTI to prevent new renal scars is still not well understood.
- It should stay a case-by-case analysis because some patients will have more benefits with the prophylaxis.
- It is ethical to consider doing a randomized controlled trial comparing an oral vaccine with a placebo-only population if we exclude the higher risk population.

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to show a difference in the rate of UTIs or new renal scars (NRS). Three RCTs found a deleterious effect with CAP. Other studies were able to prove a benefit for patients with dilatation of the urinary tract without obstruction and high-grade VUR combined with BBD. The major adverse event found was antimicrobial resistance.
Conclusions: High-risk patients benefit from CAP. The potential consequences of UTIs makes it unethical to use a placebo-only control group for them; however, CAP use seems difficult to justify in a low-risk population.

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INTRODUCTION

Given the potential consequences associated with febrile UTIs and the risk of kidney damage,[1] it has become standard practice to use CAP in children, even if it is still controversial. Moreover, repeated UTIs, frequent antibiotic consumption, and hospitalizations put a toll on children and their families. Two Cochrane Reviews, updated in 2019, have questioned the benefits of CAP, one addressing children with VUR and the other with no major anatomic anomalies. Despite those major studies, the conclusion remains uncertain because CAP does not seem to deliver its attributed benefit,[2,3] with different results depending on the characteristics of the studied population.

Sublingual MV140, a vaccine consisting of a preparation of whole-cell inactivated bacteria, showed promising results in a recent placebo-controlled RCT for the prevention of recurrent UTI (rUTI) in adult women with no genitourinary tract anomalies.[4] This treatment may potentially become a new tool in infection prevention in children and while developing a RCT research protocol for it, it became imperative to determine whether it would be ethical to use a placebo-only control group against MV140. What is the real efficacy of CAP on children's UTI? In this rapid review, we compiled the significant studies studying the efficacy and effectiveness of CAP in a pediatric population with risk factors for UTI.

METHOD

Search strategy

We searched Medline, Embase and the Cochrane Library from 2005 to 2022, restricted to English and French. The expertise of a medical librarian was used to create a comprehensive search strategy; all search terms are available in the appendix. We followed the structure of a rapid review as recommended by the WHO guidelines.[5] This review was not registered; thus, no research protocol is available.

Covidence was used to import, review, and classify all studies. We included only RCTs, quasi-RCTs and systematic reviews with or without meta-analysis. We excluded all editorial texts or letters of opinion, unpublished studies, scoping reviews and reviews with unclear search methodology. We included guidelines only if they had a systematic review structure. The search

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was limited to children younger than 19 years of age, with risk factor for UTIs including VUR, CAKUT and BBD. We identified studies that compared CAP to a placebo or no treatment. We excluded the one comparing CAP to a surgical treatment, different types of antibiotics, and when used with urological manipulation or on a transplant or immunosuppressed population.

A single independent reviewer screened all the titles and abstracts obtained from the search, then subsequently retrieved and reviewed the corresponding full-text PDFs. Outcomes focused on rUTI including pyelonephritis (PN) and NRS. Data extraction included: adverse events, AMR, baseline characteristics of the population (VUR grade, hydronephrosis (HN) or other urinary tract anomalies) and details about treatment (type of antibiotic, placebo or observation).

No meta-analysis was performed, considering the high heterogeneity of data.

Risk of bias

We used RoB 2: a revised Cochrane risk-of-bias tool to evaluate RCTs. It uses 5 domains of bias.[6]

We used the ROBIS guide to evaluate risk of bias in systematic reviews.[7]

We decided to evaluate only systematic review where a meta-analysis was performed; qualitative reviews could not be evaluated by this tool.

RESULTS

We identified a total of 638 studies: 124 were duplicates, 346 were judged irrelevant after reviewing titles and abstracts. A total of 116 other studies were rejected after full text assessment, mostly because of their study designs. Therefore, a total of 53 studies were retained and analyzed for this review. The PRISMA flow diagram is presented in Fig. 1.

In table 1, using the Rob 2 assessment tool, only 3 studies were at low risk of bias. Methodological issues, sometimes fundamental, were present in most of them and it made the interpretation of the results more difficult.

In table 2, the ROBIS showed that most systematic reviews were of good quality in terms of methodology and risk of bias.

Summary tables were made for RCTs and meta-analyses (table 3 and 4). The qualitative reviews are summarized in the text.

KNOWLEDGE SYNTHESIS: RANDOMIZED CONTROLLED TRIAL

Vesicoureteral reflux

A total of 9 RCTs investigated the efficacy of CAP in children with VUR.

No Benefit from CAP

Roussey-Kessler et al. followed patients under the age of three with grade 1 to 3 VUR. They reported 17% of rUTI in the CAP group and 26% in the surveillance group, which was not statistically significant (p=0.15), but when stratified, males with grade 3 VUR had a significant benefit from CAP (p=0.04). A caveat in the methodology was the inclusion of asymptomatic

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bacteriuria (AB) and the use of collector bags for urine culture.[8] Montini et al. did not find a significant difference of episode of febrile UTI between the two groups: 9.45% surveillance group vs 7.11% CAP group (risk difference: 2.34%, 95% confidence interval (CI): 3.8%–8.4%). The number needed to treat (NNT) to prevent one UTI was 41.7 children for 1 year of treatment.[9]

Deleterious effect from CAP
Garin et al., followed 218 children and did not find a difference in the UTI rate between patient on CAP regardless of presence of VUR (p=0.063). Most importantly, there were more febrile UTIs in the group on CAP (7 CAP, 1 surveillance, p=0.029). This study included grade 1 to 3 VUR and many patients were lost during follow-up.[10]

Hari et al. enrolled 93 children up to 12 years of age with grade 1 to 4 VUR. Surprisingly, the CAP group had a 14.8% absolute increase in the risk of UTI compared to the placebo group (95% CI 1– 28, p=0.03). This study excluded children under one year of age and every patient that had a treatment failure (two UTIs in six months).[11] Pennesi, who studied grade 2 to 4 VUR, found that the risk of developing at least one PN recurrence was slightly higher but not statistically significant in the intervention compared to the control group (RR 1.2, 95% CI 0.68–2.11).[12]

Benefit from CAP
The Swedish reflux trial only enrolled children from one to two years of age with grade 3 and 4 VUR. Girls had more benefit from CAP (19% CAP group, 54% surveillance, p=0.0002),[13] with more UTIs in those with higher grade VUR (p=0.0095). They were unable to show an advantage of CAP in boys.[14] These authors were among the few to find that NRS occurred more often in the surveillance than in the CAP group (p=0.0054) with a higher proportion of girls compared to boys (p=0.0258) and a strong association when linked to febrile rUTI.[15]
PRIVENT included 576 patients under 18 years of age with and without VUR and showed a slight improvement in the proportion of UTI and PN: respectively 13% CAP group and 19% placebo group (Hazard ratio (HR) 0.61, 95% CI 0.40-0.93), 7% and 13% (HR 0.49, 95% CI 0.28-0.86, p=0.01).[16]

RIVUR, the largest trial completed with 607 patients VUR grade 1 to 4 aged 2 to 71 months compared to a placebo-controlled group. A reduction of UTIs by half was noted in the group taking CAP (HR 0.50, 95% CI 0.34-0.74). The NNT to prevent one UTI over two years was 8.[17] They also noted an increased risk of rUTI in patients with grade 3-4 VUR vs. grade 1-2 (22.9% vs. 14.3%, p=0.003). Adverse events, hospitalizations or emergency room visits did not differ between groups.[17]

Both PRIVENT and RIVUR did not find any difference in the development of NRS, consistent with other RCTs evaluating this outcome.[16,17] The RIVUR study data were secondarily reanalyzed post-hoc by different investigators like Wang et al. that looked for the

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relationship between development of NRS and episodes of PN: UTI-associated NRS was more common in the placebo than in the CAP arm (5.3% and 2%; OR=2.7, 95% CI 0.9–7.6, p=0.06).[18] Using the same database, Mattoo et al., however, found no difference in NRS in children receiving prophylaxis compared with placebo (6% vs 7%, respectively). This result persisted even when evaluating individually the renal units (4% for both).[19]

An attempt was made to stratify the RIVUR data into a risk classification system. The groups were separated into mild risk of rUTI versus high risk. Uncircumcised boys, girls with BBD and grade 4 VUR were classified as high risk, and a benefit of CAP was noted only in these (p=0.001). The high-risk group had a 73% reduced risk after two years of follow-up (HR = 0.27, 95% CI 0.13-0.57, p=0.001).[20]

Other genitourinary anomalies

A RCT looked at the impact of BBD on rUTI using the populations from RIVUR and CUTIE studies [21] (181 children). The combination of BBD with VUR was the study group with the highest rate of rUTI.[22] CAP was shown to decrease rUTI in children with BBD (HR=0.22, 95% CI 0.08–0.61, p=0.04) but not in children without BBD (HR=1.46; 95% CI, 0.45–263 4.79).[22] In our review, only perinatal mild to moderate HN was also studied with a randomized design. After 12 months, the study was stopped prematurely for futility. The neonatal patients receiving CAP were having a 38% higher risk of developing a UTI (HR: 1.38, 95% CI 0.37–5.16, p=0.63) while their chance of having a resistant infection was 4 times greater (RR 4.0, 95% CI 1.2–13.5, p=0.02).[23]

KNOWLEDGE SYNTHESIS: SYSTEMATIC LITERATURE REVIEW

Vesicoureteral reflux

No benefit from CAP

Hewitt et al. reviewed 7 RCTs, 1427 patients, and found no statistically significant impact between CAP and no CAP on the development of NRS (Relative risk (RR) 0.83, 95% CI 0.55–1.26).[24] Alsubaie et al. also stated that they were unable to conclude that CAP can prevent NRS.[25] NRS was often considered one of the most critical outcome, but the results analyzed must be interpreted with caution, studies lacking data and rigor regarding this issue.[26-28] Furthermore, of 11 studies analyzed, a 2010 review found that rUTI was not significantly reduced by CAP (RR 0.83, 95% CI 0.66-1.05, p=0.13).[29] William and Craig believed that the data were too sparse. They calculated a RR of UTI of 1.02 (95% CI, 0.58–1.78) for CAP relative to surveillance.[30] A NNT of 16 patients was calculated to prevent one UTI after one year of CAP, considering it insufficient when balancing the emergence of AMR.[31]

Costers' review found that it appeared safe to discontinue CAP in a multitude of patients: school-aged children, lower grade VUR, normal voiding patterns, normal kidneys, and normal urogenital anatomy,[32] this conclusion being in line with Ansari asserting that the decision should be individualized and made after a discussion with the patient's family.[33] However, Mori et al.

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did not find any difference when comparing groups with and without VUR (RR 0.96, 95% CI 0.69–1.32).[34]

Benefit from CAP

The 2019 Cochrane VUR review mentioned that CAP seems to make little or no difference to the risk of rUTI (RR 0.77, 95% CI 0.54-1.09, low certainty evidence) or febrile UTIs (RR 0.83, 95% CI 0.56-1.21; low certainty evidence) for an average follow- up of one to two years.[2] De Bessa et al. included 1593 VUR patients in their meta-analysis: 20.9% of high-grade VUR had rUTI on CAP compared to 29.0% in those without CAP (RR 0.72, 95% CI 0.56-0.92), for a NNT of 12.2 (p=0.008). In low grade VUR, rUTIs occurred in 6.4% vs. 12.9%, respectively (RR=0.51, 95% CI 0.32-0.79), for a NNT of 15.4 (p=0.002).[35] Another review from 2015 also found a significant benefit of CAP in reducing the risk of symptomatic UTIs in children with VUR (Odds ratio (OR) 0.63, 95% CI 0.42-0.96, p=0.03). [36]

Larcombe et al. found a slight benefit in the CAP group, but this result varied depending on the type of statistical analysis used and they concluded that they were against the routine use of CAP.[37] Similarly, Mathew et al. found that rUTI were reduced in the CAP group, when pooling children with and without VUR (RR 0.73, CI 0.56-0.95). However, this difference was no longer noticeable when stratified with VUR status (RR=0.82, CI 0.62-1.08 vs. RR=0.72, CI 320 0.43-1.20).[38] RIVUR was helpful in determining a benefit of giving CAP to girls with dilating VUR.[39] Tullus, in 2020, agreed and emphasized the important role of CAP for patients with severe VUR.[40]

Greenfield recognized that sex and circumcision are likely confounding factors affecting the occurrence of UTI. Physicians should consider these elements before deciding to prescribe CAP.[41]

General guidelines

The American Urological Association (AUA) recommend CAP for children under one year of age with either VUR and a history of febrile UTI or a grade 3-5 VUR. It may be necessary to use CAP on children older than one year of age if they have rUTI, febrile or not.[42] The American Academy of Pediatrics (AAP) did not find a statistically significant difference in the recurrence of PN with CAP (RR=0.77, 95% CI 0.47–1.24) even with VUR (RR=0.78, 95% CI 0.48 –1.26). In 2011, they stopped recommending a voiding cystourethrogram (VCUG) after the first episode of PN, mentioning that it is impossible to propose clear recommendations on management afterward.[43] In 2009, the National Institute for Health and Care Excellence (NICE), like the Italian guideline, had reservations about the use of CAP and decided that it should not be routinely recommended following first-time UTI,[44,45] but should be considered for patients awaiting diagnosis, with grade 4-5 VUR, or with more than three febrile UTIs.[45] The Swiss Consensus and the European Association of Urology (EAU) recommend giving CAP only to children with high risk of UTI and renal damage: CAKUT, high grade VUR or BBD.[46,47]

Other genitourinary anomalies

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When we look at the impact of CAP on a non-VUR pediatric population, meaningful data are even more difficult to obtain and interpret. Data from a Cochrane Review showed a modest decrease or no decrease at all in the risk of rUTI (RR=0.75, 95% CI 0.28-1.98), representing a reduction of 6% over a 1-year follow-up.[3] In 2020, Leigh et al. included infant less than one year old with HN and asymptomatic VUR in their review and reported 15.4% of patients with at least one UTI in their first year of life despite CAP.[48] Easterbrook et al. also reviewed perinatal HN for a total of 3909 patients included. They were not able to demonstrate an advantage of CAP, with an overall OR=0.84 (95% CI 0.451.55). They noted that UTI predisposing factors appeared to be VUR, female gender and a protective effect of circumcision.[49] Using the same study population, Braga et al. found that the number of UTIs was similar in those with and without CAP (9.9%, 95% CI 4.6–17.1 vs 8.3%, 95% CI 2.9–16.0,16 p=0.21). However, they found an advantage in those with severe HN (p=0.01).[50]

Rohner et al. looked specifically at patients with mega-ureter. Of the 16 heterogenous reviewed studies, the prevalence of UTI in patients on CAP was 10.3% compared to 33% for those without CAP. The NNT was 4.3. Boys less than one year of age, with a mega- ureter larger than 11 mm, with obstruction at the uretero-vesical junction or uncircumcised, would benefit most from CAP.[51] Castagnetti et al. looked at the impact of CAP in CAKUT pediatric patient but were unable to support any recommendations.[52] In a previous study, Castagnetti had suggested that it was safe to give only CAP to patients with ureterocele and duplex system, unless there was an obstruction, severe dilatation, or severe VUR.[53] A 2021 review found no evidence that CAP was beneficial in patients with a single functional kidney. These results must be treated with caution because their data were scarce, single kidneys being often excluded from studies.[54]

General guidelines

The Indian Society of Nephrology suggested to give CAP to postnatally confirmed moderate or severe HN or dilated ureter while awaiting evaluation. Once VUR is confirmed, keep the child on CAP until one year of age.[55] The 2017 EAU found it impossible to establish if CAP was beneficial for moderate to severe HN,[56] consistent with the recommendations of the Canadian Urological Association (CUA) and stating that individualization of care is the best approach.[57]

Bacterial resistance

Most articles presented in this review demonstrated increased AMR with CAP.[8,10,13,23,58] Groups on CAP had an almost threefold higher likelihood of bacterial resistance (RR 2.97, 95% CI 1.54-5.74)[2] and (RR 2.40, 95% CI 0.62-9.26).[3] AMR is a major public health problem and the *World Health Organization* considers it as one of the 10 worst threats to global health.[59] Knowing the efforts made to decrease antimicrobial use, this adverse event can not be overlooked. Selekman et al. confirmed an increased risk of AMR in the first rUTI when on CAP (p<0.001) and the greater need for broad-spectrum antibiotic (p=0.004).[60]

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DISCUSSION

In 2017, the CUA concluded that the benefit of CAP for children with VUR and prenatal HN was too uncertain.[49,57] The Cochrane Reviews also had difficulty giving clear recommendations.[2,3] Moreover, insufficient data exist for patients with UTI risk factors other than VUR. Despite these uncertainties, CAP is still widely used.

This equipoise stems from the discrepancy in the characteristics of the population studied, and the associated biases. Results are too divergent and heterogenous, with even one study showing an increase of rUTI in children on CAP.[11] For instance, the methods used to identify rUTI was sometimes inadequate, such as sampling systematic cultures with collecting bags,[8] or the size of the population was too small to obtain a statistically conclusive result.[12] Some included only low grade VUR[9,10], forgetting to consider potentially relevant patients.

Because of its size and excellent methodology, RIVUR is one of the most important studies about CAP. Yet, the population was 92% females from 2 to 71 months old, making it difficult to generalize the results.[17] Brandström also demonstrated the efficacy of CAP, but only in girls with high grade VUR, and not in all other patients.[14] BBD has also an impact on UTI, but it is rarely considered in studies. Only Shaikh was able to demonstrate an association between BBD, VUR, and rUTI risk.[22]

Most studies evaluated the occurrence of UTI or NRS, but few looked at other impact like the physical, psychological, or financial burden of rUTI for families and the social impact of increased healthcare and hospitalization needs.

The main limitation of our study comes from the inherent structure behind a rapid review like having a single reviewer. To reduce risk of errors, data were compiled conscientiously and rigorously and verified by an experienced research team.

CONCLUSIONS

Given the disparities in current knowledge and despite a large body of literature, it is still difficult to know exactly which patients will benefit most from CAP and it seems clear that an individualized approach remains the best option.

The usefulness of CAP is difficult to prove in a low-risk population, but the effectiveness is greater in high-risk group like moderate to high grade perinatal HN, high grade VUR or CAKUT with severely dilated structures, BBD combined with VUR and <1 year old uncircumcised boys with another risk factor.

This literature review provides the information for a RCT protocol to test MV140 on children, demonstrating the possibility of using a placebo-controlled group if our population is well selected. These results remind us that antibiotics are not a panacea, and the importance of deepening our knowledge about rUTI and treatment options.

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FIGURES AND TABLES

Figure 1. Identification of studies via Embase, Medline, Cochrane Library.

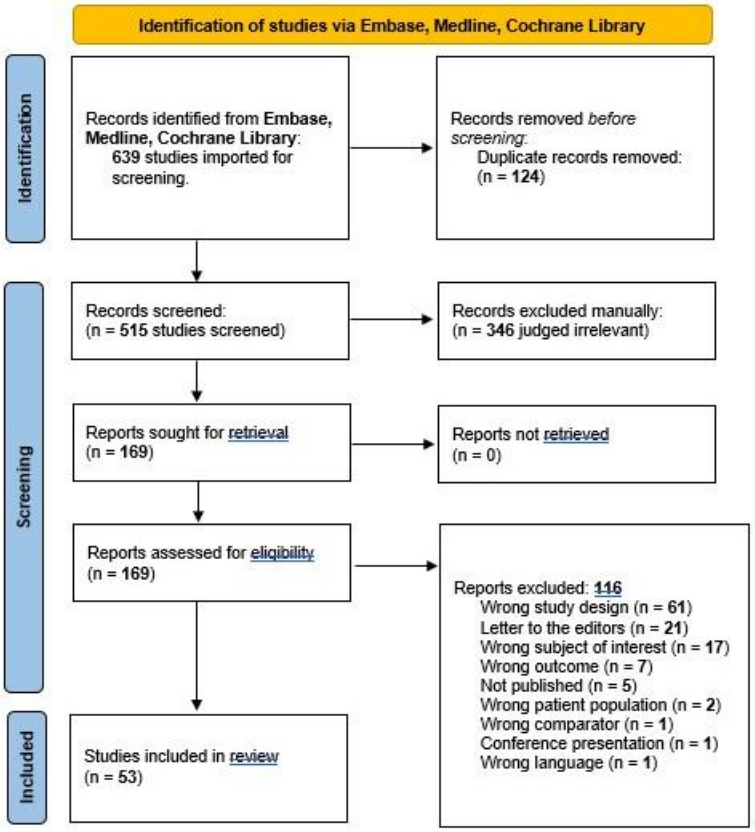

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Table 1. Rob-2: Randomized controlled trial bias assessment						
Study ID	**D1**	**D2**	**D3**	**D4**	**D5**	**Overall**
PRIVENT, 2009	+	+	+	+	+	+
Montini, 2008	+	!	+	!	+	!
Hari, 2015	+	+	+	+	+	+
RIVUR, 2014	+	+	+	+	+	+
Brandström, 2011	+	+	+	!	+	!
Pennesi, 2008	+	!	+	!	!	!
Roussey-Kesler, 2008	+	!	+	-	+	-
Rianthavor, 2020	+	!	+	+	+	!
Wang, 2019	+	+	+	+	!	!
Wang, 2018	+	+	+	+	!	!
Mattoo, 2016	+	+	+	+	!	!
Garin, 2006	!	-	-	+	+	-
Shaikh,2016	+	!	+	!	!	!

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Table 2. ROBIS results: Systematic review bias assessment					
Review	**Phase 2**				**Phase 3**
	1. Study eligibility criteria	**2. Identification and selection of studies**	**3. Data collection and study appraisal**	**4. Synthesis and findings**	**Risk of bias in the review**
Hewitt, 2017	+	+	+	+	+
Cochrane UTI, 2019	+	+	+	+	+
Cochrane VUR, 2019	+	+	+	+	+
Selekman, 2018	+	+	+	+	+
Finnell, 2011	+	!	+	!	!
Dai, 2010	+	+	+	+	+
Mathew, 2010	+	-	-	!	-
Mori, 2009	+	-	+	!	-
De Bessa, 2015	+	-	!	!	-
Wang, 2015	+	+	+	+	+
Easterbrook, 2017	+	+	+	+	+
Silay, 2017	+	+	+	+	+
Braga, 2013	+	+	+	+	+
Rohner, 2022	+	+	+	+	+
Leigh, 2020	+	+	!	-	!

+ = low risk; - = high risk; ! = unclear risk

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Table 3. Summary randomized controlled trial							
Study ID	**Country**	**Population (n)**	**Demographic characteristic**	**Experimental**	**Comparator**	**Outcome**	**Result**
PRIVENT, 2009	Australia	576	<18 years old, UTI recurrence with or without VUR	Trimethoprim–sulfamethoxazol	Placebo	Microbiologically confirmed symptomatic UTI	13% in CAP and 19% in placebo (HR CAP, 0.61; 95% CI, 0.40 to 0.93; P=0.02)
Montini, 2008	Italy	338	From 2 months to 7 years old, PNA recurrence with or without VUR	Trimethoprim-sulfamethoxazole or amoxicillin-clavulanate	Surveillance	Febrile UTI	9.45% in surveillance, 7.11% in CAP (risk difference: 2.34% [95% CI: 3.8%–8.4%]) NNT 41,7
Hari, 2015	India	93	< 12 years old, with VUR grade 1-4	Trimethoprim-sulfamethoxazole	Placebo	Recurrent symptomatic UTI	CAP had 14.8 % absolute increased risk of UTI (95 % CI 1–28; P=0.03)
RIVUR	United States	607	From 2 to 71 months old, with VUR grade 1-4	Trimethoprim–sulfamethoxazole	Placebo	Febrile or symptomatic recurrent UTI	UTI was reduced by half with CAP compared to placebo, and the difference between them widened over time (HR 0.50, 95% CI 0.34 to 0.74)
Brandström, 2011	Sweden	203	From 1 to 2 years old, with VUR grade 3-4	Trimethoprim	Surveillance	Recurrent UTI	In girls: 19% with CAP and 57% in surveillance (p = 0.0001). In boys: few recurrences with no differences between group (p = 0.28)
Pennesi, 2008	Italy	100	From 1 to 30 months old, with VUR grade 2-4	sulfamethoxazole-trimethoprim	Surveillance	Recurrence of PNA	Higher in CAP, but not statistically significant (RR: 1.2 [95% CI: 0.68–2.11])
Roussey-Kesler, 2008	France	225	From 1 month to 3 years old,	Trimethoprim-sulfamethoxazole	Surveillance	Recurrent UTI	17% in CAP, 26% in surveillance, p = 0.15

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			with VUR grade 1-4				
Rianthavor, 2020	Thailand	80	From 7 to 30 days old with diagnosed low or moderate antenatal HN	Trimethoprim-sulfamethoxazole	Surveillance	UTI	38% higher in CAP, (HR 1.38, 95% CI 0.37–5.16; p=0.63)
Wang, 2019	United States	489	2 to 71 months old, with VUR grade 1-4	Trimethoprim-sulfamethoxazole	Placebo	Recurrent UTI-associated new renal scar	5.3% in placebo and 2% in CAP (OR=2.7, 95%CI: 0.9–7.6, p=0.06)
Wang, 2018	United States	385	2 to 71 months old, with VUR grade 1-4	Trimethoprim-sulfamethoxazole	Placebo	Febrile or symptomatic UTI	Low risk: placebo vs CAP (19.2% vs 13.8%, p = 0.151), High risk: placebo vs CAP (31.5% vs 11.4%, p = 0.001)
Mattoo, 2016	United States	599	2 to 71 months old, with VUR grade 1-4	Trimethoprim-sulfamethoxazole	Placebo	Renal scarring	6% in CAP, 7% in placebo, p= 0.77
Garin, 2006	United States and Spain	218	< 18 years old, with DMSA proven PNA with or without VUR grade 1 to 3	Sulfamethoxazole-trimethoprim or nitrofurantoin	Surveillance	Recurrent UTI	22.4% in no RVU No CAP, 23.3% in RVU with no CAP (P = 0.9999). 8.8% in no RVU with CAP, 23.6% in RVU with CAP (p = 0.0633). PNA in 7 with CAP and 1 without CAP (P = 0.0291)
Shaikh,2016	United States	181	2 to 71 months old, with VUR grade 1-4	Trimethoprim-sulfamethoxazole	Placebo	Recurrent UTI	association between CAP and recurrent UTIs was stronger (p = 0.04) with BBD (HR = 0.22; 95% CI, 0.08–0.61) than without BBD (HR = 1.46; 95% CI, 0.45–4.79)

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Table 4. Summary systematic review with meta-analysis								
Study ID	**Country**	**Articles/ Population (n)**	**Type of population**	**Type of studies**	**Experimental**	**Comparator**	**Outcome**	**Result**
Hewitt, 2017	Italy	7/ 1427	<18 years old, needing CAP	RCTs	antibiotic prophylaxis	surgical treatment or surveillance	worsening renal scars	no differences between CAP and no CAP (RR, 0.83; 95% CI, 0.55–1.26)
Cochrane UTI, 2019	Australia	16/ 2036	<18 years old with prior UTI	RCTs, quasi-RCTs	antibiotic prophylaxis	placebo or surveillance	recurrent UTI	little or no difference of CAP (RR 0.75, 95% CI 0.28 to 1.98)
Cochrane VUR, 2019	Australia	9 (about CAP, not considering comparison with surgical treatment)/ 1667	< 18 years old with VUR	RCTs, quasi-RCTs	antibiotic prophylaxis	placebo or surveillance. They also consider every others option for VUR treatment in the studies.	recurrent symptomatic UTI	little or no difference of symptomatic UTI (RR 0.77, 95% CI 0.54 to 1.09; low certainty evidence) and febrile UTI (RR 0.83, 95% CI 0.56 to 1.21; low certainty evidence) at one to two years
Selekman, 2018	International	6/ 1299	< 18 years old with VUR	RCTs	antibiotic prophylaxis	placebo or surveillance	multidrug resistant recurrent UTI	CAP more likely of having multidrug resistance (33% vs 6%, P < .001)
Finnell, 2011	United States	6/ 946	2 to 24 months old with prior UTI	RCTs	antibiotic prophylaxis	placebo or surveillance	recurrent UTI	no significant difference RR of 0.77 (95% CI: 0.47–1.24)
Dai, 2010	China	11/ 1717	<18 years old, needing CAP	RCTs, quasi-RCTs	antibiotic prophylaxis	placebo or surveillance	recurrent symptomatic UTI	not significantly reduced by CAP (RR 0.83, 95% CI 0.66 to 1.05, p=0.13)
Mathew, 2010	India	3/ 1132	<18 years old, needing CAP	RCTs and systematic review	antibiotic prophylaxis	placebo or surveillance	recurrent UTI and worsening renal scar	reduced with CAP (RR=0.73; CI=0.56-0.95; I2=0%)

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Mori, 2009	Japan	4/ 656	<18 years olf with prior UTI	RCTs	antibiotic prophylaxis	placebo, surveillance or other non-surgical therapy	recurrent PNA or worsening renal scar	no evidence of difference in all the group, RR 0.96 (95% CI: 0.69–1.32)
De Bessa, 2015	Brazil, Canada	7/ 1593	Children with VUR	RCTs, quasi-RCTs	antibiotic prophylaxis	placebo, surveillance or other antibiotics	recurrent febrile UTI	High grade VUR , 20.84% vs 29.03% (CAP vs no CAP), RR 0.72 (95% CI 0.56-0.92), ARR 8.23%, NNT 12.15, p=0.008. Low grade VUR, 6.44% vs 12.94% (CAP vs no CAP), RR 0.51 (95% CI 0.32-0.79), ARR 6.51%, NNT 15.36, p=0.002
Wang, 2015	United States	8/ 1594	<18 years old with VUR	RCTs	antibiotic prophylaxis	placebo or surveillance	symptomatic or febrile UTI	CAP significantly reduced the risk of UTI in children with RVU (OR 0.63, 95% CI 0.42-0.96, p = 0.03)
Easterbrook, 2017	Canada	10/ 3909	prenatal HN, < 2 years of age	observational and comparative trial	antibiotic prophylaxis	surveillance	UTI	CAP group (9.9%; 95% CI 8.4–11.4) similar to surveillance group (7.5%; 95% CI 6.4–8.6). I2 = 77%
Silay, 2017	Europe	63/ 10019	asymptomatic antenatal HN diagnosed before 1 year of age	RCT, non-randomised comparative, case series	antibiotic prophylaxis	surveillance	UTI	It is unclear whether CAP makes any difference as ORs varied from 0.17 (95% CI 0.01-3.82) to 13.57 (95% CI 0.60-306.64)
Braga, 2013	Canada	21/ 3876	antenal HN < 2 years of age	Observational trials: 13	antibiotic prophylaxis	surveillance	UTI	Cap and surveillance were similar (9.9% [95%

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				retrospective and 8 prospective				CI: 4.6–17.1] vs 8.3% [95% CI: 2.9–16.0], P = 0.21)
Rohner, 2022	Germany, Switzerland	16/ 749	Primary megaureter < 18 years of age	1 RCT, 15 observational trials	antibiotic prophylaxis	surveillance	prevalence of acute PNA	with CAP 10.3 % (95 %CI: 4.8–20.8; I2 = 74 %; 9 studies; n = 275 patients), without CAP 33% (95 %CI: 16.5 55.1; I2 = 79 %). NNT = 4.3
Leigh, 2020	Canada	18/ 829	asymptomatic VUR diagnosed during first year of life because of antenatal HN	prospective and retrospective cohort trials	antibiotic prophylaxis	surveillance	Prevalence of UTI	15.4% UTI in CAP group. No meta-analysis possible because no strong comparator group.

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