Antibiotic prophylaxis in vesicoureteral reflux: A practice revisited

Jessica Robinson, BScPharm, BMSc, RPh

Patient case

A mother of 2 children approaches her community pharmacist. The pharmacist knows that the daughter had been diagnosed with grade I vesicoureteral reflux (VUR) when she was an infant but that it has since resolved. The mother's younger son (2 years old) was screened and has also been diagnosed with grade I VUR, although he has never had a urinary tract infection (UTI). Her daughter took prophylactic antibiotics until her VUR resolved, but her son has not been prescribed an antibiotic. The mother asks the pharmacist's opinion about the value of antibiotic prophylaxis in VUR.

Introduction

Vesicoureteral reflux is the flow of urine from the bladder back up the ureter toward the kidney.¹ It can be categorized as either primary or secondary. Primary VUR, the most common presentation, is caused by a congenitally abnormal ureterovesical junction, while secondary VUR is an acquired condition as a result of an overwhelmed or unstable ureterovesical junction. The incidence of VUR in healthy newborns is approximately 1% to 3%, although the invasive procedure needed to diagnose VUR may underestimate this condition.^{2,3} In children diagnosed with a febrile UTI, the incidence increases to approximately 30% to 40%, with a female to male prevalence of 4 to 1. Vesicoureteral reflux is often inherited, with a 32% incidence in siblings of children diagnosed with the condition.²

The gold standard for diagnosis and classification of VUR is fluoroscopic voiding cystourethrography. Vesicoureteral reflux is classified into 5 grades, with grade I being the

mildest and grade V being the most severe. All grades of primary VUR may spontaneously resolve over time.⁴ When UTIs are prevented, as many as 87% of grade I, 63% of grade II, 53% of grade III and 33% of grade IV VUR will spontaneously resolve within 3 years. Grade V reflux spontaneously resolves after the first year of life in only approximately 9% of patients. The spontaneous resolution over time is thought to be due to the lengthening of the submucosal segment of the ureter as the child grows taller.⁴

Vesicoureteral reflux is associated with UTIs, which may lead to pyelonephritis, renal scarring, hypertension and chronic renal insufficiency that can result in chronic kidney disease and, ultimately, end-stage renal disease.⁵ Both repeat UTIs in patients with VUR and renal dysplasia associated with severe VUR (congenital form) can damage the kidney, leading to reflux nephropathy.⁴ Surgical correction is curative in approximately 98% of patients; however, it is associated with the risk of morbidity and therefore is no longer considered the standard of care for all cases of VUR.² Antibiotic prophylaxis (Table 1) for the prevention of UTIs and watchful waiting are currently the most common treatments for VUR used in practice.^{1,4}

Practice controversy

Continuous antibiotic prophylaxis (CAP) for VUR was initially studied in the 1970s and further investigated in the 1980s. The 1997 guidelines of the American Urological Association (AUA) recommended that CAP be used to manage children younger than 10 years with grades I to IV VUR.⁶ This recommendation was based on the observation that children on CAP had fewer

TABLE 1 Commonly used oral antibiotics and suggested dosing in prophylactic regimens for vesicoureteral reflux^{1,4,6}

Antibiotic	Suggested dose, mg/kg	Frequency
Amoxicillin	10	Once daily
Amoxicillin-clavulanic acid	15	Once daily
Cefadroxil	5	Once daily
Cephalexin	10	Once daily
Nitrofurantoin	1–2	Once daily
Trimethoprim-sulfamethoxazole	0.5–3.0*	Once daily
	5*	Twice weekly
Trimethoprim	0.5–2.0	Once daily

*Based on trimethoprim.

UTIs and consequently less renal scarring. The patients would remain on CAP until their VUR spontaneously resolved or until the risk of reflux was thought to be low.⁶ The duration of antibiotic prophylaxis in the trials included in a recent meta-analysis ranged from months to 5 years.¹

Concern is growing among medical practitioners about the long-term use of CAP in VUR patients. A study by Allen et al.⁷ demonstrated that children who received antibiotics for more than 4 weeks in the previous 6 months had more resistant strains of *Escherichia coli* compared with those without such treatment (odds ratio, 13.9; 95% confidence interval [CI], 8.2–23.5; $p < 0.001$). Adverse drug reactions will occur in approximately 10% of children on long-term prophylaxis. Poor adherence is also common; in one study, urine screening revealed that only 31% of children took their medications.⁸ These arguments against long-term antibiotic use have led to a reevaluation of the use of CAP.

Evidence

Continuous antibiotic prophylaxis for the prevention of UTI in patients with VUR has become common practice. However, 3 recent meta-analyses of the use of CAP that included patients with all grades of VUR have led to a revision of the AUA recommendations.

The systematic review completed by Mori et al.⁹ analyzed 8 randomized controlled trials that included 677 children with a previous symptomatic UTI or with VUR. Three of the included trials compared CAP with no treatment in children with VUR following

symptomatic UTI. The trials included children from 1 day to 12 years of age, with grades I to V VUR. When these 3 studies were pooled, there was no statistically significant difference between those receiving and not receiving CAP for the incidence of new or deteriorated renal parenchymal defects, recurrence of symptomatic UTI or prevalence of bacteriuria at the end of prophylaxis. Only 1 of 8 trials evaluated children of any age with any grade of VUR, regardless of previous history of symptomatic UTI. This trial compared daily antibiotics, antibiotics given 3 times a week and no antibiotics for 1 year. The differences between the 3 treatment arms were not statistically significant for the incidence of new or deteriorated renal parenchymal defects or prevalence of bacteriuria.⁹

The meta-analysis completed by Mattoo¹⁰ included 5 studies, representing 809 patients from 1 day to 18 years of age with grades I to V VUR, and compared antibiotic prophylaxis with surveillance or placebo. There was no statistically significant benefit of CAP in preventing UTIs or renal scarring.¹⁰

A meta-analysis of 20 randomized controlled trials assessing interventions for primary VUR was conducted by Nagler et al.¹ and included patients with all grades of VUR from 6 days to 18 years of age. There was no statistically significant difference between CAP and placebo for the outcomes of symptomatic UTI (5 studies, $n = 846$; relative risk (RR), 0.68; 95% CI, 0.39–1.17) or febrile UTI (6 studies, $n = 946$; RR, 0.77; 95% CI, 0.47–1.24) over a 2-year follow-up or for repeat positive urine culture (6 studies, $n = 636$; RR, 0.84; 95%

TABLE 2 Summary of AUA guideline on management of primary vesicoureteral reflux in children¹²

Age	Grade	History, signs and symptoms	2010 AUA guideline recommendations and options
Less than 1 year old	All grades	History of febrile UTI	CAP is recommended
	III–V	No history of febrile UTI	CAP is recommended
	I–II	No history of febrile UTI	CAP may be offered
Older than 1 year	All grades	Presence of bladder/bowel dysfunction	CAP is recommended
	All grades	History of UTIs without bladder/bowel dysfunction	CAP may be considered
	I–IV	Absence of bladder/bowel dysfunction, recurrent febrile UTI, renal cortical abnormalities	Observational management may be considered
	V	No specific recommendations	

AUA, American Urological Association; CAP, continuous antibiotic prophylaxis; UTI, urinary tract infection.

CI, 0.57–1.25). In addition, there was no significant difference between treatment arms for children with new renal damage or progression of existing renal abnormalities, but there was a significant difference after a 3-year follow-up when these 2 outcomes were combined (3 studies, $n = 446$; RR, 0.35; 95% CI, 0.15–0.80). The use of antibiotics increased the risk of bacterial drug resistance threefold (4 studies, 132 urine cultures; RR, 2.94; 95% CI, 1.39–6.25), although the definition of resistance was not disclosed. Overall, the use of CAP did not significantly reduce the incidence of symptomatic or febrile UTI. However, renal damage was significantly less with CAP.¹

The AUA guideline on the management of primary vesicoureteral reflux in children was updated and released in September 2010 (Table 2).¹¹ For children younger than 1 year with any grade of VUR and a history of febrile UTI, CAP is recommended due to the greater morbidity risk in this population. If a child younger than 1 year is diagnosed with grades III to V VUR, CAP is recommended even in the absence of previous febrile UTI. In those same children with grade I or II VUR, CAP is an option but not mandatory. Children younger than 1 year are considered separately from older children, because infants are often diagnosed with VUR in the early postnatal period due to a diagnosis of prenatal hydronephrosis. There is a body of evidence suggesting that CAP has more benefit

in infants with VUR discovered during the postnatal workup for prenatal hydronephrosis than in children older than 1 year.¹¹

For children older than 1 year, observational management without CAP may be considered for VUR grades I through IV in the absence of bladder/bowel dysfunction, recurrent febrile UTIs or renal cortical abnormalities. Observational management is a new addition to these guidelines and reflects the questionable benefit of CAP in low-grade VUR. No specific recommendations are provided regarding management of children with grade V VUR.¹¹

Since the release of the 2010 AUA guideline, Finnell et al.¹² have published a meta-analysis on the use of CAP to prevent recurrent UTI in children with VUR. This study concluded that CAP did not significantly reduce the rate of recurrent pyelonephritis regardless of patient age or grade of reflux. The analysis did find a slight but significant reduction in the rate of occurrence of any type of UTI when the results of all children with VUR were included. However, when patients without previous UTI were excluded, the results were no longer significant.¹²

Finally, the American Academy of Pediatrics' recent clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children ages 2 to 24 months addresses the issue of CAP in children with VUR.¹³ This meta-analysis did not detect a statistically

significant benefit of CAP in preventing recurrence of febrile UTI in children with grades I through IV VUR, and there were not enough data to evaluate CAP in grade V VUR.¹³

Conclusion

Emerging evidence indicates that not all patients diagnosed with VUR require antibiotic prophylaxis. Most patients with high-grade (III–V) VUR, bladder/bowel dysfunction, recurrent febrile UTIs or renal cortical abnormalities will still receive antibiotic prophylaxis. However, patients with low-grade (I or II) VUR and no history of febrile UTI may avoid antibiotic prophylaxis and be observed for spontaneous resolution.

More evidence is needed to determine strict criteria for patients requiring antibiotic prophylaxis. The Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) study is an ongoing, multicentre, prospective, randomized, placebo-controlled study

comparing trimethoprim-sulfamethoxazole (3 mg/kg of trimethoprim once daily) with placebo.¹⁴ The primary outcome is recurrent febrile or symptomatic UTI during the 2-year follow-up. The study is expected to be completed in late 2013, and the results should be very helpful in making conclusions regarding the use of CAP in treating VUR.

Back to the case

A 2-year-old child with grade I VUR and no history of UTI is a perfect candidate for observational management without CAP. The pharmacist can advise the mother that in the past, it was thought that all children with VUR required CAP to prevent UTI. However, emerging evidence suggests that not all patients require CAP and that medical observation is a suitable option for her child. The pharmacist could also advise the mother about some of the potential disadvantages of CAP, including increased antibiotic resistance and adverse drug reactions.^{7,8}

From The Ottawa Hospital, Civic Campus, Ottawa, Ontario. Contact jessrobinson@toh.on.ca.

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