Original Article

Any Undiagnosed Vesicoureteral Reflux Following the Adoption of Thai Pediatric Nephrology Association-Endorsed Clinical Practice Guideline 2014 on Urinary Tract Infection in Children Aged 2 Months to 5 Years

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Objective: To assess the diagnosis for vesicoureteral reflux (VUR) among children aged 2 months to 5 years comparing between the Thai Pediatric Nephrology Association endorsed clinical practice guideline (CPG) 2014 and urinary tract infection (UTI) CPG 2010.

Materials and Methods: The medical records of febrile children (age 2 months to 5 years) who were admitted to the HRH Princess Maha Chakri Sirindhorn medical center during January 2002 to December 2012 were retrospectively reviewed. The CPG 2014 and 2010 were applied and the diagnosis of VURs were assessed.

Results: A total of 71 UTI patients were included in the present study. By using the CPG 2014 and CPG 2010, VUR was detected in five and ten patients respectively. The severity of VUR detected only by using CPG 2010 in five patients was only low-grade severity. Of note, two patients with high grade VUR were detected by both CPGs.

Conclusion: The application of CPG 2014 was able to detect high grade VURs which might further need a surgical management. The long term follow-up was recommended for all children with UTI due to possibly undiagnosed low-grade VUR in some cases.

Keywords: Urinary tract infection, Ultrasound, voiding cystourethrogram, High grade vesicoureteral reflux, Low grade vesicoureteral reflux, Thai pediatric guideline 2014

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Urinary tract infection (UTI) is a common cause of fever without localizing sign in children. Vesicoureteral reflux (VUR) is the crucial risk factor for acute pyelonephritis and recurrent UTI in children of any age. These conditions can result in renal scarring with the risk of later hypertension and chronic renal failure.

Nowadays, there are several consensus guidelines for UTI. In Thailand, UTI clinical practice guideline (CPG) in 2 months to 5 years old children has developed by Thai Pediatric Nephrology Association (TPNA) in 2010 and modified to the new CPG in 2014[1]. The vast difference between previous and new CPG is the indications of voiding cystourethrogram (VCUG) in first episode of UTI. The 2010 CPG suggested routinely VCUG for all first febrile UTI patients but the new 2014 CPG recommended VCUG only in the patients at risks of VUR in the following cases:

1) Recommendation for VCUG in patients who have abnormal findings on diagnostic imaging by renal ultrasound such as hydronephrosis, ureteric dilatation, renal hypoplasia, renal scar, duplicated system and bladder abnormalities or renal impairment.

2) Consideration for VCUG in patients who have history of VUR in first degree relatives, abnormal bladder emptying, non-*E. coli* infections, septicemia or non-compliance.

Narchi et al found 56% potentially missed of VUR if the new American Academy of Pediatrics (AAP) imaging guideline was applied to recommend only ultrasound for the first episode of UTI[2]. While Ristula et al described that the new AAP guidelines recommended VCUG only to a selected patient with predisposing factors which have benefit to reduce the number of unnecessary VCUG procedures[3]. Capone et al showed that the prevalence of a pathology identified in children with VUR and normal renal ultrasound was similar between both guidelines[4].

Since the 2010 CPG was introduced until 30 June 2016, there had been no study assessing the clinical outcome, particularly the diagnosis rate of VUR documented by VCUG,

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by comparing the new 2014 CPG to the previous 2010 CPG. This study aimed to provide the outcome for supporting further guideline development in the future.

Materials and Methods

Participants

The authors performed a retrospective chart review study of children who were admitted for the first febrile UTI treatment in HRH Princess Maha Chakri Sirindhorn medical center, Thailand during 1st January 2002 to 31st December 2012. Ethical approval for this study was granted by the ethic committee of Srinakharinwirot University (SWUEC-252/59E).

All children aged between 2 months and 5 years who were diagnosed for the first acute pyelonephritis confirmed by urine culture were recruited. The children who were diagnosed with congenital anomalies predisposing to UTI, such as renal dysplasia, renal agenesis, posterior urethral valve, ureteropelvic junction obstruction, ureterovesicle obstruction, hypospadias and neural tube defects, were excluded.

Data collection

A standard renal ultrasound and VCUG in all patients were performed in accordance with the 2010 CPG. The researcher gathered the essential information including age, sex, ultrasound and VCUG findings.

Statistical analysis

The differences with the proportion of the diagnosis of VUR and the reduction of unnecessary VCUG between the CPG 2010 and the CPG 2014 was tested by Chi-square. The relative risk of VUR detection in the patients who had indications for VCUG compared with the patients who had no indications for VCUG was calculated using SPSS version 22.

Results

A total of 71 patients with acute pyelonephritis were enrolled in the study. Sixty five percent were male, 78.9% were under 1 year of age and the mean age was 7 months. Renal ultrasound and VCUG were performed on all patients according to 2010 CPG. The ultrasound showed abnormal findings in 13 patients (18.3%) consisting of 9 unilateral (12.7%) and 4 bilateral (5.6%) hydronephrosis. VCUG showed VUR in 10 patients (14%) consisting of 8 low-grade (11.2%) and 2 high-grade (2.8%) VUR. Among the 58 patients with normal renal ultrasound, 6 patients (10.3%) had VUR consisting of 1 grade I, 3 grade II and 2 grade III VUR. Among the 13 patients with abnormal renal ultrasound, 4 patients (30.8%) had VUR consisting of 1 grade I, 1 grade III and 2 grade V VUR. The sensitivity and specificity of renal ultrasound for VUR detection were 40% and 85.2%, respectively. Table 1 showed sensitivity and specificity of renal ultrasound for VUR detection.

In accordance with the 2014 CPG, VCUG would be indicated in 26 patients. This recommendation resulted in a reduction of 40 patients (56%) for unnecessary VCUG procedure. VUR would be missed in 5 patients (50%) as shown in Table 2. All the undiagnosed VUR were low-grade severity. The grading of VUR that would be detected and missed according to the 2014 CPG was shown in Table 3 and Figure 1. The relative risk of VUR detection in the patients who had indications for VCUG is 1.731 (p-value = 0.343) compared with the patients who had no indications for VCUG.

Discussion

Most of the patients with UTI in HRH Princess Maha Chakri Sirindhorn medical center in this study were under 1 year of age corresponding to the previous study reported[5]. The study results showed that renal ultrasound had poor sensitivity in predicting VUR, which was around 40%. The previous study in Lampang, Thailand with a larger sample size confirmed that the sensitivity of abnormal renal ultrasound for detecting VUR were only 38.1%[6]. Similarly, the other studies[7-9] were reported low sensitivity of renal ultrasound for detecting VUR and recommended VCUG as the complementary test to identify VUR.

In the present study, the 2014 CPG application resulted in missing around 50% of VUR detection. This result was similar to the previous study by Narchi et al conducted in 2015 "renal tract abnormalities missed in a historical cohort of young children with UTI if the NICE and AAP imaging guidelines were applied" that showed missing 56% of VUR detection after new AAP imaging guidelines were implemented[2]. In other words, VCUG done only in the patients at risks of VUR resulted in missing about half of VUR patients compared with routinely VCUG for all first UTI patients.

The present study demonstrated five VUR patients detected by 2010 CPG but not in 2014 CPG. All these patients were found to have only low-grade VUR. Of note, all patients with high grade VUR which further might need a surgical management could be detected by the new CPG. This results differed from the "Consequences of following the new American Academy of Pediatrics guidelines for imaging children with urinary tract infection" by Ristola and Hurme published in 2015 that described higher rate of missing high grade VUR. Of the 36 patients who had high grade VUR, six (17%) would have been missed if the AAP guideline was applied. In addition, five patients (15%) would not have undergone surgical treatment or it would have been delayed[3]. This difference may be caused by the additional recommendation of Thai 2014 CPG that added other indications such as renal impairment, history of VUR in first degree relatives, abnormal bladder emptying, non-*E. coli* infections, septicemia and non-compliance to AAP guideline. These finding had impact on the new CPG to detect more high-grade VUR.

"Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis" by Garin et al found no statistically significant differences between low grade VUR and no VUR patients with respect to rate of recurrent UTI and

Table 1. Sensitivity and specificity of renal ultrasound for VUR detection

Renal ultrasound findings	VUR (n = 10)	No VUR (n = 61)	Sensitivity (%)	Specificity (%)
Abnormal	4	9	40	85.2
Normal	6	52		

Table 2. Comparison of results of imaging studies according to the 2010 and 2014 CPG

Imaging studies	Studies performed, n	Abnormalities detected, n (%)	Studies performed, n	Abnormalities detected, n (%)	Abnormalities missed, n (%)
Renal ultrasound	71	13 (18.3)	71	13 (18.3)	0 (0)
VCUG	71	10 (14)	26	5 (19.2)	5 (50)

Table 3. Comparison of VUR detections between the patients with and without indication for VCUG according to the 2014 CPG

Indications for VCUG	VUR		No VUR	Total, n (%)
	High-grade	Low-grade		
Indicated	2	3	21	26 (37)
Not indicated	0	5	40	45 (63)

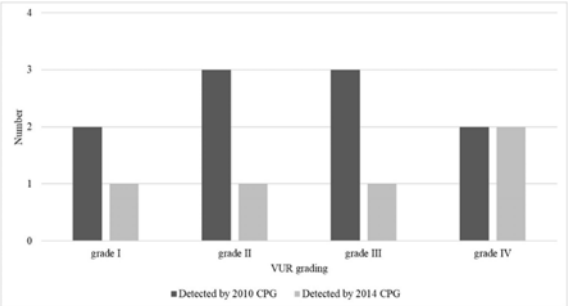

Figure 1. Comparison of the number of VUR detections according to the 2010 CPG and 2014.

development of renal scars[10]. This practice could support the safety of 2014 CPG that even if the low grade VUR was not detected, the incidence of recurrent UTI or renal scarring after acute pyelonephritis did not increase. Moreover, the 2014 CPG resulted in reduction of 56% in unnecessary VCUG. This benefit was also found in other previous studies in the same topics[3].

The strengths of the present study compared with the previous reports were that this study was the first report that reviewed the impact of the new Thai Pediatric Nephrology Association 2014 CPG compared to the 2010 CPG on VUR rates in children 2 months to 5 years old. This study also had the limitations included the allocation bias because of the nature of unrandomized trial and the ascertainment bias because of the nature of retrospective study. Furthermore, retrospective chart review could not provide complete data in all UTI cases. A larger sample size and long term follow-ups are warranted to further establish the validity and reliability.

Conclusion

The application of the new 2014 CPG was able to detect all of high grade VURs which further might need a surgical management. However, the patients who had not received voiding cystourethrogram should have long term follow up for UTI surveillance.

What is already known on this topic?

The previous study results showed that renal ultrasound had poor sensitivity in predicting VUR. After new AAP imaging guidelines were implemented, recommending for VCUG only in the patients at risks of VUR. This practice resulted in missing about half of VUR patients compared with routinely VCUG for all first UTI patients.

What this study adds?

The rate of VUR among children 2 months to 5 years old using the new Thai pediatric nephrology association UTI 2014 CPG was compared with the rate of VUR using the old 2010 CPG.

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Potential conflicts of interest

The authors declare no conflict of interest.

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