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# Cases of Pediatric Pyelonephritis: A Single-Center Retrospective Study from an Extended-Spectrum β-Lactamase-Producing Escherichia coli Endemic Area in Japan

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## ABSTRACT

**Background** Extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* has been increasingly recognized as the cause of upper urinary tract infection (UTI) in children. We have been using flomoxef at our department since 2017 as the first-line empiric therapy for children diagnosed with UTIs, and we avoid using carbapenems, which are considered the first-line treatment for ESBL-producing *E. coli*. However, reports on the use of flomoxef for UTIs are limited, especially for pediatric patients. The presence of vesicoureteral reflux at the onset of pyelonephritis is a concern. Severe vesicoureteral reflux can lead to repeated UTI and future deterioration of renal function, but the indication for voiding urethrography, which closely examines the presence of vesicoureteral reflux complications, is controversial.

**Methods** We retrospectively reviewed the laboratory findings, treatment, and clinical course of 96 pyelonephritis cases experienced at our department over a 7-year period from April 2014 to March 2021.

**Results** ESBL-producing *E. coli* were identified as the cause of pyelonephritis in 51% of cases, and this value was significantly higher (88%) in 2017. No significant differences were found in the febrile period or recurrence rate between the flomoxef-initiated group and other antibiotics groups. We also examined clinical indicators to predict vesicoureteral reflux and found no significant differences in ultrasonographic findings of hydronephrosis.

**Conclusion** In the present series, 51% of all pyelonephritis cases were found to be caused by ESBL-producing *E. coli*, with a significant increase in recent years. Flomoxef may be a useful alternative to carbapenem for ESBL-producing *E. coli* and the initial antibiotic of choice for upper UTIs in children. The indication for voiding cystourethrography should be carefully determined.

**Key words** ESBL infections; urinary tract infections; vesico-ureteral reflux

Enterobacteriaceae are the most frequently isolated organisms causing upper urinary tract infection (UTI) in children; however, reports have suggested the increasing percentage of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli*.[1, 2] When ESBL-producing bacteria are frequently isolated, initial treatment should be based on the assumption that ESBL-producing bacteria are the causative organisms. However, the use of carbapenems, which are the first-line treatment for ESBLs, as initial therapy for pediatric UTIs is undesirable from the standpoint of appropriate antimicrobial use.[3] Flomoxef (FMOX)—classified under the category of oxacefems—demonstrates high stability against ESBL and is a candidate agent for the treatment of ESBL-producing bacteria,[4] but reports on clinical results have been limited.

Vesicoureteral reflux (VUR) has been reported as a complication in 30%–40% of children with a history of UTI.[5] Severe reflux has been associated with repetitive UTI and future deterioration of renal function.[6] Although early diagnosis of VUR is important, in many patients, voiding cystourethrography (VCUG) tests demonstrate normal results. The indication for VCUG is controversial and varies according to the institution owing to factors such as radiation exposure, pain associated with the procedure, problems associated with medically-induced UTIs, etc. VCUG should be indicated only for patients who are at a high risk for VUR. Recently, some studies have suggested that procalcitonin is an indicator of VUR, but its use in clinical settings is yet to be realized.[7, 8]

The present study examined the prevalence of UTIs caused by ESBL and the usefulness of FMOX as an initial treatment; in addition, the clinical indicators

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Abbreviations: ESBL, extended-spectrum β-lactamase; PCT, procalcitonin; UTI, upper urinary tract infection; VCUG, voiding cystourethrography; VUR, vesicoureteral reflux

**Table 1. Characteristics of the group started treatment with FMOX and the other antibiotics group**

| | Total $n = 96$ | Started with FMOX $n = 78$ | Other Antibiotics $n = 18$ | $P$ value |
|---|---|---|---|---|
| Age (month) | 8(4–14) | 8 (5–14.8) | 4.5 (2.3–10.5) | 0.04 |
| Male/Female | 42/54 | 31/47 | 11/7 | 0.119 |
| Initial case/Recurrent case | 82/14 | 68/10 | 14/4 | 0.291 |
| Date of diagnosis(date) | 4 (2–4) | 4 (2–4) | 2 (2–4) | 0.193 |
| CRP (mg/dL) | 7.9 (4.7–12.1) | 8.1 (5.3–11.9) | 6.37 (4.2–12.3) | 0.467 |
| Leukocyte (/μL) | 19,700 (15,775–22,625) | 19,800 (16,575–23,000) | 16,700 (15,000–21,950) | 0.291 |
| Procalcitonin (ng/mL) | 1.3 (0.3–3.9) | 1.3 (0.3–3.5) | 1.4 (0.3–9.8) | 0.688 |
| Febrile period (hour) | 20 (15–42) | 20 (15–42) | 27 (17–40) | 0.369 |
| Duration of treatment (day) | 14 (14–15) | 14 (14–15) | 15 (14–16) | 0.366 |
| Hydronephrosis | 16/96 (16.7%) | 13/78 (16.7%) | 3/18 (16.7%) | 1 |
| Performed VCUG* | 65/96 (67.7%) | 51/78 (65.4%) | 14/18 (77.8%) | |
| VUR† | 14/96 (14.6%) | 9/51 (17.6%) | 5/16 (31.3%) | 0.295 |
| Recurrence of UTI | 15/88 (17.0%) | 12/73 (16.4%) | 3/15 (20%) | 0.3 |

*Including cases performed at other hospitals. †Including cases already known at the time of diagnosis and those performed at other hospitals. Data are expressed as median (range) or *n* (cases). CRP, C-reactive protein.

used for predicting VUR were investigated.

## MATERIALS AND METHODS

Children with pyelonephritis, excluding those diagnosed with acute focal bacterial nephritis, who were hospitalized and treated for upper UTI at our pediatric department in Matsue, Shimane Prefecture over a 7-year period from April 2014 to March 2021 were evaluated. Patient background, blood and urine test results, urine culture results, treatment outcomes, and prognosis were retrospectively reviewed using medical records. Upper UTI was diagnosed when the patient had fever with no other identifiable causes, and urine culture was obtained via intravesical sterile catheterization or, in older children, via intermediate urine culture method at $10^4$ CFU/mL or higher. Febrile period was defined as the period from the start of initial antimicrobial administration to the time when the body temperature remained below 37.5°C and fever was considered to be resolved. Body temperature was measured at four time points in the pediatric ward (7:00, 10:00, 14:00, and 19:00), although measurements obtained at other time points were also included.

### Statistical analysis

The Mann–Whitney *U* test was used to compare continuous variables, whereas Fisher's exact test was used to compare frequencies. A $p$ value of $< 0.05$ was considered to indicate a significant difference.

### Ethical considerations

This study was approved by the institutional review board of our institute (No. 4B-0015).

## RESULTS

A total of 96 pyelonephritis cases (42 boys and 54 girls) were included. The patient background is summarized in Table 1. The median age was 8 (range, 4–14) months, and 68% were < 1 year old (Fig. 1). The median date of diagnosis was 4 days. Among the included children, 16.7% showed hydronephrosis on ultrasonography, 67.7% underwent the VCUG test, and 14.6% exhibited VUR. No serious cases were noted. Urine culture results showed ESBL-producing *E. coli* in 49 cases (51%), non-ESBL-producing *E. coli* in 40 cases (41%), and *Staphylococcus aureus* in 2 cases. *Klebsiella pneumoniae*, simultaneous isolation of ESBL-producing *E. coli* and *Klebsiella oxytoca*, *Enterococcus faecalis*, *Serratia marcescens*, and *Raoultella planticola* were each found in one case (Fig. 2). As a cause of upper UTI, the number of cases with ESBL-producing *E. coli* has been increasing since 2015, with reports showing that 88% of cases in 2017 were due to ESBL-producing *E. coli* (Fig. 3). With the increase in the aforementioned causative agent, our department has selected FMOX (60–80 mg/kg/day) as the first-line treatment for children diagnosed with UTI since 2017 (Fig. 4); however, no significant differences were observed in the febrile period and recurrence rate between the FMOX-initiated group and other antibiotics groups ($P = 0.369$, 0.3) (Table

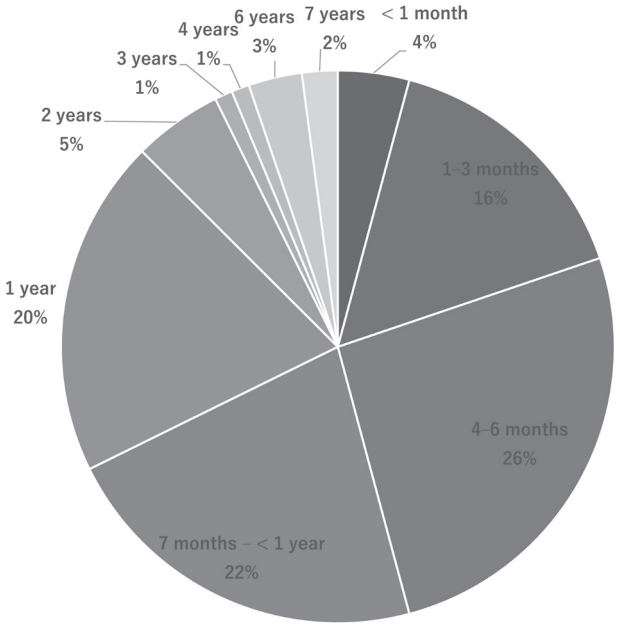


**Fig. 1.** Background: Age. Among the children with pyelonephritis, 68% were younger than 1 year.

1). Background between the FMOX initiation group and the other antibiotics groups showed a significant difference only in age. Among the 78 patients started on initial FMOX treatment, 3 (including 2 ESBL-producing *E. coli*) did not achieve resolution of fever and were switched to a broad-spectrum antibiotic, such as meropenem (MEPM). Only two patients received MEPM treatment from the beginning.

Since 2018, our department has narrowed the indications for VCUG testing to cases with abnormal ultrasonography, clinically atypical cases, recurrent cases, and cases in which the parents wanted the test performed, consequently decreasing the rate of testing (Fig. 5). The percentage of patients with VUR has remained between 11% and 43% of those who underwent VCUG. After examining only first-episode pyelonephritis, we found no significant differences in age (in months), sex, bacteria detected via urine culture (in cases where bacteria other than *E. coli* were detected), blood sampling results (i.e., procalcitonin and C-reactive protein), or complication rate of hydronephrosis via ultrasound examination in patients with or without VUR (Table 2). Notably, the study included two patients with grade III–IV VUR of initial urinary tract infection without ultrasound findings (Fig. 6). The time of the febrile period was significantly longer in the group with VUR (59 h) than in the group without VUR (20 h) ($P < 0.05$). Procalcitonin (PCT) levels were 1.8 ng/mL and 12.3 ng/mL in two patients with Grade III or higher VUR, respectively.

## DISCUSSION

ESBL-producing bacteria were first reported in Europe in the 1980s, and they have been detected in Japan from the 2000s.[3] Drug susceptibility surveillance of clinical isolates across all ages in Japan showed that 4.3% of the *E.coli* that caused UTI cases in 2006 were attributable to ESBL-producing *E. coli*,[9] with the percentages increasing to 17.1% by 2012.[10] A previous study showed

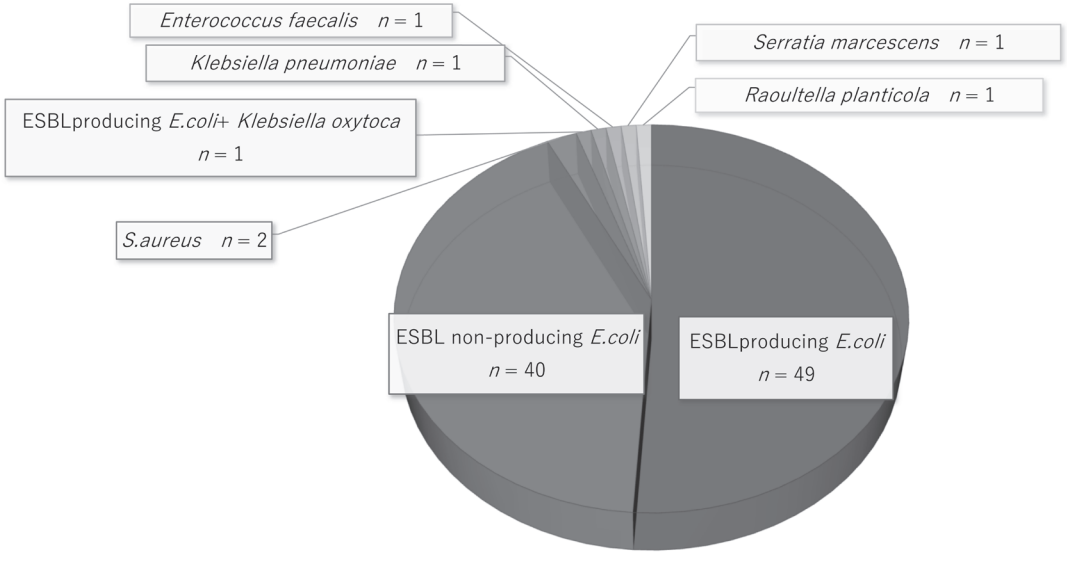


**Fig. 2.** Urine culture results. Urine culture results showed ESBL-producing *Escherichia coli* in 49 cases (51%), non-ESBL-producing *E. coli* in 40 cases (41%), and *Staphylococcus aureus* in 2 cases. *Klebsiella pneumoniae*, simultaneous isolation of ESBL-producing *E. coli* and *Klebsiella oxytoca*, *Enterococcus faecalis*, *Serratia marcescens*, and *Raoultella planticola* were each present in one case.

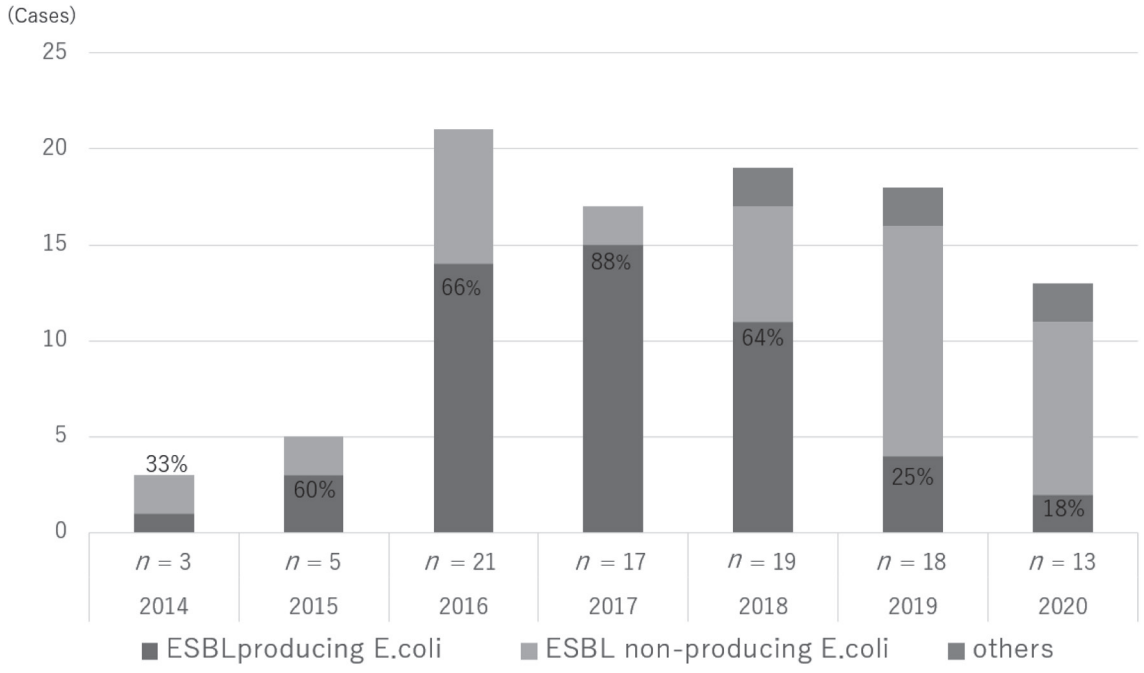


**Fig. 3.** Annual trends in ESBL-producing *E. coli*. Percentage figures indicate that of ESBL-producing *Escherichia coli.* ESBL-producing *E. coli* accounted for 51% of all cases and 88% of cases in 2017.

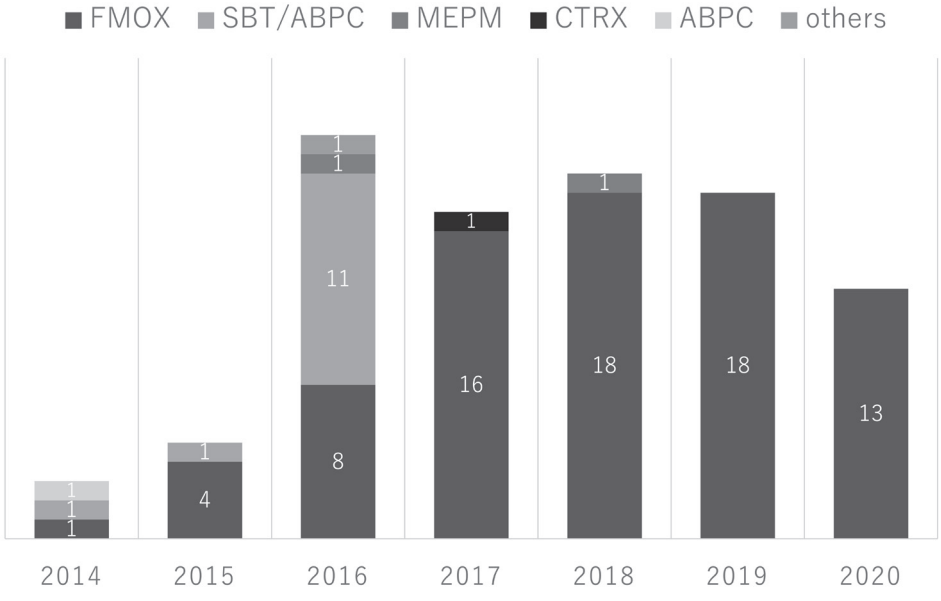


**Fig. 4.** Annual changes in initial antimicrobial selection. Our department has been utilizing flomoxef (FMOX) as the first-line treatment for children diagnosed with urinary tract infection since around 2017. ABPC, aminobenzylpenicillin; CTRX, ceftriaxone; SBT/ABPC, sulbactam/aminobenzylpenicillin.

that the detection rate of ESBL-producing *E. coli* in children from the Izumo district of Shimane Prefecture was 68% in 2016.[1] Accordingly, the current study of the Matsue district of Shimane Prefecture found a rate of 88% in 2017, which was higher than that reported in the aforementioned study. Given that the detection rate of ESBL-producing *E. coli* varies widely from one region to another, it is necessary to refer to the epidemic situation and reports in each region. When ESBL-producing bacteria are frequently isolated, initial treatment should

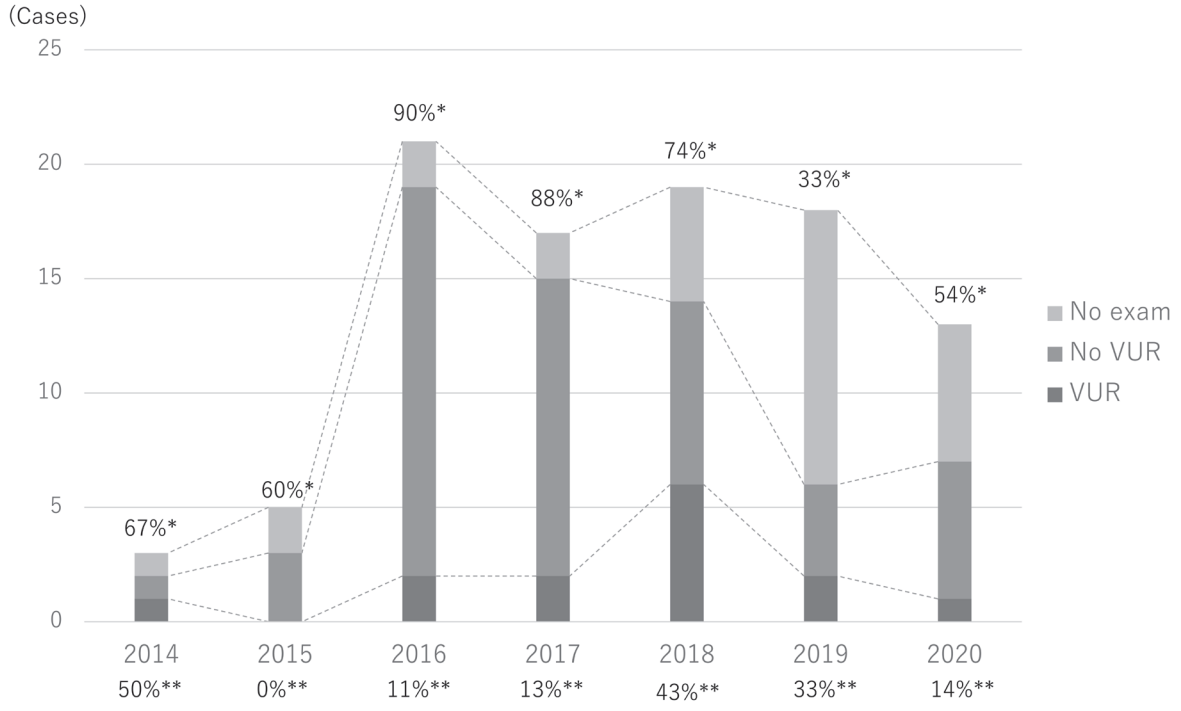


**Fig. 5.** Annual changes in the percentage of VCUG tests performed. *Percentage of VCUG tests performed. **Positive rate of VCUG tests. Since around 2018, the rate of VCUG testing at our department has decreased.

**Table 2. Differences patients between with and without vesicoureteral reflux**

| | VUR $n = 9$ | No VUR $n = 50$ | $P$ value |
|---|---|---|---|
| Age (month) | 10.0 (5–14) | 5.5(4–8.75) | 0.177 |
| Male/Female | 3/6 | 25/25 | 0.477 |
| Non *E.coli* | 0 | 2 | 1 |
| CRP(mg/dL) | 8.97 (7.45–12.1) | 9.12(5.79–13.2) | 0.966 |
| Leukocyte (/μL) | 21,800 | 19950 | 0.689 |
| Procalcitonin (ng/mL) | 1.26 (0.2–4.42) | 1.56 (0.5–6.0) | 0.482 |
| Febrile period (hour) | 59 (20–65) | 20(14.3–38.5) | 0.0117 |
| Hydronephrosis | 2 | 8 | 0.641 |

Data are expressed as median (range) or *n* (cases).

be based on the assumption that they are the causative organisms. However, the use of carbapenems, which are considered the first-line antibiotics for ESBL, for the initial treatment promotes the development of carbapenem-resistant bacteria and is undesirable from the viewpoint of suitable antibacterial drugs.[11] FMOX, classified as an oxacefem with a difluoromethylthioacetamide group at position 7, is highly stable against ESBL and is a candidate agent for the treatment of infection caused by ESBL-producing bacteria.[4] However, reports on clinical results have been limited, especially in pediatric patients. At our department, FMOX has been the first choice for children diagnosed with UTI since 2017. No significant differences were observed in the febrile period and recurrence rate between the FMOX-initiated group and other antibiotics groups, suggesting that FMOX may be a useful alternative carbapenem antibiotic for UTIs caused by ESBL-producing *E. coli*. The cause of the change in the percentage of ESBLs within the observation period is unknown, but the effect of changes in therapeutic agents is less likely. In addition, no severe cases were observed in the current report. The results of FMOX treatment in adult ESBL bacteremia have been reported to be inferior to those of carbapenems,[12] suggesting that the choice of antibiotics should be carefully considered in cases with severe infection. In addition, there were 3 cases in which treatment was initiated with FMOX but was switched to a broad-spectrum antibacterial agent such as MEPM when fever was not resided. All of the cases showed good sensitivity to FMOX in vitro. If fever is not resided, it may be required to switch to a broad-spectrum antimicrobial agent. Furthermore, as the number of cases in the MEPM-initiated group was small (2 cases), comparison with FMOX-initiated group could not be done in this study.

Estimates have shown that 30%–40% of children

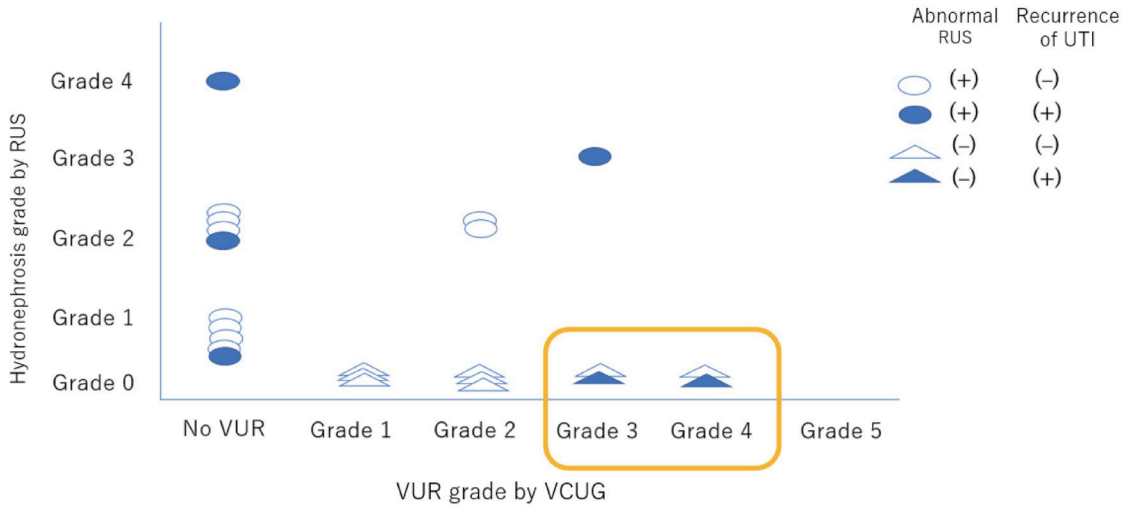


**Fig. 6.** Relationship between the findings of hydronephrosis on renal ultrasonography and results of VCUG testing and recurrence. Among the 96 cases, 65 underwent VCUG testing. A total of 44 of those 65 cases with no abnormal RUS and no VUR are excluded from the figure. There were 2 cases reported with UTI for the first time without ultrasonographic findings with grade III–IV VUR. ○: Patients without recurrence and with abnormal RUS. ●: Patients with recurrence and abnormal RUS. Δ: Patients without recurrence and without RUS abnormality. ▲: Patients with recurrence and without RUS abnormality.

with a history of UTI are complicated by VUR.[4] Examinations after a diagnosis of upper UTI are performed to prevent repeat upper UTI, renal scarring, and subsequent progression to chronic renal failure.[13, 14] The 1999 American Academy of Pediatrics (AAP) guidelines recommended VCUG and renal ultrasonography for all cases of upper UTI from 2 months to 2 years of age, even for first-time cases.[14] However, the 2011 revision does not recommend testing in all cases; rather, it recommends that VCUG testing be performed in cases of abnormal ultrasonography or clinically atypical cases.[15] The NICE guidelines also recommend ultrasonography and VCUG testing in atypical clinical or recurrent cases.[16] In their validation reports, Narch et al. and Ristola et al. suggested the possibility of missing high-level VURs.[17–19] Indications for VCUG testing vary from one facility to another. At our department, for all patients with UTI, radiologists perform ultrasonography to confirm the presence or absence of hydronephrosis, and VCUG examination is performed for patients requiring abnormal ultrasonography, for clinically atypical and recurrent cases, and for children on parents' request.

The accuracy of diagnosing VUR using ultrasonographic abnormalities is considered low, with a sensitivity and specificity of 27%–46% and 85%–91%, respectively.[20, 21] The present study also included two cases of initial UTI without ultrasound findings in patients with grade III–IV VUR (Fig. 6), emphasizing that ultrasound findings alone cannot be used to predict the presence or absence of VUR and that VUR may be overlooked.

For pyelonephritis, an association between fever duration and renal scar formation has been suggested. Karavanaki et al. described a significant increase in irreversible lesions on dimercaptosuccinic acid scintigraphy when the fever duration was ≥ 48 h after the start of treatment; however, in their multiple regression analysis, they reported that the effect of fever duration on lesions disappeared after correcting for delayed treatment initiation, presence of VUR, age, and C-reactive protein.[22] In the current study, the time of febrile period was significantly longer in the group with VUR, suggesting a higher risk of renal scarring. Although it is necessary to consider other factors, such as infection severity and timing of treatment initiation, to determine whether a longer time of febrile period could be a predictive factor for VUR, it is possible that patients with anatomical abnormalities may have difficulty in resolving fever, which may be one of the indications for VCUG testing.

Serum PCT has been suggested as a biomarker for severe VUR and reflux nephropathy. High PCT levels have been associated with high bacterial inflammation of the renal parenchyma, which may later shift from inflammatory lesions to scar lesions.[23] Leroy et al. stated that UTI in children with high PCT are highly complicated with advanced VUR.[7, 8] They suggested that VCUG testing should be performed in cases with PCT of > 0.17 ng/mL when urethral dilation is observed on ultrasound, and > 0.63 ng/mL in cases with no

dilation. Furthermore, 0.5 ng/mL was reported as an appropriate cutoff value in another meta-analysis study. In the current study, PCT values did not significantly differ between those with or without VUR. There were 2 cases with ≥ grade III VUR, which could not be examined in this study due to the small number of cases. The effect of the difference in timing of the PCT test and the fact that the VCUG examinations were not performed in all cases should also be considered.

Although early diagnosis of VUR is important, in many cases, VCUG test can reveal normal results. At our department, the indications for VCUG testing are limited based on the guidelines related to the factors such as radiation exposure, pain associated with the procedure, UTIs caused by drugs, and the appropriate use of medical resources.[24] In the present study, no clear benefits of PCT were observed. However, it was evident that ultrasonography findings alone cannot be used to predict the presence or absence of VUR, owing to which VUR may be overlooked. Despite the small number of cases and the need for further studies, we assume that the highly accurate prediction of VUR using clinical indices is difficult. The indication for VCUG testing should be further investigated, including the evaluation of long-term prognosis of renal function.

Because it is difficult to narrow the indications for VCUG based on clinical indicators, it is important to educate children and their families about the advantages (e.g., reducing the chance of missing a VUR) and disadvantages (e.g., radiation exposure) of performing VCUG. Moreover, careful follow-ups to check for a recurrence of UTI is necessary regardless of whether the test has been performed.

This study has several limitations. The small number of cases made it difficult to compare FMOX- and carbapenem-initiated groups, and there was a significant difference in age between FMOX and other antimicrobial initiated groups. It was also difficult to compare the clinical index of VUR≥3, which is clinically more important.

We herein report our experience with a series of 96 cases of pyelonephritis at our department. Notably, ESBL-producing *E. coli* accounted for 51% of all cases, with a significant increase in recent years. In conclusion, FMOX may be a useful alternative carbapenem antibiotic for ESBL-producing *E. coli* and may be the initial antibiotic of choice. Additionally, given the difficultly of predicting VUR based on clinical indicators, sufficient explanation to the children and their family about performing VCUG and possibility of reccurence of UTI, is necessary. Moreover careful follow-up is important.

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*The authors declare no conflict of interest.*

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