Original Article

Transition to oral antibiotic therapy for pyelonephritis in children under 60 days of age: An observational retrospective cohort study

David-Alexandre Lessard MD*, Thelma Huard-Girard MD*, Arnaud Tremblay, Jean-Francois Turcotte MD FRCPC

Département de pédiatrie, CHU de Québec – Université Laval, Québec, Québec

Correspondence: Jean-François Turcotte, Département de pédiatrie, CHU de Québec, 2705, boulevard Laurier, R-1742, Québec, Québec, G1V 4G2. Telephone 418-654-2282, Fax 418-654-2137, e-mail Turcotte.jean-francois@chudequebec.ca

*These authors contributed equally to this work.

Abstract

Objectives: To describe the use of antibiotics and assess if an early transition from intravenous to oral antibiotic therapy is generally safe in infants less than 60 days of age with a diagnosis of pyelonephritis.

Methods: This retrospective observational cohort study included hospitalized infants less than 60 days with a diagnosis of pyelonephritis based on fever or systemic symptoms and a positive urine culture between January 1, 2015 and July 30, 2017 at a Canadian paediatric tertiary care centre.

Results: A total of 108 infants were included. Forty-eight of them were under 1 month of age. The median intravenous (IV) antibiotic therapy duration was 3.5 days, with a longer duration of 4 days in infants less than 1 month of age. The total antibiotic therapy was almost equally divided between a shorter (10 days) and longer (14 days) duration. The recurrence of pyelonephritis within the 2 months following the initial urinary infection was 9 % in the group with IV antibiotic therapy duration of <4 days, compared to 11% in the group treated ≥ 4 days IV (P-value 0.75). There was a recurrence of pyelonephritis of 10.2% in the group treated for 10 days, compared to 11.5% of recurrence in the group treated for 14 days (P-value 1.0).

Conclusions: Our study provides limited retrospective data regarding the management of pyelonephritis in infants less than 60 days of age. Prospective research is needed to confirm those findings.

Keywords: Neonates; Pyelonephritis; Urinary tract infection.

Acute pyelonephritis is a common medical problem in infants. Many studies have assessed optimal management of this infection in older children. A Cochrane review found no significant differences between intravenous (IV) therapy alone and short IV therapy (3 to 4 days) followed by oral therapy with respect to persistent bacteriuria at the end of treatment, recurrent urinary tract infection within 6 months or persistent kidney damage. Also, no significant difference in duration of fever or subsequent renal damage was found between oral antibiotic therapy

alone and a short course of IV therapy followed by oral therapy. Therefore, treatment with oral antibiotics is now commonly recommended for nontoxic children without urinary tract malformation (1,2). However, children less than 60 days of age have been excluded from this recommendation given both the risk of bacterial sepsis as well as the lack of evidence for oral therapy in this population (2). As mentioned in the position statement of the Canadian Paediatric Society (CPS), further research is needed with regards to the management strategies for

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infants less than 60 days of age with urinary tract infection (2). For this reason, guidelines from both the CPS and the American Academy of Pediatrics (AAP) do not apply to infants aged less than 60 days (2,3). In fact, evidence to support oral antibiotic therapy in this group is quite limited, particularly in neonates.

This lack of literature leads to significant heterogeneity in the management of urinary tract infections in this population. Some experts consider that inpatient treatment with parenterally administered antibiotics is the safest initial strategy because close follow-up is warranted in this age group (1,4). However, there is no recommendation for the timing of a safe transition to oral therapy, which is a more convenient approach and leads to reduced hospitalization costs (1).

The objectives of this retrospective research were to describe the use of antibiotics in a tertiary care centre and to assess if an early switch to oral antibiotic therapy is safe in infants less than 60 days of age with a diagnosis of pyelonephritis. We hypothesized that most children would be switched to oral therapy after the first days of hospital observation and that the complication rate would be low.

METHODS

We conducted a retrospective observational cohort study at Centre Mère-Enfant Soleil (CHU de Québec), a single paediatric tertiary care centre in Québec City. This study was approved by the local ethics committee. Data was collected by using the hospital electronic patient records. Subjects were identified using the hospital medical records for every infant with a diagnosis of pyelonephritis, cystitis or urinary tract infection (ICD-10 discharge code) between January 1, 2015 and July 30, 2017. At the time of data collection, we ensured a minimum follow-up period of 6 months after discharge from the hospital. Inclusion criteria were age less than 60 days and a diagnosis of pyelonephritis, as defined by an upper urinary tract infection. Diagnosis was based on fever above 38 degrees or systemic symptoms such as vomiting, lethargy, irritability, poor feeding, or tachypnea, in association with a positive urine culture by a sterile technique (catheterization, clean-catch, or suprapubic aspirate). A culture was considered positive with $\geq 10^7$ cfu/L from a bladder catheter specimen, $\geq 10^8$ cfu/L from a clean-catch and $\geq 10^6$ cfu/L from a suprapubic aspirate (1,2). Exclusion criteria were the development of pyelonephritis in the hospital prior to the initial home discharge after birth, transfer from another hospital outside the city, severe comorbidities (congenital heart disease, metabolic disease, urinary tract instrumentation), and missing data.

Data collected in the electronic patient records included gestational age, antibiotic treatment during labour, symptoms, results of investigations, and type and duration of antibiotic therapy. The primary outcome was the percentage of pyelonephritis recurrence in the 2 months following the first episode with

regards to a shorter (<4 days) or a longer (≥ 4 days) IV antibiotic duration. This duration was based on the studies in older children where switch to oral antibiotics typically occurred by day 4 in the study group (1). It was assumed that patients would seek consultation at the same hospital since it is the only paediatric care centre in the area. In the literature, the duration of observation for the recurrence is variable but is generally between 4 and 6 weeks (1). We opted for a longer duration of 2 months after the first episode to insure a more complete follow-up. Persistent bacteriuria, another frequent outcome used to compare pyelonephritis treatments, could not be used as patients only had follow-up cultures if symptomatic. The secondary outcome was the percentage of pyelonephritis recurrence based on a total antibiotic duration of 10 days or 14 days, which are the most frequent antibiotic durations reported in the literature (1).

Data were managed and analyzed using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY). Descriptive statistics were performed for categorical and continuous variables. Descriptive data were reported as means and medians. Multivariable logistic regression was used to examine the association between the primary exposure variable and the odds of readmission for a UTI. Recurrence of pyelonephritis according to duration of antibiotic treatment was analyzed based on Pearson's chi-squared test.

RESULTS

Overall, we reviewed 160 patients; 108 were included, with a total of 48 under 30 days of age (Table 1). Fifty-two patients were excluded because they had not yet left the hospital after birth ($N=12$), had been transferred from another hospital ($N=7$), had severe comorbidities such as congenital heart disease or metabolic disease ($N=5$), had insufficient chart information ($N=6$), or did not meet criteria for a urinary tract infection ($N=12$). Boys represented 75.9% of infants. Most patients (82.4%) were febrile during their illness. The mean duration of fever during antibiotic therapy was 12.6 hours. All patients were afebrile at the time of discharge. Four patients were admitted to the intensive care unit (ICU) in the setting of urosepsis with hemodynamic instability.

Table 2 shows the results of investigations. Urine specimens were collected by bladder catheterization in 91.6% of infants ($N=99$). The remaining were collected by clean-catch. Pyuria was present in 68.6% ($N=74$) of microscopic urinalysis, which was defined by ≥ 5 white blood cells/high-power field (HPF). In our population, 82.4% ($N=89$) of cultures were positive for *Escherichia coli*, with 34.8% ($N=37$) of them resistant to ampicillin and 3.4% ($N=4$) resistant to gentamycin. When nitrites were positive, *E coli* was responsible for 92.3% of pyelonephritis ($N=100$). On admission, the mean level of CRP was 35.8 mg/L and the mean level of leukocytosis was $14.4 \times 10^9/L$. Six patients (5.6%) had a concomitant bacteremia but

Table 1. Patient characteristics

	All subjects (0–60 days)	Neonates (0–30 days)
Number of patients	108	48
Mean age at admission, days (min-max)	33.4 (6–62)	18.5 (6–30)
Mean gestational age, weeks (min-max)	39.2 (35.6–41.3)	39.3 (35.6–41.3)
Gender, n/N boys (%)	82/108 (75.9)	42/48 (87.5)
Fever at any time during illness (n/N (%))	89/108 (82.4)	38/48 (79.2)
Mean duration of fever during antibiotic therapy, hours (95% CI)	12.6 (9.5–15.7)	8.1 (3.9–12.3)
Mean hospitalization stay, days (min-max)	3.7 (1–15)	4.1 (1–13)
Mean days of IV antibiotics	3.5 (0–14)	4.0 (0–14)
Intensive care unit admission, n/N (%)	4/108 (3.7)	1/48 (2.1)

none had associated meningitis on cerebrospinal fluid culture. Blood cultures revealed *E coli* in four patients while *Enterobacter aerogenes* and *Enterococcus faecalis* were each found in one patient. All bacteremic infants had a lumbar puncture.

A total of 106 patients (98%) had a renal/bladder ultrasound (RBUS), most of them in the first days of hospitalization. Hydronephrosis was present in 71 infants, nephronia in 7 infants, and multicystic kidney in 1 infant. None had a renal abscess. On voiding cystourethrography, 11.4% (N=12) of patients had grade 4 or 5 vesicoureteral reflux. Among them, only one patient had a recurrence of pyelonephritis in the 2 months following the first episode.

The median IV antibiotic therapy duration was 3.5 days (0 to 14), with a longer duration of 4 days for infants under 30 days of age (0 to 14). Five patients had no IV antibiotics and received only oral antibiotics; one of them was under 1 month of age. Fifty-six patients had a shorter course of IV antibiotics while a 52 had a longer course. Among those, 24 were neonates aged less than 30 days. In fact, neonates were equally split between both groups (N=24 in each group). There was no statistical difference between both groups in terms of early recurrence of urinary tract infection (P=0.9).

The total antibiotic therapy duration was almost equally divided between 10 (N=49) and 14 days (N=53). Data were missing for six patients. With regards to nephronia (N=7), all patients were treated for 14 days, except for one who received over 3 weeks of antibiotics. The only patient with nephronia treated

Table 2. Investigations

	All subjects (0–60 days)	Neonates (0–30 days)
Culture technique, catheterization n/N (%)	98/107 (91.6)	45/48 (93.8)
≥5 WBC/HPF, n/N (%)	70/102 (68.6)	31/44 (70.5)
Nitrites, n/N (%)	26/105 (24.8)	18/47 (38.3)
Nitrites associated with <i>E coli</i> , n/N (%)	24/26 (92.3)	17/18 (94.4)
<i>E coli</i> , n/N (%)	89/108 (82.4)	40/48 (83.3)
Gentamycin-resistant <i>E coli</i> , n/N (%)	3/89 (3.4)	1/40 (2.5)
Ampicillin-resistant <i>E coli</i> , n/N (%)	31/89 (34.8)	10/40 (25)
Mean level of C-reactive protein on admission, mg/L (95% CI)	35.8 (26.4–45.2)	47.3 (27.8–66.9)
Mean level of WBC/HPF on admission, 10 ⁹ /L (95% CI)	14.4 (13.1–15.7)	15.3 (13.4–17.1)
Bacteremia, n/N (%)	6/97 (6.2)	4/45 (8.9)
Meningitis, n/N (%)	0/60 (0)	0/40 (0)
Nephronia, n/N (%)	7/106 (6.6)	2/48 (4.2)
Abnormal renal bladder ultrasound, n/N (%)	75/106 (70.8)	38/48 (79.2)
Grade IV-V vesicoureteral reflux, n/N (%)	9/79 (11.4)	3/38 (7.9)

CI Confidence interval.

for 10 days had a recurrence of pyelonephritis. Bacteremic patients (N=6) were all treated with IV antibiotics for at least 7 days. Four of those patients were less than 30 days of age.

For the primary outcome, the recurrence of pyelonephritis within 2 months was 9 % (N=5) in the group with a shorter IV antibiotic duration (<4 days), compared to 11% (N=6) in the group with a longer duration (≥4 days). There was no statistical difference between the two groups (P=0.75). The same trend was also seen in the neonatal period with a similar recurrence among patients treated with a shorter or longer IV therapy duration (P=1.0). Among all pyelonephritis recurrences, no pathogen was resistant to the oral antibiotic given as treatment. In our cohort, only one patient, a 55-day-old girl treated with IV antibiotics for 48 hours, had an early recurrence within 7 days of therapy as she presented with recurrent fever and a positive urine culture for the same organism (*E faecalis*). This patient was later found to have grade 3 vesicoureteral reflux. All other patients had late onset recurrence and most of them with a different organism, which suggests that treatment failure was very rare. Except for the one patient with an early recurrence,

all other patients presented with fever over 1 month following the initial pyelonephritis. None had an underlying renal malformation. All had been treated for at least 10 days for their initial urinary tract infection.

When comparing the total antibiotic duration, no statistical difference was observed as regards to recurrence. In fact, there was a 10.2% recurrence in the group treated for 10 days, compared to 11.5% in the group treated for 14 days ($P=1.0$). The same results were also observed in infants less than 1 month of age ($P=1.0$). Patient characteristics based on length of intravenous antibiotherapy (< 4 days or $\geq$ 4 days) are outlined in Table 3. Patients were equally divided between the two lengths of IV therapy.

DISCUSSION

This study provides observational retrospective data on the management of pyelonephritis in infants less than 60 days of age in a Canadian tertiary care centre. As mentioned previously, we defined pyelonephritis by a positive culture associated with other systemic symptoms such as fever, vomiting, lethargy, irritability, poor feeding, and/or tachypnea. Most studies in children over 2 months required the presence of fever to define pyelonephritis (1). However, we chose to include patients without fever but with systemic symptoms of infection since neonates with pyelonephritis appear more frequently with low-grade fever of shorter duration (or even hypothermia), whereas children present with higher temperature of longer duration. In this study, 79% of neonates presented fever. This is comparable to other studies where only 77 to 85% of neonates with urinary tract infections were febrile (5,6). Recent studies have outlined the accuracy of the urinalysis in young infants with urinary tract infections. Leukocyte esterase, nitrites, and pyuria

have been shown to have both an excellent sensitivity and specificity in infants 60 days and younger who presented urinary tract infections with and without associated bacteremia (7). In our cohort, pyuria (> 5 WBC/HPF) was present in approximately 70% of patients and nitrites in 25% of patients. As previously mentioned, we used a definition of pyelonephritis merely based on a positive urine culture. Therefore, we need to acknowledge that since urinalysis was not part of the criteria, infants with contaminated urines or asymptomatic bacteriuria and fever from a viral illness may have been misclassified as having a urinary tract infection.

With regards to the primary outcome, we found no significant difference in recurrence of pyelonephritis in the 2 months following the first episode for infants treated less than 4 days with IV antibiotic therapy compared to those treated for more than 4 days. Overall, both groups had similar numbers of recurrences ($P=0.75$). There was also no significant difference in recurrence with respect to total duration of treatment (10 days versus 14 days). Interestingly, results were similar for infants less than 30 days of age. As previously reported in other studies, *E coli* was the most common pathogen in our study (4).

Overall, 11 patients (10.2%) presented a second episode of pyelonephritis within 2 months of their initial presentation. This is similar to a prospective study in children aged 0 to 3 months in which a transition to oral treatment was made 48 hours after resolution of the fever, with a total treatment of 2 weeks. In fact, six patients (14%) had a recurrence of pyelonephritis at a mean time of 8 months following the first episode (4). In our cohort, only one patient had an early recurrence within 7 days due to an *E faecalis* infection. This patient presented with recurrent fever and a persistent positive urine culture. All other patients had a late-onset recurrence and

Table 3. Patient characteristics based on length of intravenous antibiotherapy

	< 4 days IV (N = 54)	$\geq$ 4 days IV (N=54)
Mean total antibiotherapy duration (range)	11.2 (10–14)	11.8 (10–25)
Mean IV antibiotherapy duration (range)	2.5 (0–3)	5.5 (4–14)
Gender, n/N boys (%)	42/54 (77.8)	40/54 (74.1)
Mean age at admission, days (min-max)	31.8 (6–60)	35.0 (8–60)
Mean hospitalization stay, days (min-max)	2.8 (1–15)	4.7 (1–14)
Fever at any time during illness, n/N (%)	34/54 (63.0)	41/54 (75.9)
Nitrites, n/N (%)	14/53 (26.4)	12/52 (23.1)
$\geq$ 5 WBC/HPF, n/N (%)	36/49 (73.5)	34/53 (64.2)
<i>E coli</i> + culture, n/N (%)	45/54 (83.3)	44/54 (81.5)
Normal ultrasound, n/N (%)	16/53 (30.2)	17/53 (32.1)
Hydronephrosis on ultrasound, n/N (%)	38/53 (71.7)	33/53 (62.3)
Nephronia on ultrasound, n/N (%)	1/53 (1.9)	6/53 (11.3)
Normal cystourethrography, n/N (%)	24/34 (70.6)	35/45 (77.8)
Grade IV-V vesicoureteral reflux, n/N (%)	3/34 (8.8)	6/45 (13.3)

most of them with a different organism, which suggests that treatment failure was rare.

While many studies have clearly established the safety of oral treatment for older children, far less evidence is available on the management of pyelonephritis in young infants (8). A recent CPS position statement on the management of urinary tract infections insisted that further research was needed with regards to the management strategies for infants less than 60 days of age. Data are therefore lacking regarding outpatient therapy for those infants (9). Other studies have looked at outcomes in young infants with bacteremic urinary tract infection (7) and have showed heterogeneity in the management of infants. Substantial variation in clinical practice was also reported in the practice of paediatric emergency physicians (10). The contribution of our data lies with a well-defined population of infants less than 60 days of age and a subgroup of neonates (<30 days) for whom no data have been published with regards to transition to oral antibiotics.

This study has some limitations related to its retrospective nature. A first limitation is the decision to use the recurrence of pyelonephritis as the marker of treatment failure. However, this is a frequently used outcome in other studies (1). Second, we took into consideration that patients would come back to the same tertiary care centre if they had a recurrence of pyelonephritis since it is the only paediatric centre in the area. We have to acknowledge that some patients could have sought care at another hospital outside the city or at an outpatient clinic. In order to minimize such limitation, we excluded patients transferred from another hospital outside the city. We also reviewed the provincial database to ensure those children had not received outpatient care (review of all urinalysis and urine cultures). As previously mentioned, since urinalysis was not part of the criteria, infants with contaminated urines or asymptomatic bacteriuria and fever from a viral illness may have been misclassified as having a urinary tract infection. Third, the study was not randomized and physicians may have treated patients who were initially sicker more aggressively. Another limitation is the duration of observation for recurrences after the first episode. This duration is variable among studies, usually between 4 and 6 weeks (1). Despite the retrospective nature of this study, the results were consistent with those reported recently for children over 60 days of age. Based on our data, it appears that an initial IV antibiotic treatment

duration of <4 days is safe in neonates with clinical improvement. This is certainly advantageous because oral therapy is more convenient and does not require hospitalization, thereby reducing costs (1). From a practical point of view, it remains to be better determined which infants with pyelonephritis may benefit from such early oral transition to antibiotics. Our retrospective study lacks the statistical power to make such recommendation and prospective data with a larger cohort of patients is necessary given this common infection in infants less than 60 days of age.

Therefore, our study provides limited retrospective data regarding the management of pyelonephritis in infants under 60 days of age. Prospective data are required to ascertain our findings and determine the safety of a transition to oral antibiotic therapy following a short IV antibiotic treatment, especially for neonates aged less than 30 days.

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