

# Effective Duration of Antimicrobial Therapy for the Treatment of Acute Lobar Nephronia

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## ABSTRACT

**OBJECTIVE.** Effective treatment of acute lobar nephronia (ALN) can prevent its progression to renal abscess. The goal of this prospective study was to compare the treatment efficacy for pediatric patients who had ALN with a 3- vs 2-week intravenous plus oral antimicrobial-therapy regimen.

**METHODS.** Patients who were suspected of having an upper urinary tract infection underwent a systematic scheme of ultrasonographic and computed tomographic (CT) evaluation for ALN diagnosis. Patients with positive CT findings were enrolled and randomly allocated with serial entry for either a total 2-week or a 3-week antibiotic treatment regimen. Antibiotics were changed from an intravenous form to an oral form 2 to 3 days after defervescence of fever. Follow-up clinical evaluations and urine-culture analyses were performed 3 to 7 days after cessation of antibiotic treatment. Patients with persistent infection or relapse were considered as treatment failures.

**RESULTS.** A total of 80 patients with ALN were enrolled. Forty-one patients were treated with a 2-week antimicrobial protocol, and the other 39 patients were treated with a 3-week course. Seven treatment failures, 1 persistent infection, and 6 infection relapses were identified, all of which were in the 2-week treatment group. Prolonged fever before admission and positive *Escherichia coli* growth ( $>10^5$  colony-forming units per mL) in urine culture were noted as risk factors for treatment failure. All treatment failures were managed successfully with an additional 10-day antibiotic course.

**CONCLUSION.** A total of 3 weeks of intravenous and oral antibiotic therapy tailored to the pathogen noted in cultures should be the treatment of choice for pediatric patients with ALN.

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### Key Words

acute focal bacterial nephritis, antibiotic treatment, treatment failure, efficacy evaluation, CT scan

### Abbreviations

UTI—urinary tract infection  
ALN—acute lobar nephronia  
APN—acute pyelonephritis  
CT—computed tomography  
VCUG—voiding cystourethrography  
cfu—colony-forming unit(s)  
VUR—vesicoureteral reflux

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**T**HE CLINICAL SEVERITY of acute renal bacterial infection spans continuously from an uncomplicated lower urinary tract infection (UTI) to frank abscess formation.<sup>1</sup> Among this suite of renal inflammatory diseases, acute lobar nephronia (ALN), also known as acute focal bacterial nephritis, has been diagnosed with ever-increasing frequency in patients, as a result of the advancement of noninvasive imaging-technique modalities.<sup>2</sup> ALN presents as a localized nonliquefactive inflammatory renal bacterial infection, which typically involves 1 or more lobes.<sup>3,4</sup> It has previously been indicated as a complicated form of acute renal infection, representing the progression of the inflammatory process of acute pyelonephritis (APN).<sup>5</sup> ALN may also represent a relatively early stage of the development of renal abscess.<sup>6</sup> The typical clinical presentations of ALN include fever, flank pain, leukocytosis, pyuria, and bacteriuria, which are similar to those with renal abscess or APN.<sup>1,3</sup>

Sonographically, ALN generally presents as severe nephromegaly or a poorly defined, irregularly margined focal mass with hyper-, iso-, or hypoechogenicity, depending on the temporal sequence of the lesions and the resolution of the disease.<sup>7,8</sup> Although renal ultrasonography has been considered the best and most effective screening method, various false-positive and false-negative findings have been reported previously.<sup>1,9</sup> Computed tomography (CT), instead, is currently recognized as the most sensitive and specific imaging modality for diagnosing ALN.<sup>1,2,4,7,10</sup> CT images of the ALN-infected areas typically appear as wedge-shaped, poorly defined regions of decreased nephrogenic density after contrast medium administration<sup>1,4,7</sup> and as mass-like hypodense lesions in the more severe form.<sup>11</sup> CT, however, is costly and requires the sedation of a young patient. We recently developed a systematic imaging work-up scheme using ultrasonography screening followed by CT. With this scheme, not only the efficacy of CT performance but also the sensitivity of overall diagnosing of ALN seems to be improving.<sup>12</sup>

Treatment for patients with ALN generally requires intravenous and oral antibiotic medication as does treatment for uncomplicated APN.<sup>3,7,10</sup> Surgical intervention is rarely needed for patients with ALN, except for those with concomitant urologic abnormalities, which may increase the risks for occurrence of acute bacterial infection.<sup>2</sup> Although it has been suggested that the treatment duration for ALN needs to be at least the same as that for uncomplicated APN, recommendations for the duration of antibiotic treatment still remains somewhat inconclusive, and to the best of our knowledge, for neither condition has a rigorous therapeutic efficacy comparison of relevant medication been performed.<sup>7</sup>

In this study, we sought to determine the appropriate duration of effective antibiotic therapy for the treatment of pediatric patients with ALN. Patients who first presented with febrile UTI and who later received a diag-

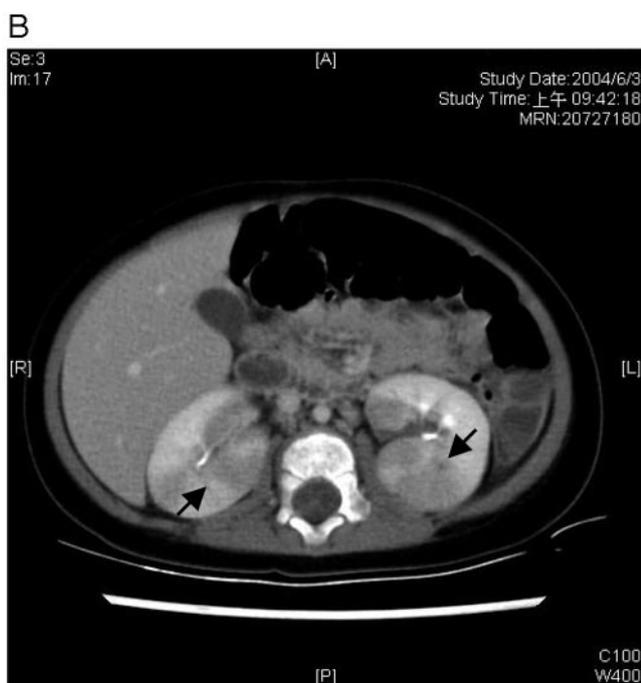
nosis with positive CT findings of ALN were entered into this study for receiving either a 2- or 3-week intravenous and oral antibiotic-therapeutic program. The demographic data and clinical results of these patients are compared herein. In addition, the identification of any clinical or laboratory factors that are likely associated with treatment failure was also attempted.

## METHODS

This prospective study commenced in January 2003 and ended in December 2004 in the 2 tertiary medical centers located in the city of Taipei and its suburb in northern Taiwan. During this period, patients who were admitted to the division of pediatric nephrology at the National Taiwan University Hospital or Chang Gung Children's Hospital and who later received a diagnosis of ALN were recruited into this study. All patients who were suspected of having a UTI (ie, who had pyuria [ $>5$  white blood cells/high-power field] and fever without focus or any symptoms/signs related to UTI, eg, knocking pain, dysuria, and frequency) underwent renal ultrasonography during the first to second days after their admission to hospital. The CT assessment followed immediately when the initial ultrasonographic findings met either 1 of these 2 criteria: evidence of (1) unilateral or bilateral nephromegaly and (2) a focal renal mass. For children who presented with borderline nephromegaly ultrasonographically, CT was performed when the patient remained febrile for 72 hours subsequent to commencement of antibiotic treatment.<sup>12</sup> ALN diagnosis was made on the basis of positive CT findings (Fig 1).<sup>1,2,4,5,7,13</sup> CT examinations were performed in both hospitals, using a GE spiral scanner (GE Medical Systems, Milwaukee, WI) with the use of an 8-mm section thickness and at 1-cm intervals. Unenhanced scanning was followed by intravenous contrast medium-enhanced scanning for every patient. Radionuclide scans, such as technetium 99m-dimercaptosuccinic acid scintigraphy that may be used to measure kidney function, were not included for ALN diagnosis.

Most of the patients who were evaluated in this study underwent voiding cystourethrography (VCUG) after complete treatment, except for girls who were older than 5 years and presented with a first episode of UTI and also for a few patients whose parents refused the procedure. All patients underwent urinalysis and urine and blood cultures. All isolates were identified using standard methods for bacterial culture. A minimum of  $10^5$  colony-forming units (cfu) per mL pathogens isolated from freshly voided midstream urine or urine collected by urinary bag and any bacteria isolated from the urine of suprapubic aspirations were considered to be positive results.

All patients with ALN, randomly allocated with serial entry, received intravenous and oral antibiotic treatment for either a total of 3 weeks or a period of 2 weeks



**FIGURE 1** Characteristic precontrast (A) and contrast-enhanced (B) CT scans for an 8-month-old patient who had ALN and presented with severe bilateral nephromegaly but without a focal mass sonographically. No attenuation area is seen in the kidney before enhancement.

instead. Informed consent was obtained from the parents or closest house members of admitted patients with ALN about the treatment duration and follow-up plan before this study. Intravenous antibiotics were shifted to an oral form 2 to 3 days after defervescence of fever. The particular choice of antibiotics was made on the basis of

the sensitivity findings of the initial urine culture. Follow-up urine cultures were checked 3 to 7 days after cessation of antibiotic treatment for all patients. Treatment failure was denoted by persistent infection or relapse.<sup>14</sup> Persistent infection was indicated by a failure to eradicate the bacterial organism as evidenced by continued positive urine culture or the recurrence of clinical symptoms, such as fever, and flank pain during the treatment course. Relapse was defined as initial bacteriologic cure followed by the recurrence of symptoms and infection with the same organism (as determined by strain, biotype, or the same antibiotic sensitivity pattern) as was the case previously.

All medical records were checked by both pediatric nephrologists, and patient compliance was ensured by close follow-up. In addition, all patients were followed up monthly to assess their clinical symptoms, urine culture results, and renal size by ultrasonography until complete recovery had been achieved.

Statistical comparison of nonparametric continuous data among or between the different treatment subgroups was performed by 1-way analysis of variance followed by application of the Student's *t* test. For comparison of nominal data,  $\chi^2$  analysis or Fisher's exact test was performed where appropriate. Difference between test groups was considered to be statistically significant at  $P < .05$ .

## RESULTS

A total of 80 patients with CT-diagnosed ALN were identified at these 2 pediatric tertiary centers within this study period. Among these, 41 patients underwent a 2-week antibiotic treatment protocol, and the remaining 39 patients were treated with a 3-week antibiotic-therapeutic regimen.

These 2 treatment groups had similar demographic data and clinical results (Table 1). Most of the patients had been febrile for ~3 to 4 days, ranging from 1 day to 2 weeks or so, before admission. Once patients had been admitted, all responded well to the initial antibiotic treatment regimen, and the fever generally subsided within ~1 week. Initial leukocyte count, leukocytosis proportion (percentage), and C-reactive protein values were statistically similar between these 2 treatment groups. CT scans indicated that 18 patients had left ALN, 12 had right ALN, and 11 had bilateral ALN in the 2-week treatment group. Corresponding figures for the 3-week treatment group were 16, 12, and 11 patients, respectively. The distribution of these ALN diagnoses was similar between the 2 treatment groups.

A total of 19 patients, 9 from the 2-week treatment group and 10 from the 3-week treatment group, presented with no apparent organism that could be isolated from urine culture. In addition to *Escherichia coli*, pathogens that were isolated from urine cultures included *Klebsiella pneumoniae* in 1 patient who was treated with the 2-week antibiotic course and *Pseudomonas aeruginosa*

**TABLE 1 Clinical and Laboratory Data for 80 Children With ALN**

	2-wk Treatment Group (n = 41)	3-wk Treatment Group (n = 39)	P
Age, mean ± SD, y	3.72 ± 4.14	4.16 ± 4.22	NS
Range	4 mo–16 y	4 mo–14 y 8 mo	
Girls, n (%)	24 (58.5)	23 (59.0)	NS
Fever duration before admission, d, mean ± SD	3.90 ± 3.06	3.97 ± 2.72	NS
Range, d	1–14	1–13	
Fever continuation following antibiotic treatment, mean ± SD, d	2.73 ± 1.28	3.43 ± 2.05	NS
Range, d	1–7	1–8	
WBC count, mean ± SD, cells per $\mu\text{L}$	19 107 ± 8772	19 600 ± 10 212	NS
Leukocytosis (>15 000 WBC/ $\mu\text{L}$ ), n (%)	28 (68.3)	25 (64.1)	NS
C-reactive protein, mean ± SD, mg/L (reference: <5)	137.7 ± 98.1	119.3 ± 74.0	NS
Urine culture, n (%)			
<i>E coli</i>	31 (75.6)	28 (71.8)	NS
<i>E coli</i> >10 <sup>5</sup> cfu/mL	25 (61.0)	25 (64.1)	NS
<i>K pneumoniae</i>	1 (2.4)	0 (0)	
<i>P aeruginosa</i>	0 (0)	1 (2.6)	
No isolatable organism	9 (22.0)	10 (25.6)	NS
Blood culture, n (%)			
<i>E coli</i>	1 (2.4)	2 (5.1)	
<i>S aureus</i>	0 (0)	1 (2.6)	
No isolatable organism	40 (97.6)	36 (92.3)	NS
Treatment failure	7 (17.1)	0 (0)	0.01

NS indicates not significant; WBC, white blood cell.

in 1 patient in the 3-week treatment group. Pyuria was commonly noted in individuals from both treatment groups. Positive blood cultures were noted in 4 patients: 1 from the 2-week treatment group with *E coli* infection and 3 others from the 3-week treatment group who demonstrated *E coli* (n = 2) and *Staphylococcus aureus* (n = 1) infection.

Sixty-nine patients with ALN, 40 from the 2-week treatment group and 29 from the 3-week treatment group, underwent VCUG evaluation. Sixteen (40%) patients in the 2-week treatment group and 11 (38%) in the 3-week treatment group had vesicoureteral reflux (VUR). Among the patients with VUR, a grade 3 or greater was noted in 8 and 9 patients, respectively, who were treated by the 2-week and the 3-week antibiotic courses. For patients who underwent VCUG, no difference regarding the presence of VUR in either frequency or severity was found between the 2 treatment groups.

Overall, treatment failure was noted in 7 patients in this study (8.8%; 95% confidence interval: 2.6–14.9%), all of whom had been treated by a 2-week antibiotic course (17.1%; 95% confidence interval: 5.6–28.6%). Statistical significance was noted in regard to treatment success rate between these 2 groups (P = .01). Among these patients with treatment failure, 1 demonstrated persistent infection during the treatment course, and 6 others were considered to have relapse by a positive *E coli* urine culture with the same antibiotic sensitivity profile as had been the case previously. One patient with relapse also presented with a high fever and another with a mild fever and a poor appetite at the time of follow-up examinations.

Table 2 lists the clinical characteristics of these 7 patients as compared with those who were treated successfully with the 2-week antibiotic course. Proportionally more girls may be noted in the failure group than in the nonfailure group, but the difference was not statistically significant (P = .21). The patients whose 2-week antibiotic treatment failed presented with a more pronounced fever duration before admission (6.00 ± 5.54 vs 3.47 ± 2.16 days; P = .04), and they were more likely to have *E coli* infection (>10<sup>5</sup> cfu/mL; 100% [7 of 7] vs 52.9% [18 of 34]; P = .03). The distribution of ALN foci, VCUG characteristics, and other clinical results revealed no difference between the failure and nonfailure groups.

For the patients whose treatment failed, the antibiotic treatment course was extended/restarted for an additional 10 days. Subsequent urine culture and clinical symptom evaluation at the follow-up examinations revealed eventual successful treatment. All 80 patients underwent regular ultrasonographic follow-up each month after treatment, and all focal masses within or nephromegaly findings for the affected kidneys normalized 3 to 4 months after treatment. No renal abscess development was noted.

## DISCUSSION

Since the first description of ALN as reported by Rosenfield et al<sup>9</sup> in 1979, the condition has subsequently also been described in a number of other studies.<sup>3,11</sup> ALN is a nonsuppurative focal form of acute bacterial infection, generally affecting 1 or more renal lobules,<sup>3,4,9,10</sup> and is considered to be a midpoint in the spectrum of upper UTI, a spectrum ranging from uncomplicated pyelone-

**TABLE 2** Comparison of Demographic Data, Clinical Characteristics, and Laboratory Results Between the Patients Who Had ALN and Whose Treatment Failed and Those With Treatment Success for the 2-Week Antibiotic-Therapy Protocol

	Failures With 2-wk Treatment Protocol (n = 7)	Nonfailures With 2-wk Treatment Protocol (n = 34)
Age, mean ± SD, y	4.07 ± 4.31	3.65 ± 4.16
Range	4 mo–9 y	4 mo–16 y
Girls, n (%)	6 (85.7)	18 (52.9)
Fever duration before admission, mean ± SD, d <sup>a</sup>	6.00 ± 5.54	3.47 ± 2.16
Range, d	1–14	1–10
Fever continuation after antibiotic treatment, mean ± SD, d	2.14 ± 1.21	2.85 ± 1.28
Range, d	1–4	1–7
WBC count, mean ± SD, cells per $\mu\text{L}$	22 257 ± 8656	18 459 ± 8781
Leukocytosis (>15 000 WBC per $\mu\text{L}$ ), n (%)	6 (85.7)	22 (64.7)
C-reactive protein, mean ± SD, mg/L (reference: <5)	107.3 ± 113.3	143.4 ± 95.9
<i>E coli</i> in urine culture, n (%)	7 (100)	24 (70.6)
<i>E coli</i> >10 <sup>5</sup> cfu/mL, n (%) <sup>b</sup>	7 (100)	18 (52.9)

WBC indicates white blood cell.

<sup>a</sup>P = .04.

<sup>b</sup>P = .03.

phritis to intrarenal abscesses.<sup>7</sup> Considering this dynamic nature of UTI, ALN may progress to renal abscess if left untreated. Hence, it is extremely important to differentiate ALN from intrarenal abscess, not only because these 2 conditions are pathologically different but also because they may be best managed differently. Surgical drainage may be required for most cases of intrarenal abscesses, whereas ALN, like APN, necessitates only antibiotic management. However, the optimal duration of antibiotic therapy for children with ALN has yet to be determined.

To the best of our knowledge, we found only 17 pediatric ALN reports<sup>2,4-7,9,10,13,15-23</sup> in the English-language literature. The treatment methods adopted for the total of 70 pediatric patients with ALN as reported in these studies, if they were mentioned, all consisted of antimicrobial-therapy regimens but of varying duration. Additional surgical procedures have been reported to correct the associated conditions such as high-grade VUR<sup>2</sup> but not for ALN itself. Mixed treatment outcomes were reported for pediatric cases of ALN in these studies; some patients recovered from this severe inflammatory process, whereas others led to frank abscess formation. In general, a total of 2 to 3 weeks of antimicrobial therapy tailored to the urinary pathogen is recommended for patients with ALN.<sup>2,4,7,8,10</sup> By contrast, uncomplicated APN was likely to be managed with a 10- to 14-day course of antibiotic treatment.<sup>24</sup>

Most of our patients with ALN presented with non-specific findings of fever and flank or abdominal pain. Pyuria, leukocytosis, and elevated C-reactive protein also usually were found. Some patients presented only with fever and had minimal symptoms such as vague flank discomfort, malaise, or even no urinary symptoms and, rarely, a few patients may have no pyuria and

negative urine cultures. Clinical or laboratory differential diagnosis of ALN from APN and renal abscess may not be possible; however, CT scanning seems to be the most sensitive and specific means of diagnosing ALN.<sup>1,2,4,7,10</sup> ALN is not a rare condition. It is probably an underdiagnosed disease entity. The characteristic appearance of a focal mass in the kidney with poorly defined margins is the hallmark of the ultrasonographic findings for ALN.<sup>2,7,8,10</sup> Unfortunately, however, the sensitivity of this ultrasonographic characteristic for ALN diagnosis is probably not satisfactory,<sup>12</sup> and it is likely that such a notion results in the CT underdiagnosis of ALN; thus, very few reports of pediatric ALN seem to have been published in the literature.

Herein, we have proposed a systematic imaging evaluation scheme for patients with febrile UTI, the scheme being a combination of renal ultrasonography and CT scanning, for ALN detection even in the relative early stages of the condition.<sup>12</sup> Among the 30 patients with ALN in the 2004 retrospective study reported by Cheng et al,<sup>12</sup> all were treated successfully with a 3-week pathogen-sensitive antibiotic protocol. This finding intrigues us and encourages us to evaluate further, prospectively, as in this study, the relative efficacy of a 3-week antibiotic-therapy protocol for ALN as compared with the 2-week therapy commonly used for APN, although, reportedly, ALN is a more severe parenchymal inflammatory disease than APN.<sup>5</sup> In addition, to the best of our knowledge, the current study is the largest series of pediatric ALN reported on to date, and the results of our study highlight the optimal treatment duration and the specific risk factors associated with treatment failure.

Among the 80 patients in this study, *E coli* was the most common pathogen cultured from the patient urine samples (59 of 61), which is consistent with the results

of previous studies.<sup>2,4,5,7,8</sup> It is interesting that the proportion (percentage) of *E coli* cultured in cases of ALN seems to be much greater than the corresponding figure reported for first-time UTIs.<sup>25</sup> Bacteremia has been reported for approximately one third of the patients in the smaller ALN group studies,<sup>3,9</sup> but it was only rarely noted in the 2 larger pediatric ALN series.<sup>2,10</sup> The incidence of bacteremia in our study was low: only 4 (5%) of the study's 80 patients proved to have bacteremia.

None of our patients revealed any evidence of underlying diseases such as diabetes or immunodeficiency; neither did any feature structural abnormality of the urinary tract system, such as neurogenic bladder, or upper or lower urinary tract obstruction apart from VUR. Reflux was noted in ~40% of the children with ALN in this study, a figure comparable to that in several previous studies.<sup>2,4,10</sup> This frequency of VUR among patients with ALN is close to that in children with UTI<sup>26</sup>; thus, VUR may not be a necessary prerequisite for the development of ALN.

From our results, all patients who had ALN and received the 3-week antibiotic course were treated successfully, whereas 7 treatment failures (17.1% of treated patients) were noted in the 2-week treatment group. This observation suggests that the 2-week antibiotic treatment, usually scheduled for APN, may not be appropriate for the treatment of ALN. Patients whose 2-week treatment modality failed were more likely to have prolonged fever before admission and to reveal positive *E coli* infection (>10<sup>5</sup> cfu/mL). The longer febrile history before admission may suggest that these patients may be prone to develop a more severe disease state than their counterparts and that, by necessity, a longer antibiotic treatment course will be needed for such individuals. Indeed, these treatment failures all were dealt with successfully by an additional 10-day antimicrobial-therapy regimen. The association between positive *E coli* infection (>10<sup>5</sup> cfu/mL) leading to ALN and 2-week treatment failure seems to be worth additional investigating. Whether host factors or the virulence of *E coli* relates to ALN and plays a role leading to treatment failure remains uncertain currently, and this remains an issue that should be clarified.

## CONCLUSIONS

It is impractical for clinicians to determine the optimal duration of antibiotic treatment variably, on a case-by-case basis. Also, additional hospital stays and laboratory analyses for 2-week treatment failures may increase unnecessary medical costs for the treatment of ALN. Henceforth, we suggest that a 3-week antimicrobial-therapy protocol should constitute the treatment of choice for all radiographically documented patients with ALN.

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