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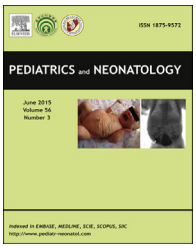

ORIGINAL ARTICLE

Comparison of Acute Lobar Nephronia and Acute Pyelonephritis in Children: A Single-Center Clinical Analysis in Southern Taiwan

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Key Words
acute lobar nephronia;
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Background: Patients with acute lobar nephronia (ALN) require a longer duration of antimicrobial treatment than those with acute pyelonephritis (APN), and ALN is associated with renal scarring. The aim of this study was to provide an understanding of ALN by comparing the clinical features of pediatric patients with ALN and APN.
Methods: We enrolled all of the patients with ALN (confirmed by computed tomography) admitted to our hospital from 1999 to 2012 in the ALN group. In addition, each patient diagnosed with APN who was matched for sex, age, and admission date to each ALN patient was enrolled in the APN group. The medical charts of patients in these two groups were retrospectively reviewed and analyzed for comparison.
Results: The fever duration after hospitalization in the ALN group and the APN group were 4.85 ± 2.33 days and 2.30 ± 1.47 days respectively. The microbiological distributions and

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the majority of susceptibilities were similar in the ALN and APN groups. The majority of clinical manifestations are nonspecific and unreliable for the differentiation of ALN and APN. The patients with ALN were febrile for longer after antimicrobial treatment, had more nausea/vomiting symptoms, higher neutrophil count, bandemia, and C-reactive protein (CRP) levels, and lower platelet count (all $p < 0.05$). In multivariate analysis, initial CRP levels, nausea/vomiting symptoms, and fever duration after admission were independent variables with statistical significance to predict ALN. Severe nephromegaly occurred significantly more in the ALN group than in the APN group ($p = 0.022$).

Conclusion: The majority of clinical manifestations, laboratory findings, and microbiological features are similar between patients with ALN and APN. Clinicians should keep a high index of suspicion regarding ALN, particularly for those with ultrasonographic nephromegaly, initial higher CRP, nausea/vomiting, and fever for > 5 days after antimicrobial treatment.

1. Introduction

The clinical severity of acute renal bacterial infections range from uncomplicated lower urinary tract infections (UTI) to frank abscess formation.[1] Among these renal inflammatory diseases, acute lobar nephronia (ALN), also known as acute focal bacterial nephritis, is a nonsuppurative focal form of acute bacterial infection, generally affecting one or more renal lobules. The reported incidence of ALN has increased as a result of advancements in noninvasive imaging techniques,[2–5] of which renal ultrasonography is considered to be the best and most effective screening method. Computed tomography (CT) is currently recognized as the most sensitive and specific imaging modality to diagnose ALN,[1,3,4,6–9] which typically appears as wedge-shaped, poorly defined regions of decreased nephrogenic density after contrast medium administration and as mass-like hypodense lesions in the more severe form.[1,7,8,10]

The clinical presentations and laboratory findings are similar between patients with ALN and acute pyelonephritis (APN), and differentiation of ALN and APN is not easy in the early stage of illness.[5] However, effective antimicrobial therapy for the treatment of ALN generally requires a longer duration than treatment for uncomplicated APN, indicating the importance of an adequate diagnosis.[6,8,11] In addition, ALN may also represent a relatively early stage of the development of a renal abscess, and ALN is associated with a very high incidence of renal scarring.[6,12,13] Clinicians should therefore have a high index of suspicion of ALN in patients with UTI. In this study, we reviewed and compared the clinical presentations, microbiological findings, and imaging results of patients with ALN and APN in our hospital from 1999 to 2012. The aim of this study was to provide an understanding of ALN in children by comparing the clinical manifestations, laboratory findings, imaging results, common pathogens, and their antimicrobial susceptibilities, treatments, and outcomes of pediatric patients with ALN and APN.

2. Methods

We retrospectively evaluated the medical records of 1039 pediatric patients (age $\leq$ 18 years) hospitalized for UTI from January 1999 to December 2012 at our hospital, a 1700-bed medical center in southern Taiwan providing both primary and tertiary medical care. The majority of patients received renal ultrasound or technetium-99m-labeled dimercaptosuccinic acid (DMSA) renal scanning within 3 days of admission. CT was performed when the patients had a focal renal mass on renal ultrasound, or remained febrile for 72 hours after susceptible antimicrobial treatment for upper UTI as localized by DMSA or renal ultrasound. Renal size was recorded by renal ultrasound, and the normal sonographic values of kidney sizes among Taiwanese children were adapted from the study by Chu et al.[5,14] Severe nephromegaly was defined as a kidney size 3 standard deviations larger than the mean.

The definition of ALN was based on positive CT findings after contrast medium administration. Patients with trauma, previous renal surgery, malignancy, and other concomitant diagnoses that may have caused a fever, such as acute gastroenteritis and balanoposthitis, were excluded. In total, 80 patients fulfilled the enrollment criteria of ALN, and all of them were enrolled in the ALN group. In addition, each patient diagnosed with APN who was matched for sex, age, and admission date to each ALN patient was enrolled in the APN group. The definition of APN was based on the admission diagnosis of UTI combined with pelvic wall thickening and renal enlargement seen in renal ultrasound, or the presence of focal or diffuse areas of decreased uptake of DMSA without evidence of cortical loss, or by the presence of diffusely decreased uptake in an enlarged kidney. The medical records of all patients in both groups were retrospectively reviewed with regard to their demographic characteristics, clinical presentations, laboratory findings, microbiological features, imaging results, treatment, and outcomes.

The attending physicians made all decisions regarding antimicrobial therapy, either prior to or after the results of susceptibility tests. Renal sonography and DMSA renal scans were performed as soon as possible after hospitalization, usually within 3 days of admission. After complete treatment, radionuclide cystography or voiding cystourethrography was arranged for vesicoureteral reflux (VUR) studies. Radiologists and nuclear medicine physicians reviewed the imaging results.

All statistical analyses were performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). We compared laboratory and clinical parameters to differentiate ALN from APN in univariate and multivariate analysis. The data are reported as the mean ± standard deviation where appropriate. Statistical comparisons of continuous data between the different groups were performed using an independent samples *t* test. For comparisons of nominal data, χ^2 or Yate's continuity correlation analysis was performed where appropriate. Stepwise logistic regression was used for multivariate analysis including significant variables ($p < 0.05$) in univariate analysis. A binary logistic regression analysis model was employed to estimate adjusted odds ratios (aOR) and corresponding 95% confidence intervals (CI) to compare ALN and APN in relation to clinical and laboratory variables.

3. Results

In total, among the 1039 pediatric patients who were diagnosed as having UTI during the study period, 160 patients (80 with APN and 80 with ALN) were included in this study. The demographic characteristics and clinical data of the patients in these two groups are summarized in Table 1. CT scans indicated that 33 patients had right ALN, 21 patients had left ALN, and 26 patients had bilateral ALN. Of the patients with ALN, 17 had complicated ALN on CT, as seen by lesions consistent with heterogeneously decreased nephrographic density after contrast medium enhancement. The other 63 patients had simple ALN on CT, which appeared as striated or wedge-shaped, poorly defined regions of homogenously decreased nephrographic density after contrast medium administration. Only one patient in the APN group received a CT scan, which revealed no evidence of ALN. The fever duration after hospitalization days in the ALN group was 4.85 ± 2.33 days. By contrast, the fever duration after hospitalization days in the APN group was only 2.30 ± 1.47 days. The patients with ALN were febrile for longer after hospitalization ($p < 0.001$) and had more nausea/vomiting symptoms ($p = 0.006$) than those with APN. A higher neutrophil count ($p = 0.047$), higher bandemia ($p = 0.034$), higher C-reactive protein (CRP) levels ($p < 0.001$), and lower platelet count ($p = 0.01$) were also noted for the patients diagnosed with ALN. The other demographic characteristics were similar between the two groups.

The microbiological findings and imaging results between the two groups are summarized in Table 2. Urine cultures were performed in 157 patients (79 in the ALN

Table 1 Comparison of demographic and clinical data between the children with acute lobar nephronia and acute pyelonephritis.

Characteristic	No. (%) of patients		*p*
	ALN group ($n = 80$)	APN group ($n = 80$)	
Age (y)	5.10 ± 4.97	4.87 ± 4.88	0.77
Females	64 (80)	64 (80)	1
Previous UTI	11 (14)	10 (13)	0.815
Fever duration before hospitalization (d)	3.09 ± 1.77	2.96 ± 2.93	0.74
Fever duration after hospitalization (d)	4.85 ± 2.33	2.30 ± 1.47	<0.001*
Hospitalization duration (d)	21.79 ± 11.55	8.94 ± 3.41	<0.001*
Clinical symptoms			
Fever	79 (99)	76 (95)	0.363
Nausea/vomiting	32 (40)	16 (20)	0.006*
Abdominal pain	24 (30)	17 (21)	0.205
Dysuria	12 (15)	15 (19)	0.527
Flank pain	8 (10)	11 (14)	0.463
Frequency	8 (10)	9 (11)	0.798
Diarrhea	6 (8)	4 (5)	0.744
Seizure	2 (3)	1 (1)	1.000
Shock	1 (1)	0	1.000
Laboratory data (serum)			
WBC, $\times 10^9$ cells/L	17.7 ± 7.2	15.6 ± 6.4	0.059
Segment, %	69.8 ± 14.2	64.7 ± 17.8	0.047*
Band, %	3.9 ± 6.5	2.0 ± 4.6	0.034*
CRP, mg/dL	16.34 ± 11.27	8.77 ± 8.75	<0.001*
Hemoglobin, g/dL	11.29 ± 1.36	11.69 ± 1.56	0.083
Platelet, $\times 10^{12}$/L	284.10 ± 96.53	327.64 ± 113.05	0.01*
Blood urea nitrogen, mg/dL	11.17 ± 4.75	11.08 ± 5.4	0.925
Creatinine, mg/dL	0.62 ± 0.33	0.59 ± 0.24	0.496

Data are mean ± standard deviation or *n* (%) of the indicated characteristic.
*$p < 0.05$.
ALN = acute lobar nephronia; APN = acute pyelonephritis; CRP = C-reactive protein; UTI = urinary tract infection; WBC = white blood cell count.

Table 2 Comparison of microbiological findings and imaging results between the children with acute lobar nephronia and acute pyelonephritis.

Characteristic	No. (%) of patients		*p*
	ALN group ($n = 80$)	APN group ($n = 80$)	
Microbial findings			
Urine culture	79 (99)	78 (98)	NS
No finding	30 (38)	35 (44)	NS
Escherichia coli	44 (55)	37 (46)	NS
Proteus mirabilis	1 (1)	3 (4)	NS
Klebsiella pneumoniae	2 (3)	0	NS
Pseudomonas aeruginosa	1 (1)	1 (1)	NS
Staphylococcus saprophyticus	1 (1)	0	NS
Streptococcus viridans	0	1 (1)	NS
Enterococcus aerogenes	0	1 (1)	NS
Morganella morganii	0	1 (1)	NS
Blood culture	80 (100)	78 (98)	NS
No finding	76 (95)	78 (98)	NS
E. coli	4 (5)	0	NS
Image findings			
Ultrasonographic findings*			
Severe nephromegaly	34 (44)	21 (27)	0.022
Severe nephromegaly without focal mass	25 (33)	21 (27)	NS
Severe nephromegaly with focal mass	9 (12)	0 (0)	NS
Focal mass without severe nephromegaly	9 (12)	0 (0)	NS
Neither severe nephromegaly nor focal mass	34 (44)	58 (73)	NS
Decreased uptake in DMSA†	71 (96)	67 (93)	NS
DRC or VCUG‡			
Normal	55 (82)	50 (77)	NS
Grade I—III VUR	6 (9)	8 (12)	NS
Grade IV—V VUR	6 (9)	7 (11)	NS

ALN = acute lobar nephronia; APN = acute pyelonephritis; DMSA = dimercaptosuccinic acid; DRC = radionuclide cystography; NS = not significant; VCUG = voiding cystourethrography; VUR = vesicoureteral reflux.

* Data were available in 77 patients in the ALN group and 79 patients in the APN group, severe nephromegaly was defined as a renal length of 3 standard deviations greater than the mean for age.

† Data were available in 74 patients in the ALN group and 72 patients in the APN group.

‡ Data were available in 67 patients in the ALN group and 65 patients in the APN group.

group and 78 in the APN group). Of these 157 patients, 65 (30 in the ALN group and 35 in the APN group) had no apparent organism that could be isolated from urine culture, and 92 had positive urine cultures. Among these 92 patients, *Escherichia coli* was the most common urinary pathogen ($n = 81$, including 44 in the ALN group and 37 in the APN group), followed by *Proteus mirabilis* ($n = 4$), *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* ($n = 2$ each), *Staphylococcus saprophyticus*, *Streptococcus viridans*, *Enterococcus aerogenes*, and *Morganella morganii* ($n = 1$ each). Only one patient with APN had urine cultures with mixed bacterial growth, composed of *E. coli* and *P. mirabilis*. Positive blood cultures were noted in four patients, all of whom were in the ALN group, and all were caused by *E. coli*.

Compared with the APN group, *E. coli* isolated from the urine cultures in the ALN group had a similarly high resistance rate to ampicillin (68% vs. 62%, $p = 0.57$), but a higher resistance rate to trimethoprim—sulfamethoxazole (59% vs. 27%, $p = 0.004$) and piperacillin (77% vs. 54%, $p = 0.027$). Although we used cefazolin and/or gentamicin as the empirical therapy for pediatric UTI from 2000,[15,16] the resistance rate to cefazolin (24% in ALN vs. 21% in APN, $p = 0.611$) and gentamicin (27% in ALN vs. 24% in APN, $p = 0.626$) did not increase significantly. Only three patients (2 in the ALN group and 1 in the APN group) with *E. coli* isolated from their urine cultures had resistance to both cefazolin and gentamicin. However, extended-spectrum β-lactamase (ESBL)-producing organisms were found in three *E. coli* isolations, including two in the ALN group and one in the APN group, all of which were isolated after 2010.

Among the 160 patients, 74 in the ALN group and 72 in the APN group underwent DMSA renal scans, and 77 patients in the ALN group and 79 in the APN group underwent renal sonography. There was no difference in the DMSA findings between the two groups ($p = 0.97$). When using the definition of severe nephromegaly to define ALN as a renal length of 3 standard deviations greater than the mean for age,[5] severe nephromegaly occurred significantly more frequently in the ALN group than in the APN group (34 patients vs. 21 patients, $p = 0.022$). A renal focal mass was

found sonographically in 18 patients in the ALN group. None of the patients had any evidence of underlying diseases such as diabetes or immunodeficiency, neurogenic bladder, or upper or lower urinary tract obstructions. Among the 160 patients in the two groups, 132 (67 in the ALN group and 65 in the APN group) underwent VUR studies after complete treatment, including 100 radionuclide cystography, 17 voiding cystourethrography, and 15 for both. Twelve (17.9%) patients in the ALN group and 15 (23.1%) patients in the APN group had VUR, among whom a Grade IV or greater was noted in six patients in the ALN group and seven in the APN group. Most patients (84.6%, 11/13) who had severe VUR (Grade IV or V) were younger than 5 years. Among the patients who underwent VUR studies, no difference in either frequency or severity of VUR was found between the two groups.

All children received cefazolin and/or gentamicin initially, and treatment was modified according to culture results and clinical response. Sixty-seven children in the APN group received intravenous antibiotic treatment with cefazolin and/or gentamicin, compared to only 23 patients in the ALN group. The other 57 children in the ALN group received modified intravenous antimicrobial treatment, including cefazolin plus amikacin ($n = 27$), third generation cephalosporins ($n = 22$), and others ($n = 8$). There was no statistical difference in the number of hospitalization days between the patients receiving different antimicrobial regimens (cefazolin + gentamicin: 21.5 ± 13.2 days; cefazolin + amikacin: 22.9 ± 8.4; third generation cephalosporins: 18.8 ± 5.3days; other antibiotics: 22.8± 9.5 days; $p = 0.498$). The duration of hospitalization in the ALN group was 21.79 ± 11.55 days, with 21.34 ± 9.5 days of intravenous antimicrobial treatment. By contrast, the duration of hospitalization in the APN group was only 8.94 ± 3.41 days, with 7.96 ± 3.16 days of intravenous antimicrobial treatment. This difference was significant ($p < 0.001$). No cases of mortality were found in either group. Only one previously healthy 10-year-old girl progressed to septic shock after initial admission and was admitted to an intensive care unit for 3 days. She recovered well later after antimicrobial treatment.

Univariate analysis revealed statistically significant differences ($p < 0.05$) in fever duration after hospitalization, nausea/vomiting symptoms, segment, band, CRP, platelet, and severe nephromegaly in ultrasonographic findings between the ALN and APN groups. These independent variables were then used in stepwise logistic regression for multivariate analysis, and there were three independent variables with statistical significance to predict ALN in logistic multivariate analysis, which were initial serum CRP (aOR, 1.06; 95% CI, 1.02−1.10), nausea/vomiting symptoms (aOR, 2.65; 95% CI, 1.05−6.68), and fever duration after hospitalization (aOR, 2.07; 95% CI: 1.57−2.72).

4. Discussion

ALN was not uncommon in our series, with an incidence of 7.7% in patients with UTI, which is similar to a report by Cheng et al[9] conducted in northern Taiwan (8.6%). However, Yang et al[17] reported the incidence of ALN to be as high as 19.2% in children with a first-episode of febrile UTI. ALN is therefore not a rare condition, and it is probably an underdiagnosed disease entity.[18]

Whether ALN presents as an early stage of renal abscess is controversial.[5,6,9,12,13,19,20] However, the evolution of ALN into a renal abscess and an association with a very high incidence of renal scarring has been reported.[4,6,12,13,18] Therefore, it is extremely important to differentiate ALN from APN, not only because these two conditions are pathologically different, but also because ALN may be best managed by a longer duration of antimicrobial treatment than APN. In general, a total of 2−3 weeks of antimicrobial therapy tailored to the urinary pathogen is recommended for patients with ALN.[4,6−8,19,21] By contrast, uncomplicated APN has been reported to be best managed with a 10−14-day course of antimicrobial treatment.[22] Similar to the reports by Cheng et al[19] and Klar et al,[6] most young children in our series who were diagnosed with ALN presented with nonspecific symptoms such as vomiting, diarrhea, and abdominal pain, which could easily be thought to be associated with other more common diseases.[18] Dysuria was present in 12 patients, and moreover, specific symptoms such as flank pain were found only in older children with a mean age of 12.6 years, which highlights that routine urine examinations should be arranged for children with fever of unknown origin.

There were three independent variables with statistical significance to predict ALN in logistic multivariate analysis, including initial serum CRP, nausea/vomiting symptoms, and fever duration after hospitalization. However, these parameters are all nonspecific and unreliable for differentiation of infection sources, and, additionally, fever duration after hospitalization is not helpful for clinicians to make a decision upon admission of children. From this point of view, clinicians should keep a particularly high index of suspicion for complicated UTI, especially for those with initial higher CRP, nausea/vomiting symptoms, and longer duration of fever after antimicrobial treatment during hospitalization.

CT is considered the most sensitive and specific imaging modality for ALN.[1,4,6−8,19] However, it is expensive and requires sedation for young patients.[4,5] Sonography remains the initial study of choice because of its noninvasive nature, lack of ionizing radiation, and ability to detect inflammatory lesions and any congenital abnormalities.[5,8] In our series, severe nephromegaly occurred significantly more in the ALN group than in the APN group ($p = 0.022$). Similar to Cheng et al,[5] CT was not performed in our series for the majority of the APN group since they did not have a focal renal mass on sonography or their fever subsided after 72 hours of susceptible antimicrobial treatment. Since antimicrobial susceptibility tests usually take 48 hours, the findings are generally compatible with the modified recommendations from another study by Cheng et al[9] in that the use of CT can be reduced and limited to the patients with UTI, ultrasonographic nephromegaly, and a fever for > 5 days after antimicrobial treatment.

The microbiological distributions were similar in the ALN and APN groups. Among the 160 patients in this study, *E. coli* was the most common pathogen cultured from urine samples (81/92), which is consistent with the results of previous studies.[6,8,18,19] Bacteremia accounted for four (5%) of 80 episodes in our ALN group, which is similar to

other studies that reported rates of 4—6%.[6,18,19] The prevalence of ESBL-producing Enterobacteriaceae is increasing rapidly worldwide.[23] ESBL-producing organisms were found in three (3.7%) *E. coli* isolates in our study, and all were isolated after 2010. Similar to our ALN patients, a prevalence rate of 4.4% of ESBL-producing *E. coli* strains in UTI of infants aged < 4 months was reported in our hospital from 2001 to 2009.[15] It seems that ESBL *E. coli* is not related to severity of UTI. However, few samples of ESBL *E. coli* were present in our series. Therefore, further systemic studies are needed, as well as long-term follow-up.

The duration of treatment for ALN is controversial. A 2—3-week course of antimicrobial therapy has been suggested in recent prospective studies.[19,20,24] In our series, the majority (71%) of the ALN patients received modified intravenous antimicrobial treatment for an average of 21.3 ± 9.5 days, which led to a longer hospital stay. Further studies are warranted to elucidate the potential benefits of a longer or shorter duration of intravenous treatment for ALN.

In our series, the prevalence of VUR among the patients with ALN was similar to the previously reported prevalence of VUR among the patients with UTI in our hospital.[16] There was no difference in the frequency or severity of VUR between the ALN and APN groups in our series. As reported by Cheng et al,[19] VUR may not be a prerequisite for the development of ALN.

There are some limitations to this study that should be highlighted. Our data come from a single medical center in southern Taiwan, and therefore the results should not be applied generally because of geographic diversity. In addition, only one patient in the APN group received a CT scan, and the detailed condition of those who did not receive CT scans in the APN group is not clear. Twenty-one of the 80 APN cases in our study had severe nephromegaly on sonography, but without further CT data they were classified into the APN group based simply on their faster clinical response to antimicrobial treatment. This further highlights the difficulty for clinicians to differentiate ALN from APN without CT. Current knowledge on the clinical diagnosis of ALN is still limited, and further studies are warranted that should include long-term follow-up and more detailed imaging data such as CT scans. In addition, radionuclide cystography imaging was used for the diagnosis of VUR in the majority of our patients in the study. This method is unable accurately to delineate the detailed changes of the structure of the collecting system in order to grade appropriately, and it cannot perform correct VUR grading, both of which could affect the results.

In conclusion, ALN is not a rare condition. However, the majority of clinical manifestations are nonspecific and unreliable for the differentiation of ALN and APN. The microbiological distributions were similar in the ALN and APN groups. Cefazolin and gentamicin are still generally sensitive in both groups, although they have been the first-line empirical antimicrobial agents for > 1 decade. Clinicians should maintain a high index of suspicion towards ALN, particularly for those patients with ultrasonographic nephromegaly, initial higher CRP, nausea/vomiting symptoms, and a fever for > 5 days after receiving antimicrobial treatment during hospitalization.

Conflicts of interest

All authors have no conflicts of interest to report.

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