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Studies on Clinical Characteristics, Urovirulence Factor and Host Susceptibility Gene in Pediatric Acute Lobar Nephronia

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1. Introduction

Urinary tract infections (UTIs) have been described as one of the most common serious bacterial diseases affecting infants and young children. Approximately 3% of prepubertal girls and 1% of prepubertal boys are diagnosed with UTIs (Riccabona 2003; Ma and Shortliffe 2004). The clinical severity of acute renal bacterial infection spans continuously from an uncomplicated lower urinary tract infection (i.e. cystitis) to frank abscess formation (Soulen et al., 1989). Among these UTIs, renal parenchymal infections, including uncomplicated acute pyelonephritis (APN), acute lobar nephronia (ALN), and intrarenal abscess, are considered to be more serious forms of UTI.

Acute lobar nephronia (ALN), also known as acute focal bacterial nephritis, is an acute localized bacterial renal infection presenting as an inflammatory mass without liquefaction (Rosenfield et al., 1979; Zaontz et al., 1985; Kline et al., 1988; Klar et al., 1996; Uehling et al., 2000). The typical clinical presentations include fever, flank pain, leukocytosis, pyuria and bacteriuria, similar to presentations of patients with renal abscess or acute pyelonephritis (Zaontz et al., 1985; Soulen et al., 1989). It has previously been indicated as a complicated form of acute renal infection, representing the progression of the inflammatory process of APN (Nosher et al., 1988). ALN may also represent a relatively early stage of the development of renal abscess (Shimizu et al., 2005). The management of these renal parenchymal infections differs widely. Most patients with renal abscess require intensive medical therapy with or without surgical intervention, whereas treatment of those with ALN, like uncomplicated APN, entails only intravenous and oral antibiotics (Zaontz et al., 1985; Rathore et al., 1991; Klar et al., 1996). Hence it is important to differentiate these renal parenchymal infections. In this Chapter, we would like to review the diagnosis scheme, treatment modality, bacterial urovirulence factors, host susceptibility gene and the renal scar outcome of ALN.
2. Effective ultrasonographic predictor for the diagnosis of acute lobar nephronia

Sonographically, ALN generally presents as severe nephromegaly or a poorly defined, irregularly marginated focal mass with hyper-, iso- or hypoechogenicity, depending on the temporal sequence of the lesions and the resolution of the disease (Rathore et al., 1991; Boam and Miser, 1995). Although renal ultrasonography (US) has been considered as the best and most-effective screening method, various false positive and false negative findings have been reported previously (Rosenfield et al., 1979; Soulen et al., 1989). Computed tomography (CT), instead, has been currently recognized as the most-sensitive and -specific imaging modality for diagnosing ALN (Kline et al., 1988; Soulen et al., 1989; Rathore et al., 1991; Klar et al., 1996; Uehling et al., 2000). CT images of the ALN-infected areas typically appear as wedge-shaped, poorly defined regions of decreased nephrogenic density after contrast medium administration (Figure 2.1) (Kline et al., 1988; Soulen et al., 1989; Rathore et al., 1991; Cheng et al., 2004), and mass-like hypodense lesions in the more-severe form (Lee et al., 1980). CT, however, is costly and requires the sedation of a young patient.

![Fig. 2.1. The characteristic non-enhanced (a) and contrast-enhanced (b) CT scans for a 2-year-old patient with acute lobar nephronia, who presented with severe left nephromegaly while without a focal mass sonographically. Note no attenuation area seen in the kidney before enhancement (Cheng et al., 2004).](image-url)

A new systemic radiologic imaging evaluation scheme, the combination of renal US and CT scanning, was proposed to assist ALN diagnosis in pediatric patients. Enlarged kidneys and/or focal masses were utilized to be the sonographic preselection features for subsequent CT evaluation. CT scan is used when the patient shows (1) a markedly enlarged kidney or focal mass on the initial US scan; or (2) poor response to the initial 72 hours antibiotic treatment while his/her kidneys appear borderline nephromegaly sonographically (Cheng et al., 2004).

From our results (Cheng et al., 2004), severe nephromegaly (i.e. renal length greater than mean +3 SD for age) on at least one side of the kidneys is very sensitive for the diagnosis of ALN. A higher sensitivity was achieved when US focal mass findings were included with severe nephromegaly as the diagnosing criteria. In terms of the kidneys, focal masses on US scans correlated much better with the final ALN diagnosis than other US characteristics evaluated. The use of focal mass findings as an effective predictor for ALN was limited since
its sensitivity was only 25% despite a specificity of 100%. Severe nephromegaly was a very useful sonographic diagnostic criterion for kidneys affected with ALN with a sensitivity of 90.0%. Sensitivity increased to 95% when severe nephromegaly together with focal mass was used as the sonographic predictor.

In summary, pediatric ALN was effectively predicted using sonographic findings of severe nephromegaly and/or focal mass prior to CT scanning.

3. Effective duration of antimicrobial therapy for the treatment of acute lobar nephronia

Treatment for patients with ALN generally requires intravenous and oral antibiotic medication as does treatment for uncomplicated APN (Zaontz et al., 1985; Rathore et al., 1991; Klar et al., 1996). Surgical intervention is rarely needed for ALN patients, except for those with concomitant urological abnormalities which may increase the risks of occurrence of acute bacterial infection (Uehling et al., 2000). 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 (Rathore et al., 1991).

We have performed a study sought to determine the appropriate duration of effective antibiotic therapy for the management of pediatric ALN patients (Cheng et al., 2006). Patients who first presented as febrile UTI and who later were diagnosed with positive CT findings of ALN were entered into this study for receiving either a two-week or a three-week intravenous and oral antibiotic therapeutic program. The demographic data and clinical results of these patients were compared. In addition, the identification of any clinical or laboratory factors that are likely associated with treatment failure was also attempted. These two treatment groups had similar demographic data and clinical results (Table 3.1). Most of the patients had been febrile for around three-to-four days, ranging from one day to two weeks or so, prior to admission. Once patients had been admitted, all responded well to the initial antibiotic treatment regimen and the fever generally subsided within about a week. CT scans indicated that 18 patients had left ALN, 12 right ALN, and 11 bilateral ALN in the two-week treatment group. Corresponding figures for the three-week treatment group were 16, 12 and 11 patients respectively. The distribution of these ALN diagnoses was quite similar between the two treatment groups.

Among the 80 patients participating in this study, *Escherichia coli* was the most-common pathogen cultured from the patient urine samples (59/61) such a finding being consistent with the results of previous studies (Kline et al., 1988; Nosher et al., 1988; Rathore et al., 1991; Boam and Miser, 1995; Uehling et al., 2000). Interestingly, the proportion (percentage) of *Escherichia coli* cultured in cases of ALN appears to be much greater than the corresponding figure reported for first-time UTIs (Hoberman and Wald, 1999).

Sixty-nine ALN patients, 40 from the two-week treatment group and 29 from the three-week treatment group, underwent VCUG evaluation. Sixteen patients in the two-week treatment group (40%) and eleven in the three-week treatment group (38%) had vesicoureteral reflux (VUR). Among the patients with VUR, a grade-III or greater was noted in eight and nine patients respectively, treated by the two-week and the three-week antibiotic courses. For patients who underwent VCUG, no difference as regards the presence of VUR in either frequency or severity was found between the two treatment groups.
| Age, years | Range | Fever duration prior to admission, days | Range, days | Fever continuation following antibiotic treatment, days | Range, days | White blood cell count, (cells/µL) | Leukocytosis (>15,000) | WBC/µL | C-reactive protein, (mg/L; normal <5) | Urine culture | Blood culture | Treatment failure |
|-----------|-------|----------------------------------------|-------------|-----------------------------------------------------|-------------|-----------------------------------|----------------------|---------|-----------------------------------|----------------|---------------|-----------------|
| Two-week treatment group (n=41) | 3.72 ± 4.14 | 3.90 ± 3.06 | 1 – 14 | 2.73 ± 1.28 | 1 – 7 | 19,107 ± 8,772 | 28 (68.3%) | 137.7 ± 98.1 | | Escherichia coli | 31 (75.6%) | 1 (2.4%) | 4 (17.1%) |
| | 4.16 ± 4.22 | 3.97 ± 2.72 | 1-13 | 3.43 ± 2.05 | 1 – 8 | 19,600 ± 10,212 | 25 (64.1%) | 119.3 ± 74.0 | | E. coli > 10^5 cfu/mL | 25 (61.0%) | -- | 2 (5.1%) |
| | 4.16 | 25 (59.0%) | | | | | 2 (5.1%) | | | Klebsiella pneumoniae | --- | -- | 2 (5.1%) |
| | | | | | | | | | | Pseudomonas aeruginosa | 1 (2.6%) | -- | 1 (2.6%) |
| | | | | | | | | | | No isolatable organism | 9 (22.0%) | 10 (25.6%) | 40 (97.6%) |
| | Three-week treatment group (n=39) | 4.16 ± 4.22 | 3.97 ± 2.72 | 1-13 | 3.43 ± 2.05 | 1 – 8 | 19,600 ± 10,212 | 25 (64.1%) | 119.3 ± 74.0 | | Escherichia coli | 28 (71.8%) | 2 (5.1%) | 0 (0%) |
| | | | | | | | | | | E. coli > 10^5 cfu/mL | 25 (64.1%) | -- | 0 (0%) |
| | | | | | | | | | | Klebsiella pneumoniae | --- | -- | 1 (2.6%) |
| | | | | | | | | | | Pseudomonas aeruginosa | 1 (2.6%) | -- | 1 (2.6%) |
| | | | | | | | | | | No isolatable organism | 36 (92.3%) | 26 (67.2%) | 26 (67.2%) |
| | | | | | | | | | | Treatment failure | 7 (17.1%) | 1 (2.6%) | 0 (0%) |

NS indicates not significant

Table 3.1. Clinical and laboratory data for 80 children with ALN enrolled for different treatment protocol (Cheng et al., 2006).

None of our patients revealed any evidence of underlying diseases such as diabetes mellitus, immunodeficiency, nor 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 about 40% of the ALN children in this study, a figure quite comparable to that in several previous studies (Kline et al., 1988; Klar et al., 1996; Uehling et al., 2000). This frequency of VUR among patients with ALN is close to that in children with UTI (Ilyas et al., 2002), thus, VUR may not be a necessary prerequisite for the development of ALN. Overall, seven treatment failures were noted in this study (8.8%; 95% CI, 2.6%-14.9%), all of which had been managed by a two-week antibiotic course (17.1%; 95% CI, 5.6%-28.6%). Statistical significance was noted in regard to treatment success rate between these two groups (p=0.01). Among these patients with treatment failure, one demonstrated persistent infection during the treatment course, and six others were considered to be relapse by revealing a positive Escherichia coli urine culture with the same antibiotic sensitivity profile as had been the case previously.

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Table 3.2 lists the clinical characteristics of these seven patients as compared with those successfully treated with the two-week antibiotic course. Proportionally more girls may be noted in the failures group than the non-failures group, but the difference was not statistically significant (p=0.21). The patients failing the two-week antibiotic treatment presented with a more-pronounced fever duration prior to admission (6.00 ± 5.54 vs. 3.47 ± 2.16 days; p=0.04), and they were more likely to be *Escherichia coli* infection positive (>10⁵ cfu/mL; 100% (7/7) vs. 52.9% (18/34); p=0.03). The distribution of ALN foci, VCUG characteristics, and other clinical results revealed no difference between the failures and non-failures groups.

For the treatment-failure patients, the antibiotic treatment course was extended/restated for an additional ten days. Subsequent urine culture and clinical-symptom evaluation at the follow-up exams revealed eventual successful treatment.

| Age, years | 4.07 ± 4.31 | 3.65 ± 4.16 |
|-----------|-------------|-------------|
| Range     | 4 mo - 9 yr | 4 mo - 16 yr|
| Girls     | 6 (85.7%)   | 18 (52.9%)  |
| Fever duration prior to admission, days† | 6.00 ± 5.54 | 3.47 ± 2.16 |
| Fever duration following antibiotic treatment, days | 1 - 14 | 1 - 10 |
| White blood cell count, (cells/μL) | 22,257 ± 8,656 | 18,459 ± 8,781 |
| Leukocytosis (>15,000 WBC/μL) | 6 (85.7%) | 22 (64.7%) |
| C-reactive protein, (mg/L; normal <5) | 107.3 ± 113.3 | 143.4 ± 95.9 |
| *Escherichia coli* in urine culture | 7 (100%) | 24 (70.6%) |
| *E. coli* > 10⁵ cfu/mL‡ | 7 (100%) | 18 (52.9%) |

†: p=0.04; ‡: p=0.03

Table 3.2. Comparison of demographic data, clinical characteristics and laboratory results between the ALN patients with treatment failure and those with treatment success for the two-week antibiotic therapy protocol (Cheng et al., 2006).

From our results, all ALN patients with the three-week antibiotic course were successfully treated, whereas seven treatment failures (17.1% of treated patients) were noted in the two-week treatment group. This observation suggests that the two-week antibiotic treatment, usually scheduled for APN, may not be appropriate for the treatment of ALN. Patients who failed the two-week treatment modality were more likely to have prolonged fever prior to admission and to reveal positive *Escherichia coli* infection (>10⁵ cfu/mL). The longer febrile history prior to 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 were
all successfully dealt with by an additional ten-day antimicrobial therapy regimen. Whether host factors, or the virulence of *Escherichia coli*, relates to ALN and plays a role leading to treatment failure remains an issue that should be clarified.

4. A high incidence of renal scarring is associated with child with acute lobar nephronia

The pathogenesis of renal scarring after a febrile UTI remains unclear. Some risk factors making children with a UTI more vulnerable to renal damage include young age at the time of infection (Winberg et al. 1982), delayed treatment (Miller and Phillips 1981; Winberg et al. 1982), the presence of vesicoureteral reflux (VUR) (Biggi et al. 2001; Chroustova et al. 2006; Faust et al. 2009), and although mentioned infrequently, the extent of kidney lesions (Biggi et al. 2001). ALN is a severe disease entity, with extensive renal parenchymal involvement (Cheng et al. 2009). Thus, we performed a prospective study to evaluate renal scar formation after ALN as compared with APN. In this prospective study (Cheng et al. 2010a), we also examined nearly all the previously proposed risk factors for renal scarring.

DMSA scintigraphy is a sensitive diagnostic method for renal scarring but does not always distinguish between new and old lesions, or differentiate renal dysplasia from acquired post-infection scars. It is possible that we might have overestimated the occurrence of renal scars that were related to the index infection. Thus, the exclusion of children with history of prior UTI or the development of recurrent UTI before DMSA scintigraphy in current study was designed to keep any overestimation of renal scarring to a minimum.

In this investigation, a total of 218 children with a first documented febrile UTI (109 APN, 109 ALN) who fulfilled our patient selection criteria and completed the final DMSA scintigraphy were analyzed. Patient characteristics were comparable between the two ALN treatment groups (Table 4.1). The frequency of renal scarring at scintigraphy was similar between the 2-week and 3-week successful treatment groups. The demographic and clinical data for the APN (all had received 10-day treatment) and ALN patients are shown in Table 4.2. Acute lobar nephronia was a more severe disease than APN, as judged by higher inflammatory indices and longer fever duration after and/or before treatment. The incidence of renal scarring was much higher in ALN than in APN patients.

Regression analysis of the 218 patients with a first febrile UTI showed that renal scarring was more likely to occur in children with higher inflammatory indices (white blood count: 19802±7652 vs. 15478±6853; and C-reactive protein: 124.6±89.8 vs. 68.4±69.6; \( P < 0.001 \)), longer duration of fever after \( (P < 0.001) \) and/or before treatment \( (P = 0.001) \), and the presence of VUR \( (P = 0.044) \). However no relationship was found between renal scarring and age at diagnosis or gender.

Higher inflammatory indices and longer fever duration after and/or before treatment were strongly correlated with ALN (Table 4.2), these factors, henceforth, were determined not to be independent predictor variables in a multiple logistic regression analysis on renal scarring. ALN was shown to be the only independent risk factor for renal scarring \( (P < 0.001; \text{Table 4.3}) \).

The duration and route of administration of antibiotics have been shown not to influence the risk for renal scarring in patients with APN (Hoberman and Wald et al. 1999; Bouissou et al. 2008). Our previous prospective study (Cheng et al. 2006) suggested that 3 weeks of antibiotic therapy was the treatment of choice for all radiographically documented ALN patients; a longer duration of antibiotic use resulted in the successful treatment for ALN but did not reduce the risk for renal scarring. In most reported studies, including ours, the
outcome in terms of renal scarring seems to be unrelated to the mode and duration of antibiotic treatment.

| Parameter                        | 2-wk Treatment ALN Group | 3-wk Treatment ALN Group | \( P \) |
|----------------------------------|--------------------------|--------------------------|--------|
| Patient number                   | 54                       | 55                       |        |
| Male/Female                      | 25/29                    | 24/31                    | NS     |
| Age (years)                      | Median: 1.00             | Median: 1.33             | NS     |
|                                 | Range: (0.25, 15.00)     | Range: (0.07, 9.42)      |        |
| WBC count, cells/\( \mu l \)    | 21144 ± 7205             | 22014 ± 9608             | NS     |
| C-reactive protein, mg/L         | 156.1 ± 94.4             | 150.0 ± 85.1             | NS     |
| Vesicoureteral reflux            | 48.1% (25/52)            | 35.9% (19/53)            | NS     |
| \( E. \ coli \) percentage in urine culture\( ^a \) | 95.1% (39/41)           | 85.7% (36/42)            | NS     |
| Fever duration before treatment, days | 3.54 ± 2.23         | 4.07 ± 3.37              | NS     |
| Fever duration after treatment, days | 3.19 ± 1.76         | 4.02 ± 2.81              | NS     |
| Time from ALN to DMSA renal scan, years | 1.27 ± 1.02     | 1.40 ± 1.18              | NS     |
| Renal scar formation             | 88.9% (48/54)            | 89.1% (49/55)            | NS     |

\( \text{WBC, white blood cell; DMSA, dimercaptosuccinic acid; NS, not significant.} \ ^a \) excluding urine cultures showing no growth.

Table 4.1. Demographic and clinical data for 109 patients with ALN (Cheng et al. 2010a).

| Parameter                        | APN                        | ALN                        | \( P \) |
|----------------------------------|----------------------------|-----------------------------|--------|
| Patient number                   | 109                        | 109                         |        |
| Male/Female                      | 49/60                      | 49/60                       | NS     |
| Age (years)                      | Median: 1.00               | Median: 1.16               | NS     |
|                                 | Range: (0.16, 15.00)       | Range: (0.07, 15.00)       |        |
| WBC count, cells/\( \mu l \)    | 14729 ± 4656               | 21583 ± 8475               | < 0.001|
| C-reactive protein, mg/L         | 53.4 ± 46.5                | 153.0 ± 89.5               | < 0.001|
| Vesicoureteral reflux            | 34.6% (36/104)             | 41.9% (44/105)             | NS     |
| \( E. \ coli \) percentage in urine culture\( ^a \) | 78.8% (82/104)           | 90.4% (75/83)              | 0.033  |
| Fever duration before treatment, days | 1.90 ± 1.62         | 3.81 ± 2.86                | < 0.001|
| Fever duration after treatment, days | 1.02 ± 0.75         | 3.61 ± 2.37                | < 0.001|
| Time from APN or ALN to DMSA renal scan, years | 1.21 ± 1.06     | 1.34 ± 1.10                | NS     |
| Renal scar formation             | 34.9% (38/109)             | 89.0% (97/109)             | < 0.001|

\( ^a \) excluding urine cultures showing no growth.

Table 4.2. Demographic and clinical data for patients with APN and patients with ALN (Cheng et al. 2010a).
Table 4.3. Multiple logistic regression analysis for scar formation (Cheng et al. 2010a).

| Variable                      | aOR | 95% CI Lower | 95% CI Upper | P       |
|-------------------------------|-----|--------------|--------------|---------|
| Disease                       |     |              |              |         |
| APN                           | 1.00| --           | --           | --      |
| ALN                           | 13.56| 6.53         | 28.19        | < 0.001 |
| Gender                        |     |              |              |         |
| Male                          | 1.00| --           | --           | --      |
| Female                        | 0.95| 0.47         | 1.93         | NS      |
| Age                           |     |              |              |         |
| < 1 year                      | 1.00| --           | --           | --      |
| 1-5 years                     | 0.85| 0.39         | 1.86         | NS      |
| > 5 years                     | 0.91| 0.35         | 2.33         | NS      |
| Vesicoureteral reflux (VUR)   |     |              |              |         |
| No VUR                        | 1.00| --           | --           | --      |
| VUR                           | 1.83| 0.90         | 3.74         | 0.096   |

The severity of APN as evaluated by the extent of renal lesions on acute DMSA scanning has been suggested to be a predictor for renal scarring (Biggi et al. 2001; Chiou et al. 2001). Our data on higher renal scar odds ratio in ALN, a more severe form of acute renal infection than APN, as well as in higher inflammatory indices and longer fever duration after and/or before treatment strongly support this suggestion.

The role of VUR in the development of renal scars remains controversial (Hoberman and Wald et al. 1999; Gordon et al. 2003; Hoberman et al. 2003; Moorthy et al. 2005). Some recent prospective studies (Hoberman et al. 2003; Chroustova et al. 2006; Polito et al. 2006; Bouissou et al. 2008) and a cross-sectional meta-analysis (Faust et al. 2009) have shown a significant association between the presence of VUR and the risk for renal scarring. However, the presence of VUR was a weak predictor of renal scarring in the present study. The additional effect of VUR above that achieved by including only the presence of ALN (nephromegaly and/or severity of infection) in the multiple logistic regression model was not statistically significant for predicting renal scarring.

In conclusion, our results showed a new finding that ALN is associated with a very high incidence of renal scarring, in comparison to APN, irrespective of the duration of antibiotic treatment.

5. Comparison of urovirulence factors and genotypes for bacteria causing acute lobar nephronia and acute pyelonephritis

*Escherichia coli* is the most common cause of various UTIs, including cystitis, prostatitis and pyelonephritis (Johnson and Kuskowski et al. 2005). Our early studies showed that *E. coli* was the most common pathogen cultured from the patients with ALN (Cheng et al. 2004, 2006), having a higher percentage of pathogens than the first-time UTIs (Hoberman and Wald 1999). This finding has led us to this investigation of the pathogenetic association of the bacterial virulence factors as well as the genotypes of the *E. coli* isolates in pediatric ALN.

Henceforth, we have sought to determine the role of *E. coli* urovirulence factors in the development of ALN as compared to APN in pediatric patients who have no underlying
diseases or urinary anatomical anomalies except vesicoureteral reflux (VUR) (Cheng et al., 2007). Through our previous published systematic diagnostic scheme (Cheng et al. 2004, 2006), patients who first presented as febrile UTIs and later were diagnosed with positive CT findings of ALN or positive technetium 99m-dimercaptosuccinic acid scintigraphic ($^{99m}$Tc-DMSA) findings of APN were enrolled into this study.

Patients were included for study only if *E. coli* was the sole isolate recovered from their urine specimens. Single colonies of the *E. coli* were randomly selected from the initial culture plate and stored in 20% glycerol at -70°C until used. Urovirulent factors examined included genes associated with various fimbrial and nonfimbrial adhesins (*pap*G I, *pap*G II, *pap*G III, *fimH*, *sfu*, *foc*, *afa*), aerobactin receptor (*iutA*), hemolysin (*hlyA*), and cytotoxic necrotizing factor I (*cnf1*) (Tseng et al. 2001, 2002; Johnson 2003; Johnson and Russo 2005). The difference in the prevalence of various *E. coli* urovirulent factors for the pediatric patients with ALN or APN was statistically analyzed. In addition, genotyping of these *E. coli* isolates was also performed to examine the possible clonal differences.

A total of 88 patients who fulfilled enrollment criteria were included for study. Among these, 46 patients were diagnosed with ALN and 42 cases with APN. Seventy-two patients, 42 from the ALN group and 30 from the APN group, underwent VCUG evaluation. Seventeen (40.5%) patients in the ALN group and 12 (40%) in the APN group had VUR. Among the patients with VUR, grade-IV reflux or greater was noted in 3 patients each with APN and ALN. Among patients who underwent VCUG, no difference in the presence of VUR in either frequency or severity was found between the two disease categories.

Among the 88 *E. coli* clinical isolates, *pap*G adhesin genes (including classes I to III) were detected in 44 of the ALN isolates and 32 of the APN ones (95.7% vs. 76.2%, p<0.05). The class II allele was more commonly noted in the group of ALN (95.7% vs. 73.9%, p<0.05; Table 5.1) (Cheng et al., 2007). In contrast, no significant difference was found for the class III allele between the two groups. None of the isolates had the class I allele. In addition, *pap*G II allele was noted in all ALN patients with normal VCUGs (25/25) while only in 16 of the 18 APN patients with normal VCUGs. The genetic determinant for type 1 fimbriae, *fimH*, was the most common virulence factor (95.5%) found among the isolates; however, no statistically significant difference between the two groups was noted. Similarly, the remaining genetic determinants for other virulence factors did not reveal any significant difference between the two groups. Multivariate logistic regression analysis revealed that *pap*G II allele was significantly associated with ALN (p<0.005; odds ratio, 17.16, 95% CI: 2.76-106.70). This association was independent of the presence of VUR.

To cause bacterial infections of the upper urinary tract, the microorganisms need to reach the kidney through ascending or hematogenous routes. Bacterial adherence to the uroepithelial cells by fimbrial or nonfimbrial adhesins is considered to be an important factor in the development of upper urinary tract infection via the ascending route (Tseng et al. 2001). Among these adhesins, *pap*G variants, which are located at the tip of P-fimbriae and bind preferentially to different Gal (α 1-4) Gal-containing glycolipids in the human epithelium of proximal and distal tubules and in collecting ducts, have been implicated to be associated with the severity of renal infection (Källenius et al. 1981; Johnson 1991; Wang et al. 2002; Johnson and Russo 2005). Previous studies have shown that the *pap*G II allele is associated with acute pyelonephritis (APN) (Johanson et al. 1993; Otto et al. 1993; Jantunen et al. 2000), while the *pap*G III allele predominates in less severe genitourinary infections, such as acute cystitis and prostatitis (Johanson et al. 1993; Johnson et al. 1998; Ruiz et al. 2002).
Table 5.1. Comparison of virulence factors of *Escherichia coli* isolated from patients with ALN and APN (Cheng *et al.*, 2007).

| Virulence factor          | ALN group (n=46) | APN group (n=42) | P     |
|---------------------------|------------------|------------------|-------|
| *pap*G (P-fimbriae)       |                  |                  |       |
| Class I                   | 0 (0%)           | 0 (0%)           | ---   |
| Class II                  | 44 (95.7%)       | 31 (73.8%)       | 0.01  |
| Class III                 | 5 (10.9%)        | 4 (9.5%)         | NS    |
| *fimH* (type 1 fimbriae)  | 44 (95.7%)       | 40 (95.2%)       | NS    |
| *sfa* (S-fimbriae)        | 7 (15.2%)        | 4 (9.5%)         | NS    |
| *foc* (F1C-fimbriae)      | 5 (10.9%)        | 8 (19.1%)        | NS    |
| *afa* (afimbrial adhesins) | 3 (6.5%)         | 4 (9.5%)         | NS    |
| *iutA* (aerobactin receptor) | 35 (76.1%)    | 32 (76.2%)       | NS    |
| *hlyA* (hemolysin)        | 21 (45.7%)       | 23 (54.8%)       | NS    |
| Cnf1 (cytotoxic necrotizing factor 1) | 8 (17.4%)  | 14 (33.3%)       | NS    |

NS indicates not significant

Results in this study (Cheng *et al.*, 2007) also indicated that *pap*G II was significantly more prevalent in pediatric patients with ALN than those with APN. This finding provides further evidence that the *pap*G II allele might play a more important pathogenic role than other adhesins in the development of severe renal infectious diseases. In addition, this finding may offer an insight for the future development of vaccine against such severe renal parenchymal inflammatory diseases.

The *fimH* gene sequence which encodes the type I fimbriae was present uniformly in most of the isolates from either ALN or APN patients. This is in accordance with the fact that type I fimbriae is present in nearly all *E. coli* isolates from patients with various UTIs, ranging from cystitis, prostatitis to APN (Johnson and Stell 2000; Johnson and Russo 2005). This study further extends the proposed mechanism that *fimH* gene (i.e. type I fimbriae) was generally required for renal bacterial infection disease to be occurred, no matter what degree of severity it is. In contrast, other fimbrial and nonfimbrial adhesins (i.e. *sfa, foc, and afa* genes) were rarely detected among our isolates and their pathogenic roles in ALN and APN are likely of less importance, a finding similar to those reported previously in the less severe renal infection categories (Siitonen *et al.*, 1993; Blanco *et al.*, 1997; Mitsumori *et al.*, 1998).

Host compromise can decrease the requirements for bacterial virulence in causing severe urinary tract infections, and, henceforth, change the distribution of *pap*G pathogenetic determinants among the clinical isolates studied (Jantunen *et al.*, 2000; Tseng *et al.*, 2001, 2002; Johnson and Russo 2005). In this study, the lack of influence of VUR, the only host compromising factor revealed, on the determination of urovirulence factors could be due to the similar distribution and severity of VUR between these two groups. Such similarities in VUR severity distribution and occurrence frequency were also reported in our earlier studies and many others (Kline *et al.*, 1988; Sargent and Stringer 1995; Uehling *et al.*, 2000; Cheng *et al.*, 2004, 2006). In addition, this frequency of VUR among patients with ALN or APN (~ 40%) is close to that in children with UTI (Ilyas *et al.*, 2002). Thus, VUR may not be a necessary prerequisite (i.e. significant predisposing host factor) for the development of ALN.
A total of 85 genotypes were found among the 88 *E. coli* isolates. Some representative banding patterns are shown in Figure 5.1 (Cheng et al., 2007). These isolates from both ALN and APN patients demonstrated a variety of genotypes. A total of 85 genotypes contained multiple isolates, and 2 genotypes contained isolates from both ALN and APN groups, suggesting that isolates of the same clone could be associated with either entity. In summary, PFGE analysis indicated that no major genotype was associated with the disease category among these 88 clinical *E. coli* isolates. As to the urovirulence factors examined, the *papG* class II gene was the most strongly associated pathogenic determinant for the pediatric ALN patients who have no underlying diseases except VUR. Furthermore, even without VUR, patients can still develop clinical symptoms and radiographic characteristics associated with ALN in the presence of *papG* II gene.

6. Comparison of bacterial urovirulence genotypes among patients with urosepsis, acute pyelonephritis, and acute lobar nephronia

Complex pathogen-host interactions determine the patient’s susceptibility to bacterial infections (Rushton 1997; Ma and Shortliffe 2004). Various virulence factors have been identified that enhance *E. coli* uropathogenicity, including the facilitation of colonization and invasion of the host, avoidance or disruption of host defense mechanisms, injury to host tissue, and/or stimulation of a noxious host inflammatory responses (Rushton 1997; Johnson and Stell 2000). Furthermore, some virulence factors are more prevalent in specific urinary tract infectious diseases, thus offering insights into future vaccine development (Jantunen et al. 2000; Ruiz et al. 2002; Tseng et al. 2002).

We sought to further elucidate the roles of *E. coli* virulence factors in the development of urosepsis and two other severe renal parenchymal infectious diseases, APN and ALN, in
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pediatric patients who show no host-compromising factors, except for vesicoureteral reflux (VUR) (Cheng et al., 2010b). Twenty-five virulence factors were analyzed, including genes associated with fimbral and nonfimbrial adhesins (papAH, papC, papEF, papG I, papG II, papG III, sfaS, focG, afa, bmaE, gafD, nfaE, fimH), toxins (hlyA, cnf1, cdtB), siderophores (fuuA, iutA), capsule synthesis (kpsMT II, kpsMT III), invasion of brain endothelium (ibeA), serum-resistance (traT), markers for virulence-associated E. coli serogroup O4 (rfc) and colcin V plasmids (cvcC), and the coding region of PAI from the uropathogenic strain CFT073 (PAI) (Johnson and Stell 2000; Jantunen et al. 2000; Tseng et al. 2002; Johnson and Kuskowski et al. 2005; Cheng et al. 2007). Moreover, the prevalence rates of these 25 urovirulence genes for patients with the three invasive UTIs (i.e. APN, ALN, and urosepsis) will also be compared with those for patients diagnosed as cystitis.

The inclusion criteria and diagnostic scheme for patients with documented episodes of ALN or APN were the same as those stated in our earlier publication (Cheng et al. 2007). Urosepsis was defined as a patient with bacteremia arising from a urinary tract source (Johnson et al. 1988). Cystitis was defined as afebrile pediatric patients with just only localizing symptoms such as dysuria, frequency, urgency, cloudy urine or lower abdominal discomfort. Exclusion criteria included any evidence of underlying diseases such as diabetes or immunodeficiency, or any structural anomalies such as neurogenic bladder, posterior urethral valve, urinary diversion, bladder diverticulum, ureterocele, and urinary tract obstruction apart from VUR.

Among the 123 E. coli isolates from APN, ALN and urosepsis, the overall prevalence rate of various virulence factors ranged from 2% (nfaE, nonfimbrial adhesin-1) to 97% (fimH, Type I fimbiae). In addition, all but one APN clinical isolate presented at least one adhesin. Of the 25 virulence factors examined, 17 showed a statistically significant distribution among these three invasive UTI categories (Table 6.1). ALN isolates differed significantly from other invasive UTI isolates (i.e. APN and urosepsis) due to their lower prevalence of cdtB and a medium prevalence of cvcC. Moreover, ALN isolates showed a higher prevalence of papAH, papC, papEF, and papG II, compared with APN isolates, and a lower prevalence of papG I, focG, afa, bmaE, hlyA, cnf1, iutA, kpsMT III, rfc, and traT compared with urosepsis isolates. APN isolates were significantly different from other two types of invasive isolates due to a lower prevalence of cvcC. Additionally, APN isolates had a lower prevalence of papG I, focG, afa, bmaE, iutA, kpsMT III, rfc, traT, and PAI compared with urosepsis isolates. Finally, urosepsis isolates significantly differed from all other two types of invasive UTI isolates due to a higher prevalence of papG I, focG, afa, bmaE, iutA, kpsMT III, rfc, cvcC, and traT (Table 6.1).

In contrast, among the 24 clinical isolates from cystitis, eight virulence genes were not noted, and in which, six were bacterial adhesins (i.e. papG I, sfaS, afa, bmaE, gafD, nfaE). However, the highest prevalence rate (100%) was noted in fimH adhesin, the virulence gene sequence encoding type I fimbiae. As compared to the combination of three invasive UTI diseases (i.e. APN, ALN and urosepsis), the cystitis isolates had a lower prevalence of papAH, papC, papEF, papG II, sfaS, afa, bmaE, hlyA, cdtB, fuuA and ibeA (Table 6.1).

In this investigation, none of the patients presented with any evidence of underlying disease or structural anomalies except VUR, and a similar distribution of severity and frequency of occurrence of VUR was noted among the three different invasive UTI disease groups; APN, ALN, and, urosepsis. Hence, distinct syndrome-specific differences in distribution for certain virulence factors, but conservation across syndromes for others, is likely related to differences in bacterial urovirulence and uropathogenicity among these three invasive bacterial urinary infectious diseases.

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| Virulence factor | Cystitis group (n = 24) | APN group (n = 45) | ALN group (n = 48) | Urosepsis group (n = 30) | Cystitis vs. (APN+ ALN+ Urosepsis) | APN vs. ALN | ALN vs. Urosepsis | APN vs. Urosepsis |
|------------------|------------------------|-------------------|-------------------|--------------------------|----------------------------------|------------|-----------------|-----------------|
| **Adhesin**      |                        |                   |                   |                          |                                  |            |                 |                 |
| **papAH (P-fimbriae)** | 8 (33%)               | 32 (71%)          | 43 (90%)          | 24 (80%)                 | <0.0001                          | 0.0242     | ---             | ---             |
| **papC (P-fimbriae)** | 6 (25%)               | 32 (71%)          | 45 (94%)          | 25 (83%)                 | <0.0001                          | 0.0038     | ---             | ---             |
| **papF (P-fimbriae)** | 6 (25%)               | 34 (76%)          | 44 (92%)          | 26 (87%)                 | <0.0001                          | 0.0348     | ---             | ---             |
| **papG (P-fimbriae)** | 6 (25%)               | 34 (76%)          | 44 (92%)          | 26 (87%)                 |                                  |            |                 |                 |
| **Class I**      | 0 (0%)                 | 0 (0%)            | 0 (0%)            | 13 (43%)                 | ---                              | ---        | <0.0001         | <0.0001         |
| **Class II**     | 4 (17%)                | 33 (73%)          | 44 (92%)          | 26 (87%)                 | <0.0001                          | 0.0192     | ---             | ---             |
| **Class III**    | 4 (17%)                | 4 (9%)            | 6 (13%)           | 6 (20%)                  | ---                              | ---        | ---             | ---             |
| **spa5 (S-fimbriae)** | 0 (0%)                | 6 (13%)           | 7 (15%)           | 9 (30%)                  | 0.0251                           | ---        | ---             | ---             |
| **focC (F1C-fimbriae)** | 6 (25%)               | 8 (18%)           | 5 (10%)           | 20 (67%)                 | ---                              | ---        | <0.0001         | <0.0001         |
| **afa (afimbrial adhesin)** | 0 (0%)                 | 4 (9%)            | 4 (8%)            | 27 (90%)                 | 0.0028                           | ---        | <0.0001         | <0.0001         |
| **bmaE (M blood group antigen-specific M fimbriae)** | 0 (0%)                 | 1 (2%)            | 1 (2%)            | 16 (53%)                 | 0.0446                           | ---        | <0.0001         | <0.0001         |
| **gefD (glucosaminyl-specific G fimbriae)** | 0 (0%)                 | 2 (4%)            | 7 (15%)           | 5 (17%)                  | ---                              | ---        | ---             | ---             |
| **nybE (nonfimbrial adhesion-1)** | 0 (0%)                 | 2 (4%)            | 0 (0%)            | 0 (0%)                   | ---                              | ---        | ---             | ---             |
| **fimH1 (type 1 fimbriae)** | 24 (100%)              | 43 (96%)          | 46 (96%)          | 30 (100%)                | ---                              | ---        | ---             | ---             |
| **Toxin**        |                        |                   |                   |                          |                                  |            |                 |                 |
| **hlyA (hemolysin)** | 4 (17%)                | 24 (53%)          | 22 (46%)          | 22 (73%)                 | 0.0006                           | ---        | 0.0172          | ---             |
| **CotE (cytotoxic necrotizing factor 1)** | 4 (17%)                | 14 (31%)          | 9 (19%)           | 16 (53%)                 | ---                              | ---        | 0.0015          | ---             |
| **cdtB (cytotoxical distending toxin)** | 0 (0%)                 | 21 (47%)          | 4 (8%)            | 17 (57%)                 | 0.0009                           | <0.0001   | <0.0001         | ---             |
### Table 6.1. Comparison between virulence factors among 147 *Escherichia coli* isolates from patients with cystitis, acute pyelonephritis (APN), acute lobar nephronia (ALN), or urosepsis. (Cheng et al., 2010b).

| Virulence factor | Cystitis group (n = 24) | APN group (n = 45) | ALN group (n = 48) | Urosepsis group (n = 30) | Cystitis vs. (APN+ALN+Urosepsis) | APN vs. ALN | ALN vs. Urosepsis | APN vs. Urosepsis |
|------------------|-------------------------|--------------------|--------------------|-------------------------|-----------------------------------|-------------|------------------|------------------|
| Siderophore      |                         |                    |                    |                         |                                   |             |                  |                  |
| *fhuA* (yersiniabactin receptor) | 14 (58%) | 41 (91%) | 48 (100%) | 29 (97%) | <0.0001 | --- | --- | --- |
| *iutA* (aerobactin receptor) | 16 (67%) | 35 (78%) | 36 (75%) | 30 (100%) | --- | 0.0024 | 0.0047 | --- |
| Miscellaneous    |                         |                    |                    |                         |                                   |             |                  |                  |
| *kpsMT II* (capsule synthesis, group II) | 16 (67%) | 38 (84%) | 41 (87%) | 24 (80%) | --- | --- | --- | --- |
| *kpsMT III* (capsule synthesis, group III) | 0 (0%) | 3 (7%) | 3 (6%) | 9 (30%) | --- | --- | 0.0081 | 0.0101 |
| *rfe* (marker for virulence-associated E. coli serogroup O4) | 2 (8%) | 6 (13%) | 9 (19%) | 16 (53%) | --- | --- | 0.0015 | 0.0002 |
| *ibeA* (invasion of brain endothelium gene) | 14 (58%) | 34 (77%) | 41 (85%) | 28 (93%) | 0.0090 | --- | --- | --- |
| *cscC* (marker for ColV, coelic V, plasmids) | 4 (17%) | 4 (9%) | 13 (27%) | 24 (80%) | --- | 0.0233 | <0.0001 | <0.0001 |
| *truT* (serum-resistance associated gene) | 16 (67%) | 30 (67%) | 39 (81%) | 30 (100%) | --- | --- | 0.0108 | 0.0004 |
| PAI (coding region of PAI from uropathogenic strain CFT073) | 16 (67%) | 31 (69%) | 39 (81%) | 28 (93%) | --- | --- | --- | 0.0114 |

* Data are presented as the number (%) of indicated urovirulence factors.

* The P values, as determined by $\chi^2$ analysis or 2-sided Fisher’s exact tests, as appropriate, are shown only when $P < 0.05.$
The fimH, the gene sequence that encodes type I fimbriae, was found in nearly all strains (97%) from these three invasive UTI diseases and did not vary statistically among these three syndromes. This finding further extends the proposed mechanism, namely, that the fimH gene is generally required for renal bacterial infectious disease to occur, regardless of level (Johnson and Stell 2000; Tseng et al. 2002; Johnson and Russo 2005; Moreno et al. 2005; Cheng et al. 2007).

An aggregate virulence factor score for each isolate was calculated as the number of unique virulence factors detected, with adjustment for multiple detection of pap (P-fimbriae) and sfa/foc (S/F1C fimbriae) (Johnson and Kuskowski et al. 2005). The median scores were 6.5 (range: 1-12), 9 (range: 2–12), 9 (range: 6–13), and 14 (range: 9–17) for cystitis, APN, ALN, and urosepsis isolates, respectively. A Kruskal-Wallis nonparametric one way ANOVA analysis indicated the aggregate virulence factor score was significantly different among these four disease groups (p < 0.0001). Post hoc analyses using Dunn method (2-sided) between any two disease categories indicated that urosepsis isolates presented significantly higher aggregate virulence scores than isolates from any other three diseases (urosepsis vs. cystitis, urosepsis vs. APN and urosepsis vs. ALN; p < 0.0001). Isolates from cystitis, rather, showed significantly lower aggregate virulence scores than those from any other three invasive UTI diseases (cystitis vs. APN and cystitis vs. ALN; p < 0.01; cystitis vs. urosepsis; p < 0.0001). However, no significant difference was noted between the APN and ALN isolates (p = 0.88).

In summary, for the three invasive urinary infectious diseases, distinct syndrome-specific differences in distribution for certain virulence factors, but conservation across syndromes for others is noted. This likely resulted from the differences in bacterial urovirulence and uropathogenicity. Our findings also suggested that urosepsis isolates carry more virulence factors and are therefore likely more urovirulent compared with cystitis, APN and ALN isolates.

7. Genetic polymorphisms and susceptibility for pediatric patients with parenchymal renal infections

Despite of aforementioned efforts on correlating urovirulence factors of uropathogenic E. coli with the disease severity, the intra-individual differences in clinical presentations are still noted among UTI patients. This underlies the importance of host factors, such as mechanistic dysfunctions like vesicoureteral reflux (VUR) and genetic variations, in patient’s susceptibility to the bacterial invasion and infection (Artifoni et al. 2007; Lundstedt and Leijonhufvud et al. 2007; Lundstedt and McCarthy et al. 2007; Hawn, Scholes and Li et al. 2009; Sivick and Mobley 2010).

The inflammatory response caused by the attachment/invasion of uropathogenic E. coli into the urinary tract is determined by different molecular interactions between the bacteria and epithelial cells (Artifoni et al. 2007; Sivick and Mobley 2010). The initial recognition for bacterial attachment/invasion occurs through the coordination efforts of various toll-like receptors and different Pathogen-Associated Molecular Patterns (PAMPs) such as bacterial flagellin and lipopolysaccharide (Hawn, Scholes and Li et al. 2009). Following that, potent chemoattractants secreted by the infected epithelial cells will attract inflammatory cells, and the chemokine receptors will then direct recruited inflammatory cells’ interactions with mucosal barrier. Subsequent steps in the inflammatory process will determine the balance

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between the health and the disease severity (Godaly et al. 2001; Artifoni et al. 2007). Neutrophil-dependent innate host defense system is considered to be an important antimicrobial process to maintain the sterility of the urinary tract. It starts from signal transmission by cooperative efforts of toll-like receptor 4 (TLR-4) and P fimbriae of uropathogenic E. coli, followed by the secretion of main chemotactant for neutrophils, IL-8. The IL-8 mediates its effects on neutrophil chemotaxis, transepithelial infiltration into the urinary tract, activation and phagocytosis and killing of bacteria through the receptors CXCR1 and CXCR2 (Godaly et al. 2001; Lundstedt and Leijonhufvud et al. 2007; Lundstedt and McCarthy et al. 2007).

Henceforth, we sought to determine the correlations in the polymorphisms for genes regulating the initial recognition of bacterial invasion (i.e. TLR-4, toll-like receptor 4) and subsequent neutrophil infiltration and activation for bacteria clearance (i.e. IL-8, interleukin-8; and CXCR1, CXCR2; receptors for interleukin-8) among the pediatric UTI patients with different clinical severity; namely, acute pyelonephritis (APN) and the clinically more severe UTI disease, acute lobar nephronia (ALN) (Cheng et al., 2011a). In addition, since VUR is a well-known risk factor for severe parenchymal infectious disease as APN (Orellana et al. 2004; Artifoni et al. 2007), a subgroup of APN and ALN patients without VUR will also be examined to exclude the possible effects caused by VUR.

Statistical analyses using log-additive model has revealed that only IL-8 (rs4073) showed significant difference in genotype frequency between the control group and APN, ALN or combined cases (Table 7.1) for APN vs. control; ALN vs. control and combined vs. control, respectively. In addition, the genotype AA in IL-8 (rs4073) was associated with the severe upper UTIs (i.e. APN and ALN) in comparison to the TT and TA genotypes (Table 7.1) for APN vs. control; ALN vs. control and combined vs. control, respectively. The allele frequency analyses have shown that the minor allele, “A”, in IL-8 (rs4073) is more prevalent in the severe upper UTI groups than in the control for APN vs. control; ALN vs. control and combined vs. control, respectively (Table 7.2) (Cheng et al. 2011a). Since vesicoureteral reflux (VUR) has been suggested as the significant host risk factor for upper UTIs (Orellana et al. 2004; Artifoni et al. 2007), we subsequently evaluated the results of genetic analysis in the subgroup of APN and ALN patients with no VUR. In the no-VUR subgroup of APN and ALN patients, only ALN and APN+ALN group presented a statistically significant difference in IL-8 (rs4073) genotype frequency using log-additive model (OR (95% CI): 1.47 (1.03, 2.10); 1.50 (1.09, 2.06) for ALN vs. control; and combined vs. control, respectively). In comparison to the TT and TA genotypes in IL-8 (rs4073) SNP, a significant higher AA genotype frequency was noted in the no-VUR subgroup of ALN and APN+ALN cases (recessive model, OR (95% CI): 2.31 (1.15, 4.65); 2.15 (1.13, 4.09) for ALN vs. control; and combined vs. control, respectively). These two no-VUR subgroups (i.e. ALN and APN+ALN) also presented a significant higher minor allele (i.e. “A” in IL-8 (rs4073)) frequency than in the control (OR (95%CI): 1.43 (1.02, 2.01); 1.45 (1.07, 1.96) for ALN vs. control and combined vs. control, respectively).

This investigation (Cheng et al. 2011a) has indicated that APN and ALN patients have distinctive higher AA genotype frequency and A allele occurrence in IL-8 (rs 4073) as compared to the controls. In contrast, no differences in TLR-4 (rs10759932), CXCR1 (rs16858808) and CXCR2 (rs4674258) were noted among the APN, ALN and control. The polymorphism for IL-8 (rs4073) occurs at -251A>T position in the 5’ promoter region of IL-8.
| SNP | Group       | Genotype (%) | Log-additive Model | Dominant Model (0L, 11 vs 00) | Recessive Model (11 vs 00, 01) |
|-----|-------------|--------------|--------------------|-------------------------------|-------------------------------|
|     |             | 00 | 01 | 11 | OR (95% CI) | P<sub>a</sub> | OR (95% CI) | P<sub>a</sub> | OR (95% CI) | P<sub>a</sub> |
|     | Control     | 214 | 8  | 0 (0) | 1.24 (0.40, 3.88) | 0.32 | 1.71 (0.66, 4.44) | 0.27 | 0.43 |
|     | CXCR1       | 108 | 5  | 0 (0) | 1.79 (0.73, 4.37) | 0.58 | 1.57 (0.63, 3.63) | 0.34 |          |
|     | ALN         | 156 | 9  | 1 (0.6) | 1.57 (0.68, 3.63) | 0.34 | 1.52 (0.63, 3.65) | 0.34 |          |
|     | Combined    | 264 | 14 | 1 (0.4) | 1.57 (0.68, 3.63) | 0.34 | 1.52 (0.63, 3.65) | 0.34 |          |
|     |             | CC | CT | TT | OR (95% CI) | P<sub>a</sub> | OR (95% CI) | P<sub>a</sub> | OR (95% CI) | P<sub>a</sub> |
| CXCR2| Control     | 101 | 50 | 26 | (11.8) | 1.03 (0.73, 1.43) | 0.88 | 1.06 (0.67, 1.67) | 0.80 | 0.98 (0.48, 1.98) | 0.94 |
|     | APN         | 142 | 72 | 14 | (11.6) | 0.88 (0.64, 1.19) | 0.39 | 0.90 (0.60, 1.35) | 0.63 | 0.69 (0.35, 1.37) | 0.28 |
|     | ALN         | 80  | 72 | 14 | (11.6) | 0.93 (0.72, 1.22) | 0.62 | 0.96 (0.68, 1.37) | 0.84 | 0.80 (0.45, 1.42) | 0.45 |
|     | Combined    | 130 | 122| 27 | (9.7)  | 0.93 (0.72, 1.22) | 0.62 | 0.96 (0.68, 1.37) | 0.84 | 0.80 (0.45, 1.42) | 0.45 |
| IL-8|             | TT | TA | AA | OR (95% CI) | P<sub>a</sub> | OR (95% CI) | P<sub>a</sub> | OR (95% CI) | P<sub>a</sub> |
|     | Control     | 94  | 40 | 18 | (8.2)  | 1.45 (1.03, 2.06) | 0.03 | 1.37 (0.86, 2.19) | 0.18 | 2.26 (1.13, 4.50) | 0.02 |
|     | APN         | 135 | 54 | 19 | (16.8) | 1.49 (1.09, 2.02) | 0.01 | 1.44 (0.95, 2.18) | 0.09 | 2.27 (1.21, 4.26) | 0.01 |
|     | ALN         | 57  | 81 | 28 | (16.9) | 1.46 (1.12, 1.91) | 0.01 | 1.41 (0.98, 2.03) | 0.06 | 2.26 (1.27, 4.02) | 0.01 |
|     | Combined    | 135 | 135| 47 | (16.8) | 1.46 (1.12, 1.91) | 0.01 | 1.41 (0.98, 2.03) | 0.06 | 2.26 (1.27, 4.02) | 0.01 |
Table 7.1. Genotypic analysis of single nucleotide polymorphisms (SNPs) (Cheng et al., 2011a).

| SNP   | Group | Genotype (%) | Log-additive Model | Dominant Model | Recessive Model |
|-------|-------|--------------|--------------------|----------------|----------------|
|       |       | 00 | 01 | 11 | Control | 65 | 86 (39.1) | 16 (7.3) | OR (95% CI) | P<sub>a</sub> | OR (95% CI) | P<sub>a</sub> | OR (95% CI) | P<sub>a</sub> |
|       |       | TT | TC | CC | TLR-4 (rs10759932) | 65 | 86 (39.1) | 16 (7.3) | 0.86 | (0.59, 1.24) | 0.42 | 0.82 | (0.52, 1.30) | 0.40 | 0.86 | (0.34, 2.15) | 0.74 |
|       | APN   | 68 | 7 | 6 (6.3) | 78 | 68 (41.2) | 10 (6.1) | 0.99 | (0.72, 1.37) | 0.96 | 1.04 | (0.69, 1.55) | 0.86 | 0.82 | (0.36, 1.86) | 0.64 |
|       | ALN   | 68 | 7 | 6 (6.3) | 78 | 68 (41.2) | 10 (6.1) | 0.99 | (0.72, 1.37) | 0.96 | 1.04 | (0.69, 1.55) | 0.86 | 0.82 | (0.36, 1.86) | 0.64 |
|       | Combined | 107 | 17 (6.1) | 17 (6.1) | 152 | 107 (68.3) | 17 (6.1) | 0.94 | (0.70, 1.25) | 0.65 | 0.94 | (0.66, 1.35) | 0.75 | 0.84 | (0.41, 1.70) | 0.62 |

*The P values are shown in bold when P < 0.05.
*Combined: APN+ALN
Hence, current finding is in parallel to an earlier report in which A allele in -251A>T is significantly associated with the presence of dimercapto-succinic acid scan documented APN (Artifoni et al. 2007). This has been attributed to the association of A allele with an increase in IL-8 production (Hull et al. 2001; Artifoni et al. 2007). In addition, AA genotype has been linked to the increased level of fecal IL-8 and the occurrence of enteroaggregative E. coli-associated diarrhea (Jiang et al. 2003). Therefore, the IL-8 (rs4073) SNP for APN and ALN patients could be related to the up-regulated IL-8 expression that has subsequently resulted in severe clinical inflammatory responses noted clinically. Furthermore, after elimination of VUR, the well-known risk factor for severe UTIs, from analyses, only ALN patients presented SNP in IL-8 (rs4073) while APN did not. Since the inflammatory responses in ALN patients are more severe than in APN ones (e.g. higher CRP value and longer fever duration after antibiotic treatment), this finding further supports the role of polymorphism in IL-8 (rs4073, -251A>T) in IL-8 up-regulation.

In summary, the SNP in the inflammatory chemokine IL-8, a higher frequency in AA genotype and A allele, is involved in the susceptibility and clinical responses in pediatric APN and ALN cases. In addition, after removing VUR, the significant risk factor for parenchymal infection, from statistical analysis, the IL-8 SNP is only noted in the no-VUR subgroup of clinically more severe ALN patients. This suggests IL-8 (rs4073) SNP is correlated to the clinical severity of parenchymal infection, likely due to the up-regulated IL-8 expression by the AA genotype and A allele.

### Table 7.2. Allele frequency analysis of single nucleotide polymorphisms (SNPs) by logistic regression model. (Cheng et al., 2011a).

| SNP            | Minor allele frequencya (%) | APN vs. Control | ALN vs. Control | Combined vs. Control |
|----------------|----------------------------|-----------------|-----------------|---------------------|
|                | Control | APN | ALN | Combinedb       | OR (95% CI) | P< | OR (95% CI) | P< | OR (95% CI) | P< |
| CXCR1 (rs16858808) | 1.80    | 2.21 | 3.31 | 2.87            | 1.23     | 0.72 | (0.40, 3.81) | 0.72 | (0.74, 4.70) | 0.18 | (0.68, 3.79) | 0.28 |
| CXCR2 (rs4674258)  | 33.03   | 33.63 | 30.12 | 31.54            | 1.03     | 0.87 | (0.64, 1.39) | 0.88 | (0.74, 1.19) | 0.39 | (0.72, 1.22) | 0.62 |
| IL-8 (rs4073)      | 32.65   | 40.71 | 41.27 | 41.04            | 1.42     | 1.19 | (0.98, 1.45) | 1.44 | (1.08, 1.95) | 0.01 | (1.11, 1.86) | 0.01 |
| TLR-4 (rs10759932) | 26.82   | 23.87 | 26.67 | 25.54            | 0.86     | 0.99 | (0.72, 1.37) | 1.24 | (0.70, 1.96) | 0.94 | (0.70, 1.65) | 1.24 |

a Minor allele: CXCR1, T; CXCR2, T; IL-8, A; TLR-4, C.
b Combined: APN+ALN
c The P values are shown in bold when P < 0.05.

8. Conclusion

A new imaging scheme that combines US and CT has been developed for effective ALN diagnosis. In this scheme, patients suspected of suffering from UTI [i.e. who had pyuria (> 5
WBCs/high-power field), fever without focus or any symptoms/signs related to UTI, such as knocking pain, dysuria and frequency] underwent renal US during the 1st-2nd day following their admission to hospital. The CT assessment followed immediately when the initial US findings met either one of these two 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 antibiotic-treatment commencement. ALN diagnosis was made on the basis of positive CT findings.

Further, with this scheme, we have identified that a three-week antimicrobial therapy protocol, rather than the two-week scheme commonly used for APN treatment, should constitute the treatment of choice for all radiographically documented ALN patients. As for the likelihood in scar formation following the severe parenchymal infections, we have confirmed that pediatric patients with ALN could have higher possibility for scar formation than with APN.

Through the urovirulence factor analyses, we have noted that the papG class II gene (gene associated with P-fimbriae of uropathogenic E. coli) was the most strongly associated pathogenic determinant for the pediatric ALN patients who have no underlying diseases except VUR. But PFGE analysis indicated that no major genotype was associated with the disease category. Thus the major pathogenic determinants may not be unique to any specific genetic lineage. In addition, using the MDCK epithelial cells model, we have confirmed that the ability to adhere to and produce cytotoxicity against uroepithelial cells appears a prerequisite factor for E. coli to cause more severe bacterial kidney infection, such as ALN (Cheng et al., 2011b). Much more, we have confirmed that E. coli isolates from urosepsis patients carried more virulence factors as compared to those from patients with cystitis, APN and ALN. This implicated that the number of urovirulent genes found in pathogenic isolates may be correlated with the clinical severity noted in pediatric UTIs.

For the host factors that could influence the patient’s susceptibility to the severe parenchymal infections, we have identified SNP in the inflammatory chemokine IL-8, a higher frequency in AA genotype and A allele, is involved in the susceptibility and clinical responses in pediatric APN and ALN cases. Further, among the patients without VUR, this IL-8 SNP is only noted in the ALN patients while not in the APN cases. This finding implicates that this IL-8 SNP could lead to a higher IL-8 secretion level after bacterial infection, and, subsequently, more severe inflammatory responses found in the ALN patients.

Despite of abovementioned findings in the pediatric patients with ALN, we have not explored the host genetic factors for the ALN patient prone to have recurrent UTIs. These patients might have some genetic polymorphisms that increase patient’s susceptibility to UTIs. A detailed longitudinal clinical follow-up plan would be needed to further elucidate the likely polymorphisms in these recurrent-UTI-prone ALN patients. In addition, building a proper animal model for ALN study will be attempted in the future study. The IL-8 expression level among the patients diagnosed as cystitis, APN and ALN will also be compared to each other. Since the ALN patients are also likely to have renal scarring according to our previous findings, genetic polymorphisms likely to reduce the renal scars will also be evaluated in the future studies.

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10. References

Artifoni L, Negrisolo S, Montini G, Zucchetta P, Molinari PP, Cassar W, Destro R, Anglani F, Rigamonti W, Zaccello G, Murer L. (2007) Interleukin-8 and CXCR1 receptor functional polymorphisms and susceptibility to acute pyelonephritis. J Urol 177: 1102-1106

Biggi A, Dardanelli L, Cussino P, Pomero G, Noello C, Sernia O, Spada A, Camuzzini G (2001) Prognostic value of the acute DMSA scan in children with first urinary tract infection. Pediatr Nephrol 16: 800-804

Blanco M, Blanco JE, Alonso MP, Mora A, Balsalobre C, Muñoa F, Juárez A, Blanco J (1997) Detection of pap, sfa and sfa adhesin-encoding operons in uropathogenic Escherichia coli strains: relationship with expression of adhesins and production of toxins. Res Microbiol 148: 745-755

Boam WD, Miser WF (1995) Acute focal bacterial pyelonephritis. Am Fam Physician 52: 919-924

Bouissou F, Munzer C, Decramer S, Roussel B, Novo R, Morin D, Lavocat MP, Guyot C, Taque S, Fischbach M, Ouhayoun E, French Society of Nuclear Medicine and Molecular Imaging, Loirat C, French Society of Pediatric Nephrology (2008) Prospective, randomized trial comparing short and long intravenous antibiotic treatment of acute pyelonephritis in children: dimercaptosuccinic acid scintigraphic evaluation at 9 months. Pediatrics 121: e553-e560

Cheng CH, Tsau YK, Hsu SY, Lee TL (2004) Effective ultrasonographic predictor for the diagnosis of acute lobar nephronia. Pediatr Infect Dis J 23: 11-14

Cheng CH, Tsau YK, Lin TY (2006) Effective duration of antimicrobial therapy for the treatment of acute lobar nephronia. Pediatrics 117: e84-e89

Cheng CH, Tsau YK, Su LH, Lin CL, Lin TY (2007) Comparison of urovirulence factors and genotypes for bacteria causing acute lobar nephronia and acute pyelonephritis. Pediatr Infect Dis J 26: 228-232.

Cheng CH, Tsau YK, Chen SY, Lin TY (2009) Clinical courses of children with acute lobar nephronia correlated with computed tomographic patterns. Pediatr Infect Dis J 28: 300-303

Cheng CH, Tsau YK, Chang CJ, Chang YC, Kuo CY, Tsai IJ, Hsu YH, Lin TY (2010a) Acute lobar nephronia is associated with a high incidence of renal scarring in childhood urinary tract infections. Pediatr Infect Dis J 29: 624-628

Cheng CH, Tsau YK, Kuo CY, Su LH, Lin TY. (2010b) Comparison of extended virulence genotypes for bacteria isolated from pediatric patients with urosepsis, acute pyelonephritis, and acute lobar nephronia. Pediatr Infect Dis J 29: 736-740

Cheng CH, Lee YS, Tsau YK, Lin TY. (2011a) Genetic Polymorphisms and Susceptibility for Pediatric Patients with Parenchymal Renal Infections Pediatr Infect Dis J 30: 309-314

Cheng CH, Su LH, Tsau YK, Lin TY. (2011b) Comparison of Virulence Variations on MDCK Monolayers by Escherichia coli Isolated from Acute Lobar Nephronia and Acute Pyelonephritis. New Microbiol 34: 65-72
Chiou YY, Wang ST, Tang MJ, Lee BF, Chiu NT (2001) Renal fibrosis: prediction from acute pyelonephritis focus volume measured at 99mTc dimercapto-succinic acid SPECT. *Radiology* 221: 366-370

Chroustova D, Playzova D, Urbanova I, Kolska M. (2006) Results of a five-year study of 99mTc-DMSA renal scintigraphy in children and adolescents following acute pyelonephritis. *Nucl Med Rev* 9: 46-50

Faust WC, Diaz M, Pohl HG (2009) Incidence of post-pyelonephritic renal scarring: a meta-analysis of the dimercapto-suuccinic acid literature. *J Urol* 181: 290-298

Godaly G, Bergsten G, Hang L, Fischer H, Frenđeus B, Lundstedt AC, Samielsson M, Samuelsson P, Svanborg C. (2001) Neutrophil recruitment, chemokine receptors, and resistance to mucosal infection. *J Leukoc Biol* 69: 899-906

Gordon I, Barkovics M, Pindoria S, Cole TJ, Woolf AS (2003) Primary vesicoureteric reflux as a predictor of renal damage in children hospitalized with urinary tract infection: a systematic review and meta-analysis. *J Am Soc Nephrol* 14: 739-744

Hawn TR, Scholes D, Li SS, Wang H, Yang Y, Robers, PL, Stapleton AE, Janer M, Aderem, A, Stamm, WE, Zhao LP, Hooton TM. (2009) Toll-like receptor polymorphisms and susceptibility to urinary tract infections in adult women. *PLoS ONE* 4: e5990

Hawn TR, Scholes D, Wang H, Li SS, Stapleton AE, Janer M, Anderem A, Stamm WE, Zhao LP, Hooton TM. (2009) Genetic variation of the human urinary tract innate immune response and asymptomatic bacteriuria in women. *PLoS ONE* 4: e8300

Hoberman A, Wald ER (1999) Treatment of urinary tract infections. *Pediatr Infect Dis J* 18: 1020-1021

Hoberman A, Charron M, Hickey RW, Baskin M, Kearney DH, Wald ER (2003) Imaging studies after a first febrile urinary tract infection in young children. *N Engl J Med* 348: 195-202

Hull J, Akerman H, Isles K, Usen S, Pinder M, Thomson A. (2001) Unusual haplotypic structure of IL8, a susceptibility locus for a common respiratory virus. *Am J Hum Genet* 69: 413-419

Ilyas M, Mastin ST, Richard GA (2002) Age-related radiological imaging in children with acute pyelonephritis. *Pediatr Nephrol* 17: 30-34

Jantunen ME, Siitonen A, Koskimies O, Wikström S, Kärkkäinen U, Salo E, Saxén H (2000) Predominance of class II papG allele of *Escherichia coli* in infants with normal urinary tract anatomy. *J Infect Dis* 181: 1822-1824

Jiang ZD, Okhuysen PC, Guo DC, He R, King TM, DuPont HL, Milewicz DM. (2003) Genetic susceptibility to enteroaggregative *Escherichia coli* diarrhea: polymorphism in the interleukin-8 promoter region. *J Infect Dis* 188: 506-11

Johnson JR, Moseley SL, Roberts PL, Stamm WE. (1988) Aerobactin and other virulence factor genes among strains of *Escherichia coli* causing urosepsis: association with patient characteristics. *Infect Immun* 56: 405-412

Johnson JR (1991) Virulence factors in *Escherichia coli* urinary tract infection. *Clin Microbiol Rev* 4: 80-128

Johnson JR, Russo TA, Brown JJ, Stapleton A. (1998) *papG* alleles of *Escherichia coli* strains causing first episode or recurrent acute cystitis in adult women. *J Infect Dis* 177: 97-101

Johnson JR, Stell AL (2000) Extended virulence genotypes of *Escherichia coli* strains from patients with urosepsis in relation to phylogeny and host compromise. *J Infect Dis* 181: 261-272
Studies on Clinical Characteristics, Urovirulence Factor and Host Susceptibility Gene in Pediatric Acute Lobar Nephronia

Johnson JR (2003) Microbial virulence determinants and the pathogenesis of urinary tract infection. *Infect Dis North Am* 17: 261-278

Johnson JR, Kuskowski MA, Gajewski A, Soto S, Horcajada JP, Jimenez de Anta MT, Vila J (2005) Extended virulence genotypes and phylogenetic background of *Escherichia coli* isolates from patients with cystitis, pyelonephritis, or prostatitis. *J Infect Dis* 191: 46-50

Johnson JR, Russo TA (2005) Molecular epidemiology of extraintestinal pathogenic (*uropathogenic*) *Escherichia coli*. *Int J Med Microbiol* 295: 383-404

Klar A, Hurvitz H, Berkun Y, Nadjari M, Blinder G, Israeli T, Halamish A, Katz A, Shazberg G, Branski D (1996) Focal bacterial nephritis (lobar nephronia) in children. *J Pediatr* 128: 850-853

Källenius G, Mollby R, Svenson SB, Helin I, Hultberg H, Cedergren B, Winberg J. (1981) Occurrence of p-fimbriated *Escherichia coli* in urinary tract infection. *Lancet* 2: 1369-1372

Kline MW, Kaplan SL, Baker CJ (1988) Acute focal bacterial nephritis: diverse clinical presentations in pediatric patients. *Pediatr Infect Dis J* 7: 346-349

Lee JKT, McClennan BL, Melsen GL, Stanley RJ (1980) Acute focal bacterial nephritis: emphasis on gray scale sonography and computed tomography. *AJR* 135: 87-92

Lundstedt AC, Lejonhuvfud I, Ragnarsoftr B, Karpman D, Andersson B, Svanborg C. (2007) Inherited susceptibility to acute pyelonephritis: A family study of urinary tract infection. *J Infect Dis* 195: 1227-1234.

Lundstedt AC, McCarthy S, Gustafsson MCU, Godaly G, Jodal U, Karpman D, Lejonhuvfud I, Lindén C, Matinell J, Ragnarsoftr B, Samuelsson M, Truedsson L, Andersson B, Svanborg C. (2007) A genetic basis of susceptibility to acute pyelonephritis. *PLoS ONE* 2: e825

Ma JF, Shortliffe LM. (2004) Urinary tract infection in children: etiology and epidemiology. *Urol Clin N Am* 31: 517-526

Miller T, Phillips S (1981) Pyelonephritis: the relationship between infection, renal scarring, and antimicrobial therapy. *Kidney Int* 19: 654-662

Mitsumori K, Terai A, Yamamkto S, Yoshida O. (1998) Identification of S, F1C and three PapF fimbrial adhesins in uropathogenic *Escherichia coli* by polymerase chain reaction. *FEMS Immunol Med Microbiol* 21: 261-268

Moorthy I, Easty M, McHugh K, Ridout D, Biassoni L, Gordon I (2005) The presence of vesicoureteric reflux does not identify a population at risk for renal scarring following a first urinary tract infection. *Arch Dis Child* 90: 733-736

Moreno E, Planells I, Prats G, Planes AM, Moreno G., Andreu A. (2005) Comparative study of *Escherichia coli* virulence determinants in strains causing urinary tract bacteremia versus strains causing pyelonephritis and other sources of bacteremia. *Diagn Microbiol Infect Dis* 53: 93-99

Nosher JL, Tamminen JL, Amorosa JK, Kallich M (1988) Acute focal bacterial nephritis. *Am J Kidney Dis* 11: 36-42

Orellana P, Baquedano P, Rangarajan V, Zhao JH, Eng ND, Fettich J, Chaiwatanarat T, Sonmezoglu K, Kumar D, Park YH, Samuel AM, Sixt R, Bhatnagar V, Padhy AK. (2004) Relationship between acute pyelonephritis, renal scarring, and vesicoureteral reflux. Results of a coordinated research project. *Pediatr Nephrol* 19: 1122-1126

Otto GS, Sandberg T, Marklund BI, Ulleryd P, Svanborg C. (1993) Virulence factors and pap genotype in *Escherichia coli* isolates form women with acute pyelonephritis, with or without bacteremia. *Clin Infect Dis* 17: 448-456

www.intechopen.com
Polito C, Rambaldi PF, Signoriello G, Mansi L, La Manna A (2006) Permanent renal parenchymal defects after febrile UTI are closely associated with vesicoureteric reflux. *Pediatr Nephrol* 21: 521-526

Rathore NH, Barton LL, Luisiri A (1991) Acute lobar nephronia: a review. *Pediatrics* 87: 728-734

Rosenfield AT, Glickman MG, Taylor KJ, Crade M, Hodson J (1979) Acute focal bacterial nephritis (acute lobar nephronia). *Radiology* 132: 553-561

Riccabona M. (2003) Urinary tract infections in children. *Curr Opin Urol* 13: 59-62

Ruiz J, Simon K, Horcajada JP, Velasco M, Barranco M, Roig G, Moreno-Martinez A, Martinez JA, Jimenez de Anta T, Mensa J, Vila J. (2002) Differences in virulence factors among clinical isolates of *Escherichia coli* causing cystitis and pyelonephritis in women and prostatitis in men. *J Clin Microbiol* 40: 4445-4449

Rushton HG. (1997) Urinary tract infections in children: epidemiology, evaluation, and management. *Pediatr Clin N Am* 44: 1133-1169

Sargent MA, Stringer DA. (1995) Voiding cystourethrography in children with urinary tract infection: the frequency of vesicoureteric reflux is independent of the specialty of the physician requesting the study. *AJR Am J Roentgenol* 164: 1237-1241

Shimizu M, Katayama K, Kato E, Miyayama S, Sugata T, Ohta K (2005) Evolution of acute focal bacterial nephritis into a renal abscess. *Pediatr Nephrol* 20: 93-95

Siitonen A, Martikainen R, Ikaheimo R, Palmgren J, Makela PH. (1993) Virulence-associated characteristics of *Escherichia coli* in urinary tract infection: a statistical analysis with special attention to type 1C fimbriation. *Microb Pathogen* 15: 65-75

Sivick KE, Mobley HL. (2010) Waging war against uropathogenic *Escherichia coli*: winning back the urinary tract. *Infect Immun* 78: 568-585

Smithson A, Sarrias MR, Barcelo J, Suarez B, Horcajada JP, Soto SM, Soriano A, Vila, J, Martinez JA, Vives J, Mensa J, Lozano F. (2005) Expression of interleukin-8 receptors (CXCR1 and CXCR2) in premenopausal women with recurrent urinary tract infections. *Clin Diagn Lab Immunol* 12:1358-1363

Soulen MC, Fishman EK, Goldman SM, Gatewood OMB (1989) Bacterial renal infection: role of CT. *Radiology* 171: 703-707

Tseng CC, Huang JJ, Ko WC, Yan JJ, Wu JJ (2001) Decreased predominance of papG class II allele in *Escherichia coli* strains isolated from adults with acute pyelonephritis and urinary tract abnormalities. *J Urol* 166: 1643-1646

Tseng CC, Wu JJ, Liu HL, Sung JM, Huang JJ (2002) Roles of host and bacterial virulence factors in the development of upper urinary tract infection caused by *Escherichia coli*. *Am J Kidney Dis* 39: 744-752

Uehling DT, Hahnfeld LE, Scanlan KA (2000) Urinary tract abnormalities in children with acute focal bacterial nephritis. *BJU Int* 85: 885-888.

Wang MC, Tseng CC, Chen CY, Wu JJ, Huang JJ (2002) The role of bacterial virulence and host factors in patients with *Escherichia coli* bacteremia who have acute cholangitis or upper urinary tract infection. *Clin Infect Dis* 35: 1161-1166

Winberg J, Bollgren I, Kallenius G, Mollby R, Svenson SB (1982) Clinical pyelonephritis and focal renal scarring: a selected review of pathogenesis, prevention, and prognosis. *Pediatr Clin North Am* 29: 801-814

Zaontz MR, Fahiria JJ, Woffman M, Gargurevich AJ, Zeman RK (1985) Acute focal bacterial nephritis: a systematic approach to diagnosis and treatment. *J Urol* 133: 752-757

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