

New Insights for Febrile Urinary Tract Infection (Acute Pyelonephritis) in Children

Kyung-Yil Lee, M.D.

Departments of Pediatrics, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Daejeon, Republic of Korea

Corresponding author: Kyung-Yil Lee, M.D.
Department of Pediatrics, The Catholic University of Korea Daejeon St. Mary's Hospital, 64 Daeheung-ro, Jung-gu, Daejeon 34943, Korea
Tel: +82-42-220-9541
Fax: +82-42-221-2925
E-mail: leekyungyil@catholic.ac.kr

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Although asymptomatic bacteriuria, cystitis, and acute pyelonephritis (APN) have been categorized as urinary tract infections (UTIs), the immunopathogenesis of each disease is different. APN shows an age predilection; the majority of children (over 70-80%) with APN are under 1-2 years of age, with a male predominance. After 1-2 years of age, female predominance has been reported. This finding suggests that the immature immune state of infancy may be associated with the pathogenesis of APN. *Escherichia coli* is the most common etiologic agent; other uropathogens associated with UTIs originate from the host and comprise normal flora that are continuously altered by environmental factors. Therefore, uropathogens may have characteristics different from those of extraneous bacterial pathogens. Although antibiotic-resistant uropathogens, including extended-spectrum beta-lactamase-producing strains, are increasing in Korea and worldwide, treatment failure is rare in immune-competent children. The immunopathogenesis of APN remains unknown. Intact bacteria may not be the causative substances in renal cell injury; rather, smaller substances produced during bacterial replication may be responsible for renal cell injury and scarring. Moreover, substances from host cells such as proinflammatory cytokines may be involved in renal cell injury. A dimercaptosuccinic acid scan is used to detect the site of bacterial replication in the renal parenchyma, and may be influenced by the size of the focus and the stage of APN. Traditional aggressive studies used to identify vesicoureteral reflux after the first episode of APN have been modified because of rare cases of chronic kidney disease in patients with recurrent UTI.

Key words: Urinary tract infection, Pyelonephritis, Epidemiology, Uropathogen, Pathogenesis, Children

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Introduction

Urinary tract infections (UTIs) are one of the most common bacterial infections in childhood. There are three basic forms of UTIs: pyelonephritis, cystitis, and asymptomatic bacteriuria. Acute febrile UTI or acute pyelonephritis (APN) is a serious bacterial disease which can induce renal scar and renal insufficiency, especially with recurrent infections¹⁾. Childhood APN may be an age-dependent disease. Among childhood patients with APN, the majority of patients (over 70-80%) are under 1-2 years of age with a male predominance. After 2 years of age, female predominance has been noted in APN²⁻⁵⁾. These findings suggest that the immature immune state of infancy may

be associated with the pathogenesis of APN, and that uropathogens may not enter through an ascending route in young infants.

Escherichia coli (*E. coli*) and other uropathogens of UTIs originate from the host. Thus, uropathogens may have characteristics that differ from those of external bacterial pathogens that have high virulence. Antibiotic resistant uropathogens, including extended-spectrum beta-lactamase producing (ESBL) strains, are increasing in Korea and around the world^{6,7}. However presently, treatment failure of conventional antibiotic treatment seems to be rare in children with UTIs in Korea. Although the etiologic agents of APN are easily identified, the immunopathogenesis of renal cell injury in APN remains unknown. Vesicoureteral reflux (VUR) is believed to be a main risk factor for recurrent APN. However, traditional aggressive studies to identify VUR have recently changed because of rare cases of chronic kidney disease in patients with recurrent UTI⁸⁻¹⁰.

This paper discusses some unsolved issues regarding APN and briefly reviews the epidemiology, immunopathogenesis, diagnosis, and treatment of childhood APN.

Epidemiology

The prevalence of childhood UTI differs according to age and sex. It is estimated that approximately 1.6-1.8% of males and 6-7.8% of females experience a UTI during the first 6-7 years of age^{3,5}. Previous epidemiological and clinical studies on children with UTIs reported that the majority of patients are infants under 1-2 years of age with male predominance, but after 2 years, the incidence is relatively even in all age groups with female predominance²⁻⁵. Among UTIs, the proportion of asymptomatic bacteriuria or cystitis may be higher than APN. However, patients with APN have been the main subjects of UTI studies because of the possibility of chronic kidney disease. APN may be the most common systemic bacterial infection in childhood. Elderly patients with APN, especially those with underlying diseases, are susceptible to severe APN as well as other infections including influenza and hemolytic uremic syndrome^{11,12}.

In recent data from 2005 to 2015 (n= 355), we found that 83.4% of patients with febrile UTI or APN were <24 months and the male: female ratio was 1.9:1, whereas 18% of pati-

ents with APN were >2 y with female predominance (1:5.3). In addition, annual cases showed some fluctuations, and there was a trend toward increasing cases in recent years. APN occurred throughout the year, but more cases were seen in spring and summer (unpublished observation). Recent studies have also reported that childhood UTI, including patients visiting the emergency department, has been increasing¹³. During the same study period of a decade, we had 281 patients with Kawasaki disease (KD) which also predominantly occurs in young children aged <5 years of age. Nationwide epidemiological studies in Korea have reported that the annual incidences of KD were 115-134/100,000 in patients <5 years of age during 2009-2011¹⁴. Therefore, the recent annual incidence of APN per 100,000 patients <5 years of age may be calculated as slightly higher than that of KD in Daejeon, Korea. The epidemiological age predilection of APN and KD is so unique that it is rarely observed in other contagious bacterial diseases, including scarlet fever in the past, salmonellosis, or hemolytic uremic syndrome, which are caused by external pathogens. Since the majority of uropathogens in APN originate from the host intestinal microbiota (or normal flora), a breakdown of the host-microbiota relationship may be important to establish APN. The human immune system is considered to continuously mature after birth, and some aspects of immune function may be immature in infants. Infants may have immature immune function, such as weakened barriers against microbiota invasion or replication of pathogens in vivo.

Characteristics of uropathogens

UTI is considered an infectious disease, but its contagiousness to other persons is very low because the majority of UTIs are caused by microbiota of the same species. Gram-negative bacteria are major UTI pathogens. *E. coli* species are the most common (75-90%), followed by *Klebsiella* spp. and *Proteus* spp. In gram-positive bacteria, *Staphylococcus saprophyticus* and enterococcus are predominant in both sexes¹.

There are hundreds of types of microbiota in the human gastrointestinal tract that are called commensal bacteria or normal flora. Mammals and their microbiota in the in-

testines, skin, upper respiratory tract, and lower urinary tract may have co-evolved. It is believed that these bacteria groups may have initially been external pathogens that have adapted with hosts. Commensal bacteria may help to prevent from colonization of other external pathogens and provide some beneficial materials such as vitamins for the host^{15,16}. In the mucosal immune system, gut-associated lymphoid tissues (GALT) were established after colonization of microbiota. These findings suggest that microbiota and host immune systems may communicate with each other in some aspects^{15,16}. Although microbiota in intestines and in other regions can cause infections when they invade and replicate in the host, microbiota may be less virulent compared to other external pathogens. For example, bacteremic APN is not uncommon in healthy young infants, but severe sepsis is extremely rare in immune-competent infants¹⁷.

The microbiota in an individual and in a species may continuously change due to environmental factors such as diets, antibiotic use, and adaptation of a pathogen to the host and population (herd immunity). Microbiota are different in different individuals, ethnic groups, and cultural environments^{15,16,18,19}. Antibiotic-resistant microbiota (*E. coli*) can spread to other populations via unknown mechanisms, including people living in a remote area with no previous antibiotic use²⁰. It is possible that uropathogens, including *E. coli* strains, in UTIs could differ across the populations and change to milder strains over time. For example, *E. coli* was the most common agent of neonatal meningitis in the past in Korea. After the early 1990s, group B streptococcal strains (GBS) substituted *E. coli* as well as in the developed countries^{21,22}. Before the early 20th century, scarlet fever caused by group A streptococci (GAS) was a severe disease with occasional fatal cases in children. However, the severity and incidence of scarlet fever and its complications such as acute rheumatic fever and acute poststreptococcal glomerulonephritis are now milder and lower^{23,24}. Now, the prevalence of GAS carriers in healthy children is higher in the populations²⁵, suggesting that GAS strains may have adapted to being normal flora of the upper respiratory tract. Uropathogens that are resistant to antibiotics such as ampicillin, sulfa drugs, quinolones, and 3rd generation cephalosporins have been well documented²⁶. These strains, including ESBL strains, may be the chan-

ging microbiota in individuals and possibly in the populations during adaptation to hosts. Therefore, it is possible that these strains may not act as external pathogens with high virulence in immune-competent hosts.

Pathogenesis of UTIs

Asymptomatic bacteriuria, cystitis, and APN are categorized as UTIs. However, the immunopathogenesis of each disease is different. Asymptomatic bacteriuria is common in healthy children, especially in adolescent females. Earlier studies reported that approximately 1% of schoolgirls had asymptomatic bacteriuria²⁷. Although it is controversial if asymptomatic bacteriuria can induce UTI and APN in healthy children, previous data suggest that asymptomatic bacteriuria may not be a precursor to symptomatic UTI^{3,27,28}. Furthermore, it is suggested that low virulence bacteria in children with asymptomatic bacteriuria may protect against UTI as microbiota of the lower urinary tract³.

Cystitis is a localized infection without systemic symptoms such as fever, bacteremia, or renal scar, suggesting that the uropathogens of cystitis do not invade into the systemic circulation. Additionally, laboratory findings do not reflect systemic inflammation, with no leukocytosis or increased C-reactive protein (CRP) levels. In general, immune-competent patients with cystitis do not have co-infection with APN. Conversely, few APN patients have cystitis symptoms and signs such as dysuria and urinary urgency. This suggests that patients with cystitis have primary foci on the urethra and/or bladder mucosa where bacteria replicate and produce etiological substances that cause clinical symptoms as a localized infection. Conversely, patients with APN have foci located in the renal parenchyma as a systemic disease.

The majority of uropathogens, including *E. coli*, are extracellular pathogens. They replicate in the extracellular space and create a focus in the renal parenchyma for disease progression. In infectious diseases, intact bacteria themselves may not induce cell injury. The smaller substances produced during their replication processes, such as virulence factors, may be responsible for renal cell injury. Clinical symptoms and signs of APN, such as high spiking fever, malaise, vomiting, flank pain, and renal cell injuries,

may result from release of these substances into systemic circulation and nearby local regions. A focus of APN produces many substances, including replicated bacteria, bacterial exotoxins, fragments of bacterial components such as lipopolysaccharides (LPS) and pathogen-associated molecular patterns (PAMPs), materials from injured cells, including danger (or damage)-associated molecular patterns (DAMPs), and materials from activated immune cells, such as proteolytic enzymes and proinflammatory cytokines²⁹. The virulence factors of *E. coli* have been investigated to demonstrate adhesion molecules such as P fimbriae, K antigen, hemolysins, colicins, and LPS^{30,31}.

What controls these diverse substances to cause renal cell injury and subsequent renal scar? It is proposed that all infectious diseases have a focus in which etiologic substances inducing cell injury are produced, and that the host immune system controls these substances based on the size and biochemical characteristics of the substances²⁹. Etiologic substances have variable sizes and originate not only from exogenous sources but also from host cells, including DAMPs from injured host cells and cytokines from activated immune cells. Etiologic substances may also be classified as protein substances and non-protein substances. The adaptive immune system controls protein substances according to their size and characteristics. B cells control medium-sized proteins through antibody production while T cells control peptides (12-30 amino acid residues) with the TCR-associated immune response. The innate immune system, including natural antibodies, may control a variety of non-protein substances. Phagocytic cells such as monocytes and neutrophils eliminate large complex materials, such as bacteria, viruses, apoptotic bodies, and necrotic debris. Small non-protein substances, such as PAMPs and DAMPs, are controlled by pattern recognition receptors on innate immune cells, including toll-like receptors²⁹. Therefore, the fate of an APN focus depends on the immune reaction to the etiologic substances. Complications of APN include nephronia, renal abscess, interstitial nephritis, and xanthogranulomatous PN. Fatal sepsis can occur rarely, especially in immune-compromised patients. Additionally, there are various cystitis phenotypes, including acute hemorrhagic cystitis, eosinophilic cystitis, and interstitial cystitis. These various conditions may be associated with different etiologic substances against target renal or cystic

cells and corresponding immune cells.

APN with bacteremia is not uncommon in young infants, however, the prognosis may not differ in infants without bacteremia^{32,33}. It has been reported that 0.5-1% of febrile young infants who visited the emergency department show bacteremia with *S. pneumoniae* or *E. coli* or other pathogens. The incidence of *S. pneumoniae* bacteremia has markedly decreased after application of the pneumococcal vaccine. However, the incidence of *E. coli* bacteremia remains relatively constant^{34,35}. These results suggest that normal flora invade into the systemic circulation of healthy young infants not uncommonly, and *E. coli* invasion in APN may be hematogenous in infants. Uropathogens in male infants should have a long journey from the prepuce to renal parenchyma cells against a physiologic antireflux mechanism and continuously acting urine stream. They would need to penetrate the barrier of uroepithelial cells of the renal pelvis and invade into renal parenchymal tissues. It is possible that intestinal flora, possibly during construction of microbiota in early life, may penetrate intestinal cell walls and elicit a transient bacteremia. These bacteria may be removed from the circulation in the majority of immune-competent persons, but infants with maturing immune systems may allow bacteremia, and bacteria reach kidney cells via systemic circulation. *E. coli* and other uropathogens may have an affinity to renal cells, likely *E. coli* P fimbriae to uroepithelial cells, which creates a focus in the renal parenchyma. Considering the number of bacteria invading through uroepithelial cells or intestinal cells, the hematogenous route is the most likely. In addition, some patients with APN have multiple defects in both kidneys on ^{99m}technetium-dimercaptosuccinic acid (DMSA) scan.

Diagnosis

Diagnosis of UTI, including APN, depends on urine culture for confirmation (>10⁵ colony-forming units/mL)⁸⁻¹⁰. However, the methods of urine culture and urinalysis may be not standardized across laboratories³⁶. There are several methods to obtain a urine sample. Midstream urine is commonly used in toilet-trained children. A guideline recommends that for children aged 2-24 months, catheterization or suprapubic aspirate should be used as a confirmation

test⁸⁾. While in other guidelines, these methods are not obligated and are proposed as the method of choice for clean-catch urine in young children^{9,10)}. Invasive methods may be difficult to perform, especially in uncircumcised young male infants with a risk of infection or injury to the urethra or bladder wall and surrounding tissues. In clinical practice, the majority of uropathogens are intestinal flora, mainly *E. coli*. Results of urine culture obtained 2-4 days after initiating antibiotic treatment rarely influences treatment for uncomplicated APN patients. However, urine culture is helpful for complicated APN, including non-responsiveness to antibiotics and atypical bacterial infections. Since replicated pathogens and products resulting from the immune response are released from a focus in the renal parenchyma into urinary flow, leukocytes, leukocyte esterase, nitrites, bacteria, and other immune substances are detected in urinalysis.

The majority of febrile young children with APN whose urine is obtained by sterile collection bag show urinary abnormalities, including pyuria (>5 leukocyte/HPF), leukocyte esterase, nitrites, and bacteriuria via automatic urine analyzer within 1 hour in most referral hospitals in Korea. Since early treatment is essential to prevent further renal cell injury, rapid urine analysis may be useful for early treatment of febrile infants suspected to have APN before obtaining urine culture results⁹⁾. Also, the majority of infants with suspected APN subsequently show single uropathogen growth in urine culture. The sensitivity and predictive values of urine segments of pyuria, leukocyte esterase, and nitrites is closely matched to urine culture results^{1,33,37-39)}. Therefore, >2-3 positive of the 4 parameters is a strong suggestion of APN in febrile infants. Some patients who have early lesions that do not communicate with urinary flow may not show urinary abnormalities. Therefore, follow-up urine tests on infants with unexplained febrile illness are necessary⁸⁾. Contamination of lower urinary tract lesions can create false positive results. However, there are few of these cases in children with febrile UTI.

Imaging studies such as renal ultrasonography, DMSA scan, and computed tomography (CT) scan have been used to detect the site of pathogenic bacteria replication, that is, the focus of APN. However, early lesions in the renal parenchyma of febrile infants with APN may be too small to appear in these imaging studies. Ultrasonography may only

detect large lesions such as nephronia, renal abscess, and hydronephrosis. DMSA scan is helpful to detect parenchyma lesions in both experimental and clinical studies⁴⁰⁾. However, the detection rates of DMSA scan with first febrile UTI may vary (26-79%), and the age of patients and time of imaging study are not uniform among study groups⁴¹⁻⁴³⁾. Positive rates of DMSA scan are lower in infants compared to older children, suggesting early examination and/or small focal lesions in young infants. Early defects in APN were reported to resolve in over 50% of patients in follow-up studies⁴¹⁻⁴⁴⁾. Furthermore, DMSA scan studies on experimental animals with full-blown APN or older children with advanced APN show various defects; a large defect which is not compatible to clinical symptoms in one kidney, multiple defects in one or both kidneys, or total discrepant density in one kidney compared to the contralateral kidney. The positivity of DMSA scan is higher in patients with VUR than in those without, and the positive rate is correlated to the severity of VUR⁴⁵⁾. However, many patients without VUR are DMSA scan positive, and some patients with VUR have renal scars that progress without infections⁴⁶⁾. These findings suggest that the defects in DMSA scan in the acute stage may not indicate real renal cell injury but rather functional disability of renal tubular cells. It is possible that certain substances readily preformed in the primary focus may act on renal tubule cells or renal vascular cells, and this event inhibits radioactive elements (DMSA) binding to renal tubular cells. Also, existing congenital renal abnormalities such as focal dysplastic kidney with VUR may influence DMSA uptake⁴⁶⁾. DMSA imaging may have limitations for diagnosis of early APN lesions, but it is useful for follow-up of APN to detect renal scars⁸⁻¹⁰⁾. The detection rates of renal CT or renal MRI studies also vary, and may be influenced by the disease stage of APN or the size of primary foci. These methods are helpful for patients with complicated or intractable APN⁴⁷⁾.

Since APN is a systemic inflammatory reaction against substances produced from a renal focus, its severity is reflected by laboratory parameters, including leukocytosis, CRP, procalcitonin, erythrocyte sedimentation rate, and cytokines such as interleukins^{48,49)}. Although these parameters are not specific for APN, together with abnormal urinalysis findings in febrile children, they may be helpful for early treatment of APN.

Voiding cystoureterography (VCUG) is recommended for detection of VUR. VUR is a risk factor for recurrent APN and subsequent renal damage⁵⁰. Mild grade VURs are relatively common in infants, with regression over time. VUR is mainly detected in patients with their first episode of APN by routine application of VCUG⁵¹. Since prophylactic antibiotic therapy for patients with VUR does not prevent recurrent infection and infants with higher grades of VUR need follow-up period for surgical repair, VCUG is not routinely recommended for patients with first APN⁸⁻¹⁰. It is reasonable to perform VCUG in atypical or complex clinical conditions, such as abnormal ultrasonography findings or recurrent APN cases⁸.

Treatment

Acute cystitis is treated with oral antibiotics for 4-5 days at outpatient base⁸⁻¹⁰. In Korea and other countries, a significant proportion of *E. coli* strains isolated from UTI patients are resistant to ampicillin and trimethoprim-sulfamethoxazole. Recently, ESBL strains and quinolone resistant strains have also increased^{7,52}. Antibiotics for children with cystitis in Korea include oral amoxicillin/clavulanate or 3rd generation cephalosporins such as cefixime (Suprax), cefditoren (Meiact), or cefpodoxime (Banan). For acute febrile infants with suspected APN, admission based treatment with intravenous broad-spectrum antibiotics is common in Korea. Ceftriaxone, cefotaxime, or amoxicillin/clavulanate with an aminoglycoside such as gentamicin or amikacin has been recommended. After defervescence and obtaining a sensitivity test for pathogens, physicians can substitute parenteral antibiotics to oral 3rd-generation cephalosporins for early discharge⁸⁻¹⁰. Antibiotic treatment for 7-14 days may be sufficient for uncomplicated APN. Antibiotics can be changed for intractable cases based on the results of urine culture. These patients can be treated with suitable antibiotics, including carbapenems, quinolones, and aminoglycosides for children.

Although bacterial infection is a self-limited disease in the majority of immune-competent persons, early use of antibiotics is critical to reduce morbidity and prevent renal scars and mortality. However, antibiotics are not always successful, regardless of drug resistance. For example, some

patients with severe APN with or without sepsis experience treatment failure with high mortality, especially elderly patients with underlying diseases or neonates^{11,12}. Some patients with bacterial sepsis experience transient deterioration of clinical symptoms and signs after antibiotic treatment due to “cytokine storm”⁵³. A hyperactive immune response to etiologic substances is considered responsible for host cell injury, and early immune modulators (corticosteroids and intravenous immunoglobulin) may control overproduced immune substances such as proteolytic enzymes and proinflammatory cytokines²⁹. A study group reported that corticosteroid treatment with antibiotics for APN showed better renal scar outcomes⁵⁴. This treatment policy may also be beneficial to reduce morbidity for patients with prolonged fever or an intractable clinical course after suitable antibiotic treatment, but further studies are needed for confirmation.

The preventive antibiotic policy for patients with VUR has also changed. Many recent studies have reported that prophylactic antibiotic therapy is not effective in preventing recurrent UTIs in young children with VUR, and it may increase the risk of developing drug-resistant strains^{55,56}. New antibiotic-resistant strains may cause recurrent disease or bacterial invasion in APN through a mechanism other than the ascending route in infants.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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