IJMPR 2020, 4(3), 131-139

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 5.273

URINARY TRACT INFECTION IN NEWBORNS AND INFANTS THREE YEARS OF AGE AND YOUNGER

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Received on: 25/04/2020
Revised on: 15/05/2020
Accepted on: 05//06/2020

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ABSTRACT

An analysis of the literature (71 references) on urinary tract infections (UTI) in newborns and infants 3 years or less is presented. The etiology and pathogenesis of diseases, the sensitivity of pathogens to antibiotics, the use of antibiotics for the treatment and prevention of infection are considered. The characteristics of laboratory diagnostics and the clinical course of UTI are given.

KEYWORDS: Newborn, infant, urinary tract infection, pathogens, antibiotic.

INTRODUCTION

Urinary tract infection (UTI) is one of the most common pathologies in the general population. Among patients with infectious and inflammatory diseases (IID), an infection of the urinary system is ranges from 12.3%.[1] to 34.5%.[2] Interest in this problem among pediatricians is associated with a high prevalence of the disease and the development of severe complications, including wrinkling of the kidneys, development of chronic renal failure and disability of children.[3,4] Accurate and timely diagnosis of these infections is important for determining appropriate treatment and preventing long-term complications such as renal scarring, hypertension, and end-stage renal disease.[5] The UTI of newborns, especially those who are premature, also remains an urgent problem. The frequency of UTI in the structure of diseases of the urinary system in newborns is 37.3%.[6]

The rate of UTI among premature newborns with pneumonia is14%, and full-term newborns with pneumonia -10% in our clinic.

According to the literature, inflammatory changes in the clinical analysis of urine were observed in 25% of newborn infants in the intensive care unit and in the post-resuscitation period.[6] According to Kuppermann N, et al (2019), the UTI frequency in infants under 60 days of age (mean age 36 days) in a children's hospital was 8.3% among infants with infection.[7]

UTI in newborns is often the cause of the development of severe chronic kidney disease and disability.[8,9,10]

Currently, the concept of a close relationship between the pathology of the internal organs of a person and a dysfunctional course in the ante-intra- and postnatal periods of the body's development is being intensively developed.

The role of antenatal morphological and functional lesions of tissues and organs in the pathogenesis of chronic diseases is emphasized.[2,4,8,11]

One of the main damaging factors that negatively affect all organs is fetal and newborn hypoxia.[11,12] It is known that morphofunctional disorders formed antenatally can manifest not only in the neonatal period, but also in the future, months, years, and even decades later. In this regard, early detection of diseases, including urinary system before birth, in the first months and years of life

allows early treatment and to prevent chronic process.[2,9,13]

A small number of symptoms and nonspecific clinical manifestations of kidney and urinary tract diseases in newborns and children of the first three years of life make timely diagnosis difficult. The consequence is the late conduct of adequate treatment and the formation of chronic pathology.[14,15]

Difficulties in determining the localization of the pathological process in the urinary system, where inflammation has developed, especially in infants under three years of age, caused the emergence, approval and application of the term "urinary tract infection"(UTI). Currently, the term UTI includes infectious and inflammatory diseases in any part of the urinary system (pyelonephritis, cystitis, urethritis) and asymptomatic bacteriuria.[4,9,10,11,14]

It is necessary to pay attention to asymptomatic bacteriuria. Asymptomatic bacteriuria is the persistence in the urine of microorganisms in a diagnostically significant titer in the absence of clinical and laboratory symptoms of the inflammatory process in the organs of the urinary system.[11,13,16,17]

This condition can turn into an infectious process with clinical manifestations under adverse conditions, especially in infants (hypoxia, temperature disorders, nutritional changes, neurological disorders, etc.).[4,13,16]

Our study showed that asymptomatic bacteriuria was detected in 10.7% of conditionally healthy preterm infants (birth weight less than 1500 g) and 3.6% of more mature conditionally healthy preterm infants (body weight more than 1500 g; $p<0.05$). The frequency of asymptomatic bacteriuria in deeply premature infants with infectious and inflammatory diseases tended to increase (1.8 times) compared with more mature infants with the same infectious diseases and amounted to 15% and 8.5%, respectively. Asymptomatic bacteriuria in deeply preterm infants with IID was detected 1.4 times more often than in relatively healthy infants with the same gestational age, and in more mature infants with UTI - 2.4 times more often than conditionally healthy with a similar gestational age. Apparently, the lower frequency of bacteriuria in more mature infants (both conditionally healthy children and newborns with IID) compared with deeply premature infants is associated with the activity of local immunity in the former, which in most cases successfully resisted the formation of an infectious process in the organs of the urinary system.

Etiology and pathogenesis. The effectiveness of the treatment of UTI largely depends on knowledge of modern etiology and adequate antibiotic therapy. The etiological structure of UTI in newborn infants is very diverse.[2,7,15]

According to our clinic, in premature newborn infants with birth weight from 780 g to 3000 g and gestational age from 27 to 37 weeks, the majority of UTI pathogens were represented gram-negative microorganisms. Among them, most often (48-50%) bacteria of the *Enterobacteriaceae* were found (with the highest frequency of *Escherichia c*oli (*E. coli*) in 22%, *Klebsiella pneumoniae* 14%, *Proteus vu*lgaris 10%, *Enterobacter cloacae* 6%, Citrobacter spp. 2%). *Pseudomonas aeruginosa* (*Ps. aer ginosa*) was found in 8% of infants, including a hospital strain in 4%. *Stenotrophomonas maltophilia* was found in only 2% of infant. Gram positive cocci were found in 2-20% of infants. *Staphylococcus spp*. were found in 6% of infants (*S.epidermidis*, S. *haemoliticus and S. aureus, 2% each). Enterococcus faecalis (E. faecalis) was detected in 20%. Candida spp.* were found in 7-40% of infants. The etiology of UTIs in infants with a birth weight of less than 1500 g was characterized by a high frequency of bacterial and *Candida spp* associations. Asymptomatic bacteriuria was detected in 11.4% of newborns and is represented by the same spectrum of microorganisms as UTI pathogens.

According to other authors.[9,18] in infants older than one month, the main causative agents of UTI were found *Enterobacteriaceae* (over 80%) in Russia. Among them, *E. c*oli was most often found (41-83%). Species such as *Proteus spp*., *Klebsiella pneumonia* (*K. pneumonia*), *Enterobacter spp*., were found in 8% of infants. *Pseudomonas spp*., found in 5%, *Staphylococcus aureus* (*S. aureus*) in 4%. *Klebsiella oxytoca*, *Citrobacter diversus*, *Serratia marcescens*, *Acinetobacter spp*., *Streptococcus pyogenes*, *Flavobacter spp*. and *Candida krusei* were rare (≤1% of children).

Other authors also pointed out the predominance of Gram negative microflora in the etiology of UTI.[4,19] Melnikova et al. (2017) reported high inoculation *of Enterococcus faecalis* (*E. faecalis*) from the urine of newborn children in a hospital.[20]

In young children, a diverse microflora is sown from urine. Gram negative bacteria prevail over Gram-positive bacteria and occur with the following frequency: *E. coli* - 40-90%, *Klebsiella spp*. - 7-20%, *Proteus mira*bilis - 9-16%, *Staphylococcus sp*p., *E. faecalis* and Streptococcus spp. - 10-20%. The authors also found associations of bacteria (*E.clil + Klebsiella spp*., *E.coli + E. faecalis*) and viruses (*Adenoviridae, Human coxsackievirus B*).[9] A number of authors also indicate a high inoculation from the urine of *E. coli* and *K. pneumonia* in children.[21,22,23,24]

Among the general population in China, including children under three years old, gram-negative bacteria are most common: *Ps. aeru*ginosa (9.4%), *Acinetobacter baumannii*, (7.9%), *K. pneumoniae* (7.3%) and *E. coli* (6.6%)[1]. Many authors report the isolation of hospital bacteria strains from urine in patients with UTI. Among

pathogens, polyresistant strains of *K. pneumonia*, *E. coli* are most often found.[24,15,26]

In our clinic, hospital strains of Ps. aeruginosa and *Enterobacter liquefaciens* were isolated from the urine of full-term and premature newborns. These hospital strains had antibiotic resistance. The appearance of extended-spectrum β-lactamases (ESBL) in hospital strains of *E. coli* and *K. pneumoni*a was the cause of the often observed failure of empirical treatment of UTI. These isolates showed resistance to third-generation cephalosporins, ampicillin and trimethoprim-sulfamethoxazole.[27]

Hospital strains of *Enterobacteriaceae* (*K. pneumoniae*, *Enterobacter spp*., *E. coli*, *Yersinia spp*., *Proteus mirabilis*, *Salmomella enterica*, *Citrobacter koseri*, *Serratia spp*., *Providencia rettgeri* and others), *Acinetobacter baumanni* and *Ps. aeruginosa* isolated in a training hospital (Ghana, India) in patients with infection from different biomaterials, mainly from urine, showed high resistance to ampicillin (94.4%), trimethoprim / sulfamethoxazole (84.5%), cefuroxime (79%) and cefotaxime (71.3 %), but low resistance to ertapenem (1.5%), meropenem (3%) and amikacin (11%). The average multidrug resistance was 89.5% and ranged from 53.8% in *Enterobacter spp*. up to 100.0% in *Acinetobacter spp*. and *Ps. aeruginosa* According to researchers from Spain, the degree of susceptibility to antibiotics of bacteria isolated from urine in children aged 1 month to 15 years was: ampicillin 36.3%, amoxicillin / clavulanic acid 75.3%, cefuroxime 83.2%, co-trimoxazole 68.9%, ciprofloxacin 85.3%, phosphomycin 85.5%, nitrofurantoin 84.4% and 3rd generation cephalosporins. aminoglycosides (> 92%) and carbapenems (95%) maintained their highest sensitivity [28]. Thus, the spectrum of UTI pathogens and their sensitivity to antibiotics are very diverse. The choice of treatment should be based on the epidemiological situation and the sensitivity of pathogens to antibiotics in the appropriate hospital or region.[28,29,30]

E. coli confers resistance against of antibiotics due to the production of extended spectrum β-lactamase enzymes (ESBL), biofilm, etc. Biofilm produced by uropathogenic *E. coli* protects from host immune system and prevent entry of antimicrobial compounds. Shrestha R, et al. (2019) found that 51% of uropathogenic *E. coli* strains were ESBL producers and 54% were biofilm producers. In addition, a positive correlation was shown between biofilm genes pga A and pga C, and ESBL production.[25]

Violation of the intestinal microbiocenosis system is one of the mechanisms of the formation of UTI in infants up to three years of life. Intestinal microflora can contaminate the external organs of the genitourinary system with subsequent vertical infection of the urinary tract and kidneys.[3,9,11,18] There is a view that microorganisms can penetrate into the bladder bypassing the urethra, hematogenous and lymphogenous way method of the translocation from the intestine.[31] According to many authors, urodynamic disorders, primarily vesicoureteral reflux, are of primary importance in the development of microbial-inflammatory process in the kidneys in newborns and young children. Stagnation of urine in obstructive conditions provides a favorable environment for bacterial reproduction and is a recognized risk factor for UTI.[3,22,32-37]

Keren R et al. (2015) investigated risk factors for recurrent urinary tract infections (UTIs) and kidney scarring in children aged 1 to 71 months with 1 or 2 febrile or symptomatic UTIs and not receiving antimicrobial prophylaxis. Bladder-ureteral reflux (VUR) and bladder and intestinal dysfunction (BBD) are risk factors for recurrent UTIs, especially when they appear in combination. Prevention strategies for recurrent UTIs include antimicrobial prophylaxis and treatment of BBD.

UTI can develop as a complication of surgery.[3,8,11,26,34,38,39]

Catheter-associated urinary tract infections (CAUTI) are a common and serious health-related infection in infants.[26,34.41] An analysis of the experience of pediatricians showed that the effectiveness of intervention for the prevention of CAUTI in newborns and infants was achieved by following the following rules: there should be aseptic conditions when installing and removing the catheter; the urethra should be cleaned with sterile water; new silicone catheters should be used on each insert with a closed sterile drainage system using sterile technology; a daily catheter need assessment should be performed; permanent urinary catheters should only be placed for approved indications; reducing the days of urine catheterization and positioning the patient and the urine collection device to facilitate urine drainage. Positive results were achieved only when a multimodal strategy was used with at least four or more components.[41]

It is important to note that a serious risk of CAUTI is associated with each additional day of catheterization.[42]

Current research indicates a genetic predisposition to UTI. Mutations of some genes lead to the formation of congenital abnormalities at the organ and tissue level, which contribute to the development of infectious inflammation.[3,15,43-46]

Congenital malformations of the kidneys and organs of the urinary system, known in the literature under the term CAKUT (congenital anomalies of the kidney and urinary tract), cause chronic kidney disease in children, 40-60%. The prevalence of CAKUT in children is 1–8 cases per 1000 live births [47,48]. CAKUT is represented by a wide range of structural defects due to impaired morphogenesis of the kidneys and urinary tract: renal agenesis / hypodysplasia, multicystic dysplasia of the

kidneys, hydronephrosis, megaureter, doubling of the collecting system, vesicoureteral reflux, posterior urethral valve, etc.[34,49,50]

Congenital malformations of the kidneys and urinary tract often complicated by a recurring infection of the urinary system, are somewhat less likely to cause the development of arterial hypertension and renal failure in children.[50]

About 10% of CAKUT cases are due to genetic factors. In other cases, epigenetic and environmental factors may play a role in the development of CAKUT.[51] There are a number of monogenic CAKUT variants, some of which are inherited in an autosomal dominant type (*BMP4, EYA1, GATA3, HNF1B, KAL1, PAX2, RET, ROBO2, SALL1, SIX1, SIX2, SIX5, SOX17, TNXB, UPK3A, WNT4, CHD DSTYK, MUC1, UMOD*) and causes a high risk of manifestation of the disease in subsequent generations. Most familial CAKUT variants are due to the syndromes caused by the mutation *PAX*2 (oculorenal syndrome), *EYA1* (brachio-otorenal syndrome), HNF1B (renal cysts and diabetes syndrom) genes. Monogenic CAKUT variants are known that have a recessive inheritance type (*ACE, AGT, AGTR1, REN, FGF20, TRAP1, FRAS1, FRE*M2).[15]

It is known that *BMP4, EYA1, GATA3, PAX2, RET, ROBO2, SALL1, SIX1, SIX2* genes are highly expressed at an early stage of embryogenesis, therefore, mutation of these genes leads to the development of gross congenital malformations of the urinary system. *AGT, AGTR1, UMOD* genes are important for the formation of nephron in the later stages of embryogenesis.[15] The development of recurrent UTI in infants of the first three years of life may be a sign of CACUT and requires additional examination and monitoring. This will allow early diagnosis of hereditary pathology.

The formation of UTI in newborns, especially premature infants, and infants up to three years of age may be due to reduced immunological reactivity due to the morphological and functional immaturity of the immune system, characteristic of this age.[52]

Immunodeficiency in a infant may be due to a mutation of gene 1 (of human recombination activating gene 1: mutations RAG1) and cause the development of a recurrent urinary tract infection.[53]

Adverse effects of environmental factors can contribute to the formation of congenital malformations in the fetus and UTI in newborns. We found that the incidence of *Titanium, Silicon, Nickel, Silver*, and *Manganese* increased 3-10 times in the urine of infants with congenital malformations, and *Lead* was detected in every third child. With a delay in intrauterine development, the frequency of these elements increased by 20-30%, and *Copper* and *Titanium* were 2-2.5 times more common than in infants. An increased content and frequency of detection of these elements in the urine was observed in 82% of infants with infection and inflammatory diseases, including those with UTI [54]. High frequency and high concentration of heavy metals in human milk were associated with the development of infection, including UTI (*Sr, Cr, Si, Ni, Sn, Al, Pb, Ba, Ti, B*), multiple malformations (*Ti, Sn, Sr, Ni, Al, B , Ba, Cd, Si, Cr, Mn, Pb, Zn*) and intrauterine growth retardation (*Ni, B, Bi, Ba, Zn, Ti, Cr, Pb, Mn*).[55]

Laboratory diagnostics. For the initial diagnosis of UTI and dynamic observation of clinical patients in order to quickly identify recurrence of disease conduct clinical and laboratory urinalysis, microbiological urine culture, clinical blood analysis (determination of hemoglobin, erythrocytes, leucocytes, platelet).[1,3,4,10,11,15] Highly informative for detecting the infectious process is to determine the level of procalcitonin in the blood serum.[7,56]

UTI reference signs in clinical urine analysis are bacteriuria, neutrophilic leukocyturia, proteinuria, and microhematuria. It is important to note that it is necessary to take into account changes in urine tests in the form of small or moderate leukocyturia. In these cases, you need to conduct repeated and additional studies, and not regard them as defects in the samples of urine.[3,5,57]

Currently, methods for screening various indicators of urine analysis have been developed.[58,59] This allows you to quickly assess the clinical situation and reduce the cost of laboratory tests (at least 24%). The method of flow cytometry makes it possible to determine the combination of cutoffs of leukocytes and bacteria in the amount of 30 and 50 / μl, respectively. These are the best thresholds to achieve 100% negative predictive value in adult patients and children from 6 years old. However, the authors recommend the cultivation of all urine samples without a screening step in children under 6 years of age.[60]

Kuppermann N, et al. (2019) derived and validated an accurate prediction rule to identify febrile infants 60 days and younger at low risk for serious bacterial infections (SBIs) (including urinary tract infections) using the urinalysis, absolute neutrophil count (ANC), and procalcitonin levels. The prediction rule identified infants at low risk of SBIs using a negative urinalysis result, an ANC of 4090/μL or less, and serum procalcitonin of 1.71 ng/mL or less.[7]

In addition to clinical and laboratory urinalysis and bacterial culture, if necessary, other instrumental methods are used (ultrasound, CT).

Currently, great importance is attached to prenatal diagnosis of congenital malformations of the urinary system (duplex collecting systems with ureterocele, vesicoureteral reflux or nonrefluxing megaureter without

ureterocele), which allows for early endoscopic perforation and significantly reduces the frequency of infection.[35]

The clinical course of UTI. The peculiarity of the course of many diseases, in particular kidney diseases, in newborns and young children is associated with the morphological and functional immaturity of all organs and systems. In newborns, on the one hand, the inflammatory process progresses rapidly with the development of necrotic and sclerotic changes in the renal tissue and other organs,[57,62] on the other hand, there is a high plasticity, which helps to prevent adverse effects with early diagnosis and timely treatment if they are not determined by genetic factors.[3,9,11,15]

The clinical symptoms of UTI in newborns and infants up to 3 years of age and less are non-specific. The disease may resemble sepsis. In newborns, symptoms include an increase in body temperature (often> 38.0° C), loss of appetite, regurgitation, absence or slight increase in body weight, change in neurological status (convulsions, hyper excitability).[15,62,63]

In infants from 1 month to 2 years, in most cases, there is an acute onset of the disease. Of the symptoms, the most pronounced are poor weight gain, fever, intoxication, less pronounced convulsions, agitation, frequent and/or painful urination, gastrointestinal dysfunction (but this is a key sign of UTI in the neonatal period). According to E.A. Melnikova (2017), in 37% of cases in infants, inflammatory changes in urine tests were detected without clinical symptoms from the urinary tract in infants with acute respiratory disease (40%), with community-acquired pneumonia (25%), with intestinal infection (24%), damage to the central nervous system (14%), postnatal malnutrition (13%).[20]

Unmotivated temperature rises in infants and young children are always grounds to suspect UTI. You should always remember the reality of more rapid damage to the kidney tissue than in older children.[3,11,15]

In children after 1 year, local symptoms begin to prevail: urinary syndrome, pain (localized pain in the side or lower back), enuresis.

The equivalent of dysuric phenomena in a newborn can be expressed anxiety before and during urination, crying, straining, redness of the face, intermittent urination, weakness of the urinary stream.[4,8,11,58]

Urosepsis in childhood, though rare, is the most complicated possible variant. In newborns and infants, unspecific symptoms are a significant barrier to a fast and reliable diagnosis. In addition to urine and laboratory tests as well as non-invasive examinations (ultrasound), there may be an indication for invasive examinations of the kidneys (DMSA scans) in cases of a severe infection. The therapy consists of targeted parenteral antibiotic treatment and pediatric sepsis management.[36]

Treatment. UTI treatment is carried out in several directions: antibiotic therapy, immunotherapy, body hygiene, regimen, diet, exercise therapy, massage. Adequate starting antibiotic therapy largely determines the effectiveness and prognosis of the disease. As etiotropic therapy, generation II-IV cephalosporins and protected penicillins are preferred, which are able to suppress both gram negative and gram positive microflora. Nitrofurantoin (in children older than 1 month) and Fosfomycin is also used.[4,5,6,9, 11,19] There are some restrictions on taking fosfomycin in children in some countries. So, according to the instructions for the use of this drug in Russia, the appointment of Fosfomycin is possible in infants only in cases of extreme need under the supervision of a doctor.[64]

Along with those, interest in fosfomycin has increased in recent years due to its wide spectrum of action and excellent safety profile. The main indication for its use in pediatrics is community-acquired infection of the lower urinary tract. The drug is useful for urinary infections caused by *Enterobacteriaceae*, which produce extended-spectrum beta-lactamase, *S.aureus* (MRSA) and *Enterococcus spp*., resistant to vancomycin.[65]

A serious modern problem is the emergence of *Enterobacteriaceae* with extensive drug resistance or general drug resistance, especially for newborns and infants. The use of ceftazidime-avibactam in young patients has shown a good effect in the treatment of infections, including the urinary system caused by strains of *Klebsiella pneumoniae* that produce carbapenemase.[66]

Aminoglycosides are prescribed much less frequently due to nephrotoxicity.[4,15,22,67]

Antibacterial therapy should be carried out until the complete rehabilitation of the urinary tract. If necessary, an antibiotic change is carried out. An integral part of the rational prescription of antimicrobial drugs is to determine the sensitivity of pathogen strains to antibiotics. The course of treatment is usually 10-14 days.[4,11,15,26,29,68]

Monitoring at the local level (in the region, city, hospital, hospital department) for the antibiotic resistance of the main pathogens of UTI determines the tactics of choosing an antibiotic for empirical treatment, improves treatment efficiency, reduces treatment time, eliminates inactive antibiotics, reduces the risk of selection of resistant strains,[18,69,26] reduce economic costs.[2970]

Prevention of recurrence of UTI includes monitoring urine tests (bacterial culture, protein, white blood cells, red blood cells), an adequate drinking regimen, normalization of urodynamics (elimination of urination

disorders, forced urination, regular bladder emptying in age groups where possible).[8,9,11] The prophylactic use of antibiotics is advisable during surgical interventions on the organs of the urinary system.[4,9,39]

The use of antibiotics for the prevention of relapse is controversial at the present time.[4,9,12,26,30,69] Studies on this issue are ongoing. It must be remembered that long-term administration of small doses of antibiotics can lead to the formation of resistance of microorganisms. However, the detection of asymptomatic bacteriuria during the period of remission may be the basis for antibacterial treatment.[18,26,30]

Currently, the use of continuous antibacterial prophylaxis in children with vesicoureteral reflux is being questioned. The authors consider the transition to a selective risk-based approach for the treatment of possible infections.[71]

CONCLUSION

The development of the diagnosis of UTI, especially in young children, monitoring infants with perinatal and neonatal pathologies, children with congenital malformations, collecting and analyzing the history of mothers, timely and adequate antibiotic therapy, and, if necessary, surgical intervention, can stop the infectious and inflammatory process in the organs urinary system, prevent the development of complications and severe chronic kidney disease.

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