DIFFERENTIATED DIAGNOSIS OF INFLAMMATORY KIDNEY DISEASES IN CHILDREN

Recommendations for V–VI students Higher medical education institutions of the III–IV accreditation levels studying in English

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
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ДИФЕРЕНЦІЙНА ДІАГНОСТИКА ЗАПАЛЬНИХ ЗАХВОРЮВАНЬ НИРОК У ДІТЕЙ

Методичні вказівки для студентів V–VI курсів
вищих медичних закладів освіти III–IV рівнів акредитації,
що навчаються англійською мовою

Затверджено
вченою радою ХНМУ.
Протокол № 4 від 18.04.2019.

Харків
ХНМУ
2019

Differentiated diagnosis of inflammatory kidney diseases in children : Recommendations for V–VI students Higher medical education institutions of the III–IV accreditation levels studying in English / comp. M. O. Gonchar, I. S. Alenina, O. V Omelchenko. – Kharkiv : KhNMU, 2019. – 24 p

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Диференційна діагностика запальних захворювань нирок у дітей : метод. вказ. для студентів V–VI курсів вищих мед. закладів освіти III–IV рівнів акредитації, що навчаються англ. мовою / упоряд. М. О. Гончарь, І. С. Аленіна, О. В. Омельченко. – Харків : ХНМУ, 2019. – 24 с.

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INTRODUCTION

Urinary tract infection (UTI) represents the most common bacterial infection in children < 2 years of age. The incidence of UTIs varies depending on age and sex. meta-analysis showed that, in the first 3 months of life, UTIs were present in 7.5 % of girls, 2.4 % (CI: 1.4-3.5) of circumcised boys, and 20.1 % (CI: 16.8–23.4) of uncircumcised boys, who presented with fever (2). In the first year of life, UTIs are more common in boys (3.7 %) than in girls (2 %). Later, the incidence changes and ~3 % of pre-pubertal girls and 1 % of prepubertal boys are diagnosed with UTIs (2–7).

Classification of Urinary tract infection

There are five widely used classification systems according to the site, episode, severity, symptoms and complicating factors. For acute treatment, site and severity are most important.

Table 1

Classification of urinary system infections in children

according to site	Lower urinary tract (cystitis) Upper urinary tract (pyelonephritis)
according to episode	primary, recurrent (persistent, incurable, reinfectious)
according to severity	simple and heavy (with hyperthermia)
according to symptoms	asymptomatic, symptomatic
according to complicating factors	monitored and uncomplicated

Classification according to site

Lower urinary tract (cystitis) is an inflammatory condition of the urinary bladder with general signs and symptoms including dysuria, frequency, urgency, malodorous urine, enuresis, hematuria, and suprapubic pain. Upper urinary tract (pyelonephritis) is a diffuse pyogenic infection of the renal pelvis and parenchyma. The onset of pyelonephritis is generally abrupt. Clinical signs and symptoms include fever (> 38 °C), chills, costovertebral angle or flank pain, and tenderness. Older children may report cystitis symptoms along with fever/flank pain. Infants and children may have non-specific signs such as poor appetite, failure to thrive, lethargy, irritability, vomiting or diarrhea.

Classification according to episode (10)

First infection: the first UTI may be a sign of anatomical anomalies that may predispose to complications of UTI and potential renal damage (11). Anatomical evaluation is recommended (see below). Recurrent infection can be divided into unresolved and persistent infection. In unresolved infection, initial therapy is inadequate for elimination of bacterial growth in the urinary tract [inadequate therapy, inadequate antimicrobial urinary concentration (poor renal concentration/gastrointestinal malabsorption), and infection involving multiple

organisms with differing antimicrobial susceptibilities]. Persistent infection is caused by re-emergence of bacteria from a site within the urinary tract coming from a nidus for persistent infection that cannot be eradicated (e.g. infected stones, non-functioning or poorly functioning kidneys/renal segments, ureteral stumps after nephrectomy, necrotic papillae in papillary necrosis, urachal cyst, urethral diverticulum, periurethral gland, vesicointestinal, rectourethral or vesicovaginal fistulas). The same pathogen is identified in recurrent infections, but episodes of sterile urine may occur during and shortly following antimicrobial treatment.

Reinfection: each episode can be caused by a variety of new infecting organisms, in contrast to bacterial persistence in which the same infecting organism is always isolated. However, the most common general pathogenic species is E. coli, which occurs in many different serotypes. Therefore, recurrent E. coli UTI does not equate to infection with the same organism.

Classification according to severity

In simple UTI, children may have only mild pyrexia; are able to take fluids and oral medication; are only slightly or not dehydrated; and have a good expected level of compliance. When a low level of compliance is expected, such children should be managed as those with severe UTI. In severe UTI, infection is related to the presence of fever of > 39 °C, the feeling of being ill, persistent vomiting, and moderate or severe dehydration.

Classification according to symptoms

Asymptomatic bacteriuria indicates attenuation of uropathogenic bacteria by the host, or colonisation of the bladder by non-virulent bacteria that are incapable of activating a symptomatic response. In symptomatic bacteriuria, symptoms associated with UTI include irritative voiding symptoms, suprapubic pain (cystitis), fever and malaise (pyelonephritis). Cystitis may represent early recognition of an infection destined to become pyelonephritis, or bacterial growth controlled by a balance of virulence and host response.

Classification according to complicating factors (12)

In uncomplicated UTI, infection occurs in a patient with a morphologically and functionally normal urinary tract. This category includes mostly isolated or recurrent bacterial cystitis. Patients can be managed on an outpatient basis, with an emphasis on documenting resolution of their bacteriuria, followed by elective evaluation for potential anatomical or functional abnormalities of the urinary tract.

In complicated UTI, all neonates, most patients with clinical evidence of pyelonephritis, and all children with known mechanical or functional obstructions of the urinary tract are considered to have complicated UTI. Mechanical obstruction is commonly due to the presence of posterior urethral valves, strictures or stones, independent from their location. Functional obstruction often results from lower urinary tract dysfunction of either neurogenic or non-neurogenic origin and dilating vesicoureteral reflux. Patients with complicated UTI require hospitalisation and parenteral antibiotics.

Risk factors UTI

Most UTIs in children are caused by bacteria from the digestive system entering the urethra.

High-grade vesicoureteral reflux (VUR) may increase the risk for pyelonephritis, and VUR has been reported in as many as 33 % of children with acute pyelonephritis. Congenital or acquired anomalies, including dysplasia, hypoplasia, and obstruction, increase the risk for UTI, VUR, and pyelonephritis. Delayed or incomplete voiding, as seen with neurogenic bladder, obstruction, or dysfunctional voiding increases the risk for urinary stasis and overgrowth of colonizing bacteria. Constipation may impair bladder emptying, leading to stasis and ascending infection.

Catheterization may increase the risk of introducing periurethral bacteria into the bladder.

Boys who are uncircumcised have a risk of UTI that is 2.2 % higher than that of circumcised boys.

Sexual activity may cause urethral inflammation, lead to bladder colonization, and increase the risk for acute pyelonephritis.

Familial inheritance of susceptibility to pyelonephritis may be related to chemokine receptor inheritance. Host genetic factors that promote inflammation contribute to renal scarring. Interleukin (IL)-8 and CXCR1 polymorphisms, ACE insertion/deletion (ACE I/D) gene polymorphism, and tumor necrosis factor-[alpha] polymorphism have been identified as potential mediators to tissue fibrosis and subsequent renal scarring following acute pyelonephritis.

Vesicoureteral reflux

VUR is the most common anatomic abnormality diagnosed in children who have UTI. Management of VUR depends on the degree of reflux and the extent of renal scarring. Patients who have low-grade VUR (I or II) have a high rate of spontaneous resolution and most often are treated medically with low-dose antimicrobial therapy until the reflux has resolved. Higher grades of VUR are less likely to resolve without surgical intervention. Grade V VUR rarely resolves spontaneously and often requires surgical correction.

Surgical intervention with ureteral reimplantation is recommended for patients who have high-grade VUR or who have low-grade VUR and documented progressive renal scarring while receiving prophylactic antibiotics. Young children experiencing a first UTI and older children and adolescents who have recurrent UTIs should be evaluated for any risk factors that may be modified with medical or surgical intervention, the goal being to minimize damage to the kidneys and, ultimately, to preserve renal function. Scarring can be seen in up to 30 % of children after an episode of pyelonephritis. Studies have shown that prompt treatment of an acute infection and appropriate modification of identified risk factors can minimize the progression of renal scarring, thereby preventing loss of renal function. Vigilant treatment of pediatric patients may reduce the rates of end-stage renal disease and hypertension as these children become adults.

CYSTITIS

Cystitis – nonspecific microbial inflammation of the mucous membrane of the bladder. The disease proceeds with pain and pain when urinating, frequent urging, with the release of small portions of urine, urinary incontinence. In young children, intoxication and fever are often noted.

In all age groups, the most common pathogen causing cystitis is *Escherichia coli*. In neonates, group B streptococci are a particular concern. Immunocompromised hosts are at risk for infection with less typical agents, such as *Enterococcus*, BK virus, *Pseudomonas aeruginosa*, and *Candida albicans*. Adolescent girls commonly have *Staphylococcus saprophyticus* infection. Many other agents have been associated with cystitis, including a wide range of gram-negative rods and cocci, gram-positive cocci, adenovirus, and both *Chlamydia trachomatis* and *Ureaplasma urealyticum*. *Lactobacillus*, coagulase-negative staphylococci, and *Corynebacterium* are typical normal flora in children.

Diagnosis of cystitis

Medical history

Children who have cystitis often do not present with the characteristic signs and symptoms seen in adults. The history of a child who has fever should include documentation of the risk factors described previously to evaluate for UTI. Infants younger than 60 to 90 days of age may have vague and nonspecific symptoms, such as failure to thrive, diarrhea, vomiting, irritability, lethargy, malodorous urine, jaundice, and fever.

Clinical signs and symptoms

In children younger than 5 years of age, fever and gastrointestinal symptoms are most common. The classic lower urinary tract symptoms of dysuria, urgency, frequency, incontinence, and suprapubic abdominal pain are more common after 5 years of age.

Documentation of blood pressure and temperature, assessment of suprapubic and costovertebral tenderness, and sacral findings suggestive of neurogenic bladder (dimples, pits, sacral fat pad) are key components in the evaluation of a child suspected of having cystitis. External genitalia should be examined for signs of vulvovaginitis, vaginal foreign body, sexually transmitted infections, and epididymitis. Gynecologic infections are frequent causes of dysuria, even in nonsexually active females.

Physical examination

Physical examination includes a general examination of the throat, lymph nodes, abdomen (constipation, palpable and painful kidney, or palpable bladder), flank, the back (stigmata of spina bifida or sacral agenesis), genitalia (phimosis, labial adhesion, vulvitis, epididymo-orchitis), and temperature.

Laboratory examination

Urine must be collected under defined conditions and investigated as soon as possible to confirm or exclude UTI, especially in children with fever. In neonates, infants and non-toilet-trained children, there are four main methods with varying contamination rates and invasiveness to obtain urine in this age group:

– Plastic bag attached to the cleaned genitalia.
– Clean-catch urine collection
– Bladder catheterization
– Suprapubic bladder aspiration

Urinalysis

Dipsticks. These are appealing because they provide rapid results, do not require microscopy, and are ready to use. Leukocyte esterase (as a surrogate marker for pyuria) and nitrite (which is converted from dietary nitrates by most Gram-negative enteric bacteria in the urine) are the most frequent markers, and are usually combined in a dipstick test. The conversion of dietary nitrates to nitrites by bacteria requires approximately 4 h in the bladder. The test is helpful when the result is positive, because it is highly specific (i.e. there are few false-positive results).

Microscopy. This is the standard method of assessing pyuria after centrifugation of the urine with a threshold of 5 white blood cells (WBCs) per high-power field (25 WBC/μL). In uncentrifuged urine, > 10 WBC/μL has been demonstrated to be sensitive for UTI and this could perform well in clinical situations. However, this is rarely done in an outpatient setting.

Urine culture

In severe UTI, > 10^5 cfu/mL can be expected. However, the count can vary and be related to the method of specimen collection, diuresis, and time and temperature of storage until cultivation occurs. The classical definition of > 105 cfu/mL of voided urine is still used to define a significant UTI.

The recent American Academy of Pediatric Guidelines on Urinary tract İnfection suggest that the diagnosis should be on the basis of the presence of both pyuria and at least 50 000 cfu. However, some studies have shown that, in voided specimens, < 10^4 organisms may indicate a significant UTI. If urine is obtained by catheterisation, 1,000–50,000 cfu/mL is considered to be positive, and any counts obtained after SPA should be considered as significant. Mixed cultures are indicative of contamination.

Table 2

Criteria for UTI in children
(adapted from the EAU guideline on Urological Infections)

Urine specimen from suprapubic bladder puncture	Urine specimen from bladder catheterisation	Urine specimen from midstream void
Any number of cfu/mL (at least 10 identical colonies)	> 1,000–50,000 cfu/mL	> 10^4 cfu/mL with symptoms > 10^5 cfu/mL without symptoms

Pyuria without bacteriuria (sterile pyuria) may be due to incomplete antibiotic treatment, urolithiasis, or foreign bodies

The definitive diagnosis of cystitis requires a positive culture from urine obtained before the initiation of antibiotics. Suprapubic aspiration or urethral catheterizations are recommended in neonates and young children. A clean-catch specimen may be obtained from older children and young adults. Specimens should be examined soon after collection. If examination is delayed, the specimen must be refrigerated. Significant bacteriuria is defined as at least 100,000 colonies/mL from a clean-catch specimen, 50,000 colonies/mL or more from a catheterized specimen, and any number of uropathogenic bacteria from a suprapubic aspirate.

Treatment cystitis

The objectives of treating cystitis include symptomatic relief, eradication of infection, and prevention of renal parenchymal scarring. Treatment depends on factors such as age, clinical status, presence of vomiting, the predominant uropathogens in the patient's age group, and the antimicrobial resistance patterns in the community. A broad-spectrum antibiotic is recommended for empiric coverage. A healthy, nontoxic-appearing child who presumably has uncomplicated cystitis, is tolerating fluids, has reliable caretakers, and can be followed up may be treated with outpatient oral antibiotic therapy.

First-line agents include trimethoprim-sulfamethoxazole, nitrofurantoin, amoxicillin-clavulanate, and second- and third-generation cephalosporins. Because E coli is the most common pathogen causing cystitis and because approximately 50 % of E coli are resistant, amoxicillin should not be used routinely as empiric treatment. Although fluoroquinolones are effective and resistance is rare, the use of these drugs in children is still controversial because of concern about toxicity to cartilage.

An acutely ill child, an immunocompromised patient, or an infant younger than 2 months of age is assumed to have a complicated UTI and should be hospitalized for parenteral antimicrobial therapy. The combination of ampicillin or cefazolin plus gentamicin provides adequate coverage for most uropathogens. Because of a concern for nephrotoxicity and changing resistance patterns, a third-generation cephalosporin also may be used as initial monotherapy. Parenteral treatment is maintained until the child is clinically stable and afebrile for 48 to 72 hours, at which point coverage may be changed to an oral agent, based on sensitivities from the urine culture. Length of treatment remains debatable, ranging from a 3-day course for a first-time uncomplicated cystitis in an older child to a 7- to 14-day course in complicated UTI or in children younger than 2 years of age.

PYELONEPHRITIS

Acute pyelonephritis is infection of the kidneys. Pyelonephritis typically presents with systemic symptoms such as high fever, malaise, vomiting, abdominal or flank pain, and tenderness. Pyelonephritis can cause renal scarring, which is the most severe long-term sequela of UTI that can lead to hypertension and chronic renal failure. The role of imaging is to guide treatment by identifying patients who are at high risk to develop recurrent UTIs or renal scarring. However, identification of children at risk is valuable only if there is effective treatment. Current management strategy to prevent UTIs and renal scarring is based on prophylactic antibiotics and selective surgical correction of vesicoureteral reflux (VUR).

Acute pyelonephritis is a nonspecific infectious-inflammatory disease of the renal interstitial with a consistent lesion of all renal structures, which leads to the formation of focal nephrosclerosis.

Depending on the course, distinguish between acute (up to 3 months) and chronic pyelonephritis (more than 3 months). In chronic pyelonephritis, chronic renal failure is possible, therefore, the diagnosis indicates a stage of CKD. In the presence of physiologically and anatomically normal urinary tract, normal kidney function, absence of infection of the lower urinary tract, as well as disorders of the mechanisms of protection of the organism as a whole (diabetes mellitus, immunosuppressive therapy), one can speak of uncomplicated pyelonephritis.

Pyelonephritis is diagnosed in children based on the presence of pyuria and/or bacteriuria, fever, flank pain, or tenderness. Between 50 % and 64 % of children who have a febrile UTI are found to have defects on renal cortical scintigraphy (RCS) indicating acute pyelonephritis. The relationship between childhood UTIs, VUR, and renal scarring is complex and not completely understood. Children with VUR are at an increased risk for pyelonephritis and parenchymal scarring, but pyelonephritis and renal scarring commonly occur without VUR. The incidence of acute pyelonephritis in the absence of documented VUR is much too high to be explained only by intermittent VUR. Previous episodes of pyelonephritis or VUR increase the risk for recurrent pyelonephritis. Absence of fever does not exclude development of pyelonephritis. 15 % (95 % CI, 11–18 %) of the children had evidence of renal scarring after the first episode of pyelonephrytis. Contrary to common belief, renal scarring after pyelonephritis does not decrease in older children.

Diagnosis of pyelonephritis

Medical history

Medical history includes the question of a primary (first) or secondary (recurring) infection; possible malformations of the urinary tract (e.g. pre- or postnatal ultrasound screening); family history; and whether there is constipation or presence of lower urinary tract symptoms.

Clinical signs and symptoms

Neonates with pyelonephritis or urosepsis can present with non-specific symptoms (failure to thrive, jaundice, hyperexcitability and without any fever). Signs of a UTI may be vague and unspecific in small children, but later on, when they are > 2 years old, frequent voiding, dysuria and suprapubic, abdominal or lumbar pain can be detected.

Physical examination

Physical examination includes a general examination of the throat, lymph nodes, abdomen (constipation, palpable and painful kidney, or palpable bladder), flank, the back (stigmata of spina bifida or sacral agenesis), genitalia (phimosis, labial adhesion, vulvitis, epididymo-orchitis), and temperature.

Because many symptoms of pyelonephritis are nonspecific, complete physical examination is necessary to exclude other causes of the patient's symptoms.

General appearance

Most infants and children are uncomfortable and appear ill. Older children and adolescents may be mildly to moderately ill.

Fever may be present, with body temperature of more than 38 °C, and often more than 39 °C. Tachycardia may be present, secondary to fever and pain. Blood pressure is usually normal. Hypertension should raise concern for clinically significant obstruction or renal parenchymal disease. Hypotension may occur if sepsis and shock are present. Abdominal pain may be present. A mass may indicate obstruction, hydronephrosis, or another anatomic abnormality. Suprapubic pain may be present. A palpable bladder indicates obstruction or functional difficulty in starting or completing voiding. Adolescent girls may have right upper quadrant pain similar to that observed in patients with cholecystitis. Tenderness in the costovertebral angle (CVA), back, or flank is likely to be present in older children and adolescents. Sacral dimple or birthmarks overlying the spine may be associated with an underlying anomaly of the spinal cord.

Genitourinary findings. Assess for irritation, pinworms, vaginitis, trauma, or signs of sexual abuse. A bulging hymen suggests an imperforate hymen and urethral obstruction.

Neurologic findings. Weak lower extremities or diminished reflexes may be signs of spinal-cord dysfunction, and they may be associated with a neurogenic bladder.

Laboratory examination is the same as for cystitis

Urine cultures must be obtained in all children with suspected pyelonephritis. Treatment should not be commenced on the basis of urinalysis results, and normal urinalysis findings do not exclude an infection. Acute pyelonephritis may be present even if urine cultures demonstrate no growth.

A clean-catch urine specimen with more than 100,000 colony-forming units (CFUs) of a single organism is considered diagnostic of a UTI. Organisms,

such as *Lactobacillus, Staphylococcus,* or *Corynebacterium* species, may not be clinically relevant.

Cultures showing more than 100,000 CFUs of a single organism obtained by means of transurethral catheterization are 95 % sensitive and 99 % specific for UTI. Specimens growing 10^4 CFUs may be consistent with infection, but the test should be repeated if infection is not likely and if treatment has not yet commenced.

Cultures from bagged urine specimens are useful only if no growth is observed. Bagged urine specimens result in a false-positive rate of 85 %. Before treatment is started on the basis of results from a bagged-specimen test, a catheterized or suprapubic specimen should be obtained.

Structural abnormalities of the urinary tract may be associated with infections secondary to multiple organisms or unusual gram-negative bacteria, such as *Pseudomonas aeruginosa.*

Electrolyte Measurements

Some patients may have electrolyte abnormalities, which may be secondary to vomiting or diarrhea. Secondary pseudohypoaldosteronism may develop, with impaired renal tubular function, in infants with pyelonephritis. Mild hyponatremia and hyperkalemia may be present. Infants with underlying urinary-tract anomalies have an increased risk of this electrolyte imbalance, which resolves when the infection is treated.

Determination of Inflammatory Markers

An elevated WBC count is nonspecific and does not help in distinguishing lower UTI from upper UTI. In the presence of a febrile UTI, however, an erythrocyte sedimentation rate (ESR) of more than 30 mm/h is highly predictive of acute pyelonephritis.

C-reactive protein (CRP) levels are correlated with parenchymal defects on DMSA scanning. Elevated CRP concentrations are sensitive, but nonspecific, markers of renal parenchymal involvement in the febrile infant and child with UTI. CRP values may be used to distinguish bladder colonization from acute pyelonephritis in a febrile child with bacteriuria and a neurogenic bladder.

Procalcitonin is an acute inflammatory marker with a sensitivity of 70-95 % and a specificity that approaches 90 % for renal involvement in infants and children with febrile UTI. Although less sensitive than CRP, procalcitonin is more specific for the diagnosis of acute pyelonephritis. Procalcitonin values are better correlated with long-term renal scarring than is CRP.

Renal Ultrasonography

In children who have not had ultrasonography performed in the prenatal period is a noninvasive imaging method that avoids the risk of ionizing radiation and is readily available. It can detect urinary tract anomalies such as hydronephrosis, duplex renal system, hydroureter, and ureterocele. In older children, postvoid evaluation of bladder volume could be useful to assess for functional bladder abnormalities and retention syndrome. The main limitation

of US is the low sensitivity for detecting VUR and renal scarring. Renal ultrasonography is useful in the diagnosis of urolithiasis, hydronephrosis, hydroureter, ureteroceles, and bladder distention.

X-Ray Voiding Cystourethrography

Renal ultrasonography is useful for determining the size and shape of the kidneys but is generally poor for visualizing nondilated ureters. In addition, it does not provide information regarding renal function. The main role of voiding cystourethrography (VCUG) is to detect VUR. The bladder is filled with a X-ray contrast solution. In the presence of VUR, the contrast agent will be thrown into the ureter and even possibly into the kidney.

Consultations

A urologist should be consulted for an infant or child with obstruction or a clinically significant anomaly of the urinary tract. Consultation with an infectious diseases specialist is necessary only if an unusual or resistant organism is identified. Consult a nephrologist when patients have impaired renal function.

Antibiotic Therapy

The results of urine cultures ultimately dictate the choice of antibiotics. Because E coli causes more than 95 % of all cases of acute pyelonephritis in children, initial treatment should be based on regional susceptibility to this pathogen. Because of high resistance rates to amoxicillin, initial treatment should include a cephalosporin, amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole (TMP-SMZ), or aminoglycoside.

Initial therapy with IV antibiotics for 3–4 days followed by oral therapy to complete a 10–14 day course is equivalent to 10–14 days of IV therapy. Initial oral therapy with cefixime or amoxicillin-clavulanate is equivalent to IV ceftriaxone for 3 days followed by oral therapy.

A single dose of ceftriaxone given intramuscularly (IM) followed by oral therapy offers no advantage over 10 days of oral therapy alone. Hospitalization is required in similar numbers because of vomiting.

IV gentamicin may be dosed daily, rather than 3 times a day, for children who require IV treatment or who are infected with multiresistant organisms.

Inpatient Care

Hospitalization is necessary for pyelonephritis in any of the following situations:

- Toxicity or sepsis
- Signs of urinary obstruction or significant underlying disease
- Inability to tolerate adequate oral fluids or medications
- Infants and children younger than age 2 years with febrile UTI, presumed pyelonephritis
- All infants younger than age 3 months

An example of treating PN in a hospital with the scheme "3+" -:

1. Antibacterial therapy step-by-step (eg cephalosporin II–III generation (ceftriaxone/sulbactam (sulbactomaks) 100 mg/kg/day in 2 injections intravenously 3 days, then cefix 8 mg/kg/day by mouth 7 days)

2. Rehydration through the mouth and detoxification intravenously (reosorbilact 5 ml/kg / day in two injections)

3. Antipyretic and anti-inflammatory (if necessary): paracetamol 3–4 days and nimesulide up to 10 days (for children over 12 years old).

«+» – Prevention of relapse: prophylactic treatment with a furan 25 mg per night for 3-6 months.

Outpatient (not a difficult course, has no dehydration and hyperthermia): under the scheme "2+"

1. For example, a cefix once daily for 10 days or amoxicillin/clavulanate in suspension twice a day for 10 days through the mouth

2. Antipyretic and anti-inflammatory (if necessary): paracetamol 3–4 days and nimesulide up to 10 days (for children over 12 years old).

«+» – Prevention of relapse: prophylactic treatment with a furan 25 mg per night for 3–6 months.

Preventive therapy.

It is used as an outpatient stage of treatment (after taking therapeutic doses of antibacterial drugs) in young children who already had an episode of pyelonephritis, in the presence of a risk of developing scarring, in patients with infected urolithiasis, at risk of recurrence of an ACS, of chronic ACS, in the presence of congenital malformations of the urinary system , concomitant urogenital infection, neurogenic urinary bladder, diabetes mellitus, prolonged immobilization. Preparations of choice are fumigants, sulfamethoxazol / trimethoprim (biseptolum), furagin, furadonin or kanifron N. In addition to the latter, all of the above drugs are used once a day at 1/3–1/4 of the daily dose for 3–6 months, each with a total duration of admission up to 2 years. Following kidney transplantation, prophylaxis with biseptol is 1–2 mg/kg for 6 months.

Outpatient Care

Patients treated exclusively in the outpatient setting should be reevaluated in 48 hours to ensure adequate hydration and an appropriate response to therapy. For a first infection, perform renal ultrasonography. Manage constipation and voiding dysfunction.

Symptomatic therapy

Dehydration treatment is carried out by water loading, detoxification – using detoxification drugs (reosorbilact, xylitol, lipin). In case of refusal from the reception of fluid, signs of dehydration, significant intoxication syndrome, an infusion of 5 % glucose solution or saline sodium chloride is performed.

With hyperthermia, antipyretics are used – paracetamol, nimesulide (according to the instructions).

In cases of pain syndrome, anti-spastic drugs are prescribed.

If necessary, pro-, pre- and symbiotics (yoghurt, bioporin, Bifiform, fructose, lactose, extracranial, Bifillact extra, Symbiter 1,2), as well as antihistamines and antifungal drugs.

Phytotherapy is recommended by phytoning drugs (for example, kanifron H).

ACE inhibitors or angiotensin II receptor blockers (ARBs) are prescribed for chronic hypotension to inhibit the sclerotic process and antiproteinuric actions are used – enalapril, lysinopril, fosinopril, myxipril, spirapril, irbesartan, candesartan, valsartan, eprosartan, telmisartan.

Additional conditions for the treatment of microbial inflammatory diseases

Physical exercise mode.

In the period of hyperthermia – a bed rest to reduce the symptoms of intoxication, in the next – the room mode, the gradual inclusion of therapeutic physical education.

The period of remission – the general mode of age, with a limitation of prolonged orthostatic load, avoid overcooling.

Diet therapy

Medical nutrition: with the exception of irritating substances, allergens, balanced on proteins and carbohydrates, with a sufficient drinking regime. The restriction of salt is carried out in the presence of impaired renal function and/or arterial hypertension. Limits of meat – in case of impaired kidney function.

Use of liquid

It is recommended that a water load of 25–50 ml/kg/day (the adequacy of the drinking regime is estimated by the size of the diuresis – 1.5–2 l) under the control of timely emptying of the bladder (at least 1 time in 2–3 hours). Acceptance of a fluid may be limited in case of impaired renal function, arterial hypertension, obstructive uropathy. The drinking regime includes tea, alkaline mineral water, pure water, compotes (from dried fruits), dairy products, herbal medicine. In the alkaline urine reaction, an increase in sour valences is shown – morsels, cranberries, cranberries and others.

Treatment with vaccines

When treating the sequestered, separated from surrounding tissues, foci of bacterial release, autovaccine (10–14 days) is used together with the appointment of antibacterial preparations by antibioticogram (up to 10 days), 2 courses. In addition, officinal vaccines (such as Uvum, Ribomunil, bronchodilator) are used, as instructed.

TUBULOINTERSTITIAL NEPHRITIS

Tubulointerstitial nephritis (TIN) is a non-specific abacaviral inflammation of the interstitial, vessels and tubules of infectious, allergic or toxic genesis characterized by acute or chronic course and accompanied by a decrease in the functions of the kidneys (mainly tubular).

The diagnosis is verified on the basis of nephrobiosis data. If it is impossible to carry out the following criteria are used: hypoparathomy (with polyuria) or hypertension; laboratory criteria: decrease in the relative density of urine (less than 1012 for children under 7 years, less than 1018 – 18 years of age), proteinuria, abacteric leukocyturia, erythrocyturia. In acute interstitial nephritis, the level of creatinine and β_2-microglobulin of blood may be increased due to significant reduction of concentration. The development of interstitial nephritis is often preceded by intoxication, poisoning, acute renal failure.

Acute interstitial nephritis has a duration of up to 3 months, chronic – over 3 months (chronic illness).

Table 3

Etiology factors of Tubulointerstitial nephritis in children

Etiology factors	
Drug-Related	Antimicrobials NSAID's Other
Infectious – Viral	Cytomegalovirus, Hepatitis, HIV, Epstein - Barr virus, Hantavirus, Polyomavirus
– Bacterial	Salmonella, Streptococcus, Yersinia, Brucella, Leptospirosis
– Fungal	Histoplasmosis
– Parasitic	Leishmania, Toxoplasma
Localized TIN with acute pyelonephritis	
Immune-Mediated	Sarcoidosis Systemic Lupus Erythematosus Sjögren's Disease Inflammatory Bowel Disease
Idiopathic TIN	
Granulomatous TIN	Medications Sarcoidosis Tuberculosis Bacterial/Fungal infections TINU Granulomatosis with polyangiitis

Medical history

Medical history includes the question of a primary (first) or secondary (recurring) infection; possible malformations of the urinary tract (e.g. pre- or postnatal ultrasound screening); family history; and whether there is constipation or presence of lower urinary tract symptoms.

Clinical signs and symptoms

If drug-related, TIN can manifest between 1 and 3 weeks after exposure to the medication in most cases, with an average presentation of about 10 days after exposure, except for rifampin exposure when the presentation may be much faster.

The tubulointerstitial infiltrate of inflammatory cells can cause edema and painful stretching of the renal capsule, leading to abdominal, flank or loin pain. Thus, the kidneys in TIN are typically found to be normal sized or enlarged with increased cortical echogenicity by ultrasound.

Presence of extrarenal manifestations may be helpful in identifying a risk for TIN. A renal biopsy is the only definitive diagnostic modality that can confirm TIN suspected on clinical grounds. A renal biopsy should be considered with severe renal dysfunction, lack of an identifiable offending agent, lack of renal recovery, uncommon features of TIN or prior to initiation of treatment, but otherwise TIN remains a clinical diagnosis. Tubulointerstitial dysfunction should be suspected in patients who develop hyperkalemic, hyperchloremic metabolic acidosis that is out of proportion to renal dysfunction. Most patients are initially noted to have AKI (elevated BUN and/or creatinine) with further workup revealing TIN. Other presenting signs and symptoms are noted in Table 3. Tubular dysfunction can manifest as Fanconi's syndrome, so patients may present with electrolyte abnormalities (as above), metabolic acidosis, elevated fractional excretion of sodium, glycosuria, and aminoaciduria. Additionally, eosinophilia, pyuria, hematuria, eosinophiluria, and mild proteinuria are present in a variable number of cases.

Physical examination

Physical examination includes a general examination of the throat, lymph nodes, abdomen (constipation, palpable and painful kidney, or palpable bladder), flank, the back (stigmata of spina bifida or sacral agenesis), genitalia (phimosis, labial adhesion, vulvitis, epididymo-orchitis), and temperature.

On examination, it is possible to identify the following signs:

Symptoms – Fatigue, Anorexia, Weight Loss, Headache, Flank pain, Arthralgias, Myalgias

Signs – Fever, Skin rash, Costovertebral Angle tenderness.

Laboratory examination

Blood studies: Renal Failure, Anemia, Eosinophilia

Urine studies: Sterile Pyuria, Proteinuria, Eosinophiluria, White Blood Cell Casts, Micro/Macroscopic Hematuria (rare)

The differential diagnosis of both acute and chronic TIN is broad. Chronic TIN may manifest similarly to obstructive nephropathy, chronic pyelonephritis, papillary necrosis, tubulopathies including Fanconi syndrome, progressive interstitial fibrosis or Balkan endemic nephropathy (BEN), Chinese herb nephropathy, and radiation nephritis. Acute TIN has a differential diagnosis that could include acute glomerulonephritis, pyelonephritis, atheroembolic disease, or any cause of AKI (acute tubular necrosis, prerenal azotemia, urinary obstruction or drug-induced AKI).

While eosinophiluria can be helpful in the diagnosis of TIN, it is neither sensitive nor specific. Eosinophiluria can also be seen with cystitis, prostatitis, pyelonephritis, atheroembolic renal disease, acute tubular necrosis and rapidly progressive glomerulonephritis. In a study evaluating drug-induced TIN, of the patients with biopsy-confirmed TIN, 67 % had eosinophiluria whereas 33 % did not. Additionally, 13 % of patients without TIN had eosinophiluria.

Treatment Tubulointerstitial nephritis

Treatment is primarily guided by underlying pathophysiology, if it can be determined. For example, drug-induced TIN may recover spontaneously with cessation of the offending medication, particularly if identified early. Aside from treating obvious sources of infection, other treatment options for infection-related TIN have not been well-described, although in transplant patients immunosuppressive medication can be decreased or Cidofovir used in polyoma virus-associated infections. Since medication-related acute TIN usually resolves after discontinuation of the offending drug, we recommend that the first line of treatment for antibiotic-related acute TIN is its discontinuation while the infection is treated with an alternative agent. The need for additional medications such as corticosteroids should be assessed based on the subsequent clinical course. On the opposite end of the spectrum, systemic rheumatologic and inflammatory conditions associated with TIN (including TINU) are more often treated with corticosteroids or with other agents based on the systemic disease.

Treatment of interstitial nephritis involves the normalization of blood pressure, the elimination of proteinuria and inhibition / restoration of kidney function. The drugs of choice are the ACE inhibitor, the BRA (category A), cytostatics (category B), antiplatelet drugs (category C), oritropoietin stimuliuyuchi agents (category A).

ACE inhibitors – Enap with SCF more than 60 ml / min., Quadropryl, monopril – with GFR 60–30 ml/min., Moeks – with GFR less than 30 ml/min, Dose is titrated for 1–1.5 months. Monotherapy with daily proteinuria up to 300 mg/day. Reception duration – until stable elimination of proteinuria, normalization of specific weight of urine and arterial pressure

ARB II1 – irbesartan with GFR over 60 ml/min., Eprosartan – with GFR 30–60 ml/min., Telmisartan – with GFR less than 30 ml/min., Dose is titrated

for 2–3 weeks. ARB is combined with an ACE inhibitor with daily proteinuria of more than 300 mg/day and GFR ≥ 60 ml/min. Reception duration - until stable elimination of proteinuria, normalization of specific weight of urine and arterial pressure

Cytostatics (cyclophosphamide, mycophenolate mofetil, for example, Cellcept, Mifortika) – with daily proteinuria of more than 1–2.5 g/day for 1–2 years.

Antiplatelet drugs (aspirin, ticlopidine, clopidogrel). Reception duration – to permanent elimination of proteinuria

Moxonidine (if necessary), for example, Physiotens, moxogamma.

Erythropoietin stimuli agents (for example, Recormon, Eprex). Target hemoglobin for children of all ages – 110–120 g/l.

TESTS
TO DETERMINE THE LEVEL OF THE MATERIAL LEARNED

1. From urine of a 14-year-old boy with the exacerbation of secondary obstructive pyelonephritis Pseudomonas aeruginosa was isolated with a titer of 1000000 microbes per 1 ml. What antibiotic is the most advisable in this case?

A. Ciprofloxacin *C. Cefazolinum* *E. Chloramphenicol*
B. Ampicillin *D. Azithromycin*

2. A 9-year-old girl complains of fever up to 37,5 °C, headache, inertness, weakness, loss of appetite, stomachache, and frequent painful urination. Provisional diagnosis of acute pyelonephritis is made. Clinical urine analysis: specific gravity – 1018, no protein, leukocytes – 10–15 in the vision field. What investigation method can verify the diagnosis of urinary system infection?

A. Rehberg test (creatinine clearance test)
B. Bacteriological inoculation of urine
C. Zymnytsky test (measurement of daily diuresis)
D. Complete blood count
E. Clinical urine analyses, dynamic testing

3. An 8-year-old girl with complaints of painful urination, frequent low-volume urination, and leukocyturia was diagnosed with acute cystitis. 10 days before the disease onset she was treated by the gynecologist for acute vulvitis. 5 days ago she presented with mild catarrhal symptoms. Her mother ascribes the child's disease to her overexposure to cold. Specify the most likely infection route:

A. Descending *C. Hematogenic* *E. Lymphogenic*
B. Ascending *D. Contact*

4. The patient, 12 years old, complains on aching pain in loin on the right, increase of body temperature to subfebrile numbers. In the anamnesis: there was pain in the right half of loin with chill, acute increase of body temperature, leucocyturia was present 3 years ago. In the analysis of urine: protein – 0,65 g/l, L – oll field of visual, bacteriuria. What is the most posible diagnosis:

A. Renal tuberculosis *D. Renal amyloidosis*
B. Chronic glomerulonephritis *E. Hypertonic disease*
C. Chronic pyelonephritis

5. At the 7-years-old patient with tonsillities in 3 days after the beginning of treatment by ceftriacson unpleasant feeling in lumbar area, dizziness, nausea appeared. At the examination: AP – 135/750. Blood test: E – $3{,}12 \times 10^{12}$/l, Hb – 120 g/l, L – 10×10^{9}/l, blood sedimentation – 28 mm/h, in the analysis of urine: specific weight – 1006, protein – 0,85 g/l. Day's amount of urine – 3,2 l. What is primary in treatment of the patient:

A. Chronic glomerulonephritis *D. Rapidly progressive glomerulonephritis*
B. Acute glomerulonephritis *E. Acute pyelonephritis*
C. Acute tubulointerstitial nephritis

6. At the girl 8 years old, after surecooling pain in muscles, increase of body temperatures to 39 °C, headache, dysuria, positive Pasternatcki symptom appeared. Analysis of urine: leukocyturia, bacteriuria. In blood test: Hb – 103 g/l, leukocytosis with change to the left, blood sedimentation – 32 mm/h., urea of blood – 6,0 mmol/l. The most reliable diagnosis:

A. Urolithiasis *C. Acute glomerulonephritis* *E. Acute cystitis*
B. Renal tuberculosis *D. Acute pyelonephritis*

7. The girl, 10 years old, unit with complaints on frequent, painful urination. Body temperature is normal. In blood test: without pathology. In the analysis of urine – leukocytes cover all field of vision, proteinuria – 0,033 g/l. What microorganism caused the disease more credible:

A. Candida *C. Mycobacterium tuberculosis* *D. E. colli*
B. Chlamydia *E. Trichomonads*

8. The boy, 17 years old, is hospitalized for an inspection in connection with hematuria, increase of body temperature to 38 °C, pain in left side of body. What examination is the most substantial for determination of the diagnosis:

A. Zimnicky sample *D. Biopsy of kidney*
B. Cystoscopy *E. US research of kidneys and urinary bladder*
C. Excretory urography

9. The patient, 6 years old, complains on high body temperature, chill, dull pains in loin. Objectively: muscular tension of lumbar area, positive Pasternatcki symptom on both sides. In the general analysis of blood: leukocytosis to 13×10^9/l with change to the left, low proteinuria in the global analysis of urine, pyuria. What microorganism causes the infection of urinary ways:

A. Aurococcus *C. Hemolytic streptococcus* *E. Chlamydia*
B. E. colli *D. Pseudomonas aeruginosa*

10. The patient, 6 years old, complains on pains in loin, unpleasant feelings at urination. Objectively: body temperature 37,8 °C, right kidney is painful at the palpation. In blood test: leukocytosis – 11×10^9/l, neutrophils – 9 %, in the analysis of urine: protein 0,33 g/l, leukocytyes – on all field of visions. Specify the criterion, which will allow you to differentiate the infection of lower from the infection of upper urinary ways:

A. Pyuria
B. Bacteria colonies more than 5×10^4 thousand of microbial bodies in 1 ml
C. Frequent, painful urination
D. Body temperature higher than 38 °C
E. Painful palpation of kidney

Ansvers of tests

1 – A, **2** – B, **3** – B, **4** – C, **5** – C, **6** – D, **7** – D, **8** – E, **9** – B, **10** – B.

SITUATIONAL TASKS

Task № 1

A 7 year old girl complains of fever up to 38,7 °C, headache, vomiting, abdominal pain, poor feeding , dysuria, frequent painful urination. These symptoms observed 3 days.

At objective survey: The general condition is severe. Appetite is bad. Skin pale, clean, periorbital shadows. On visual exemination edema is not present. Mucous is pale, without rash. The abdomen is mild, moderately painful in the suprapubic region. Tenderness in the costovertebral angle. Urination is painful, frequent. Stool is normal.

Urine test: specific gravity – 1019, no protein, leukocytes – on the whole field of view.

Uurine culture: identified microorganism – E.coli > 10^5 cfu/mL

Procalcitonin levels – 0.7 ng/mL.

1. What is the preliminary diagnosis?

2. With what pathological conditions do you need to differentiate?

3. What is the principle of treatment of this condition?

Task № 2

A 5 year old girl was admitted to the hospital with complains of frequent urination, increased urine turbidity, burning sensation when urinating. The girl was anxious, emotional lability. Complaints appeared after after hypothermia.

At objective survey: Skin and mucous membranes were pink. Temperature was 36.5 °C. Blood pressure was 95/60 mm Hg. She had no peripheral lymphadenopathy. respiratory and cardiac systems without pathology, Ps – 92 per minute. Abdomen was soft, painful in suprapubic region during palpation.

Blood test: Hb – 120g/l, er. – 4.8×10^9/l, color index of blood – 0.9, L – 6.7×10^9/l, Stab neutrophil – 2 %, segment – 60 %, eosinophile – 2 %, lymphocyte – 30 %,monocyte – 6 %, ESR – 26 mm/h.

Uurine test: ph – slightly acid, transparency – turbid urine, specific gravity – 1018, glucose – not found, protein – traces, leukocytes – ½ of vision field, erythrocytes – 10–12 in vision field, predominantly not changed.

Urine culture – pathogenic microflora was not found.

Biochemical test of blood: urea – 5.23 mmol/l, creatinine – 0.09 mmol/l.

1. What is suggested diagnosis?

2.What additional methods to assign the child?

3. What is the principle of treatment of this condition?

Task № 3

A 12 year old boy complaints of: increase in body temperature to 37.8 °C, weakness of the child. Eight years ago he had a case of pyelonephritis. Urine analyses periodically revealed leukocyturia.

At objective survey: Growth – 144 sm; Weight – 35 kg; T – 37,8; BR – 20; HR – 76; BP – 105/65 mm Hg. The general condition is severe. The child –

weak, appetite is bad. Skin is pale, clean, with periorbital shadows. On visual exemination edema is not present. Mucous is pale, without rash. The abdomen is mild, moderately painful in the suprapubic region. Costovertebral angle tenderness. Urination is painful, frequent. Stool 1p/day.

1. What is the preliminary diagnosis?

2. What additional methods to assign the child?

3. What are the effective antibiotic options for chronic pyelonephritis?

Task№4

A 8 year old boy admitted to the hospital with complains of: periodically increase in body temperature to subfebrile figures, abdominal pain, poor appetite, weakness, fatigue. The first time the listed complaints appeared 1 year ago.

At objective survey: The general condition is severe. BP – 135/85 mm Hg. The child – weak, appetite is bad. Skin is pale, clean, with periorbital shadows. Percusion over the lungs clear pulmonary sound, auscultation – vesicular breathing. The boundaries of the onset of cardiac dullness within the limits of the age norm, heart tones are clear, rhythmic. The abdomen is mild, flank tenderness.

Blood test: Hb – 110g/l, er. – 4.1×10^9/l, color index of blood – 0.9, L – 7.7–10^9/l, Stab neutrophil – 2 %, segment – 56 %, eosinophile – 4 %, lymphocyte – 33 %, monocyte – 7 %, ESR – 12 mm/h.

Uurine test: ph – slightly acid, transparency – turbid urine, specific gravity – 1018, leukocytes – ½ of vision field, erythrocytes – 1–2 in vision field, predominantly not changed.

Cystographya: VUR Stages I and II on the left.

1. What is the most likely diagnosis?

2. What are possible complications of obstruction in urinary tract infection?

3. What is the principle of treatment this condition?

Task № 5

A 15 year old girl complains of fever up to 39,0 °C, nausea, vomiting, headache, flank pain, poor feeding, dysuria, frequent painful urination. 5 days ago she presented with mild catarrhal symptoms.

At objective survey: The general condition is severe. Appetite is bad. Skin is pale, clean, wiyh periorbital shadows. HR – 96 mm Hg .The abdomen is mild, moderately painful in the right upper quadrant. Tenderness in the back. Urination is painful, frequent. Stool is normal.

Urine test: specific gravity – 1018, no protein, leukocytes – 50–70 in the vision field.

Culture of urine: Identified microorganism – E.coli > 10^5 cfu/mL

Procalcitonin levels – 0.75 ng/mL.

1.What is the most likely diagnosis?

2. What additional methods to assign the child?

3. What is included in the inpatient care for acute pyelonephritis?

Responses to the situational task

№ 1

1. Acute pyelonephritis.
2. Bacteremia, appendicitis, urinary tract infection, urolithiasis.
3. Patients with a nontoxic appearance may be treated with oral fluids and antibiotics. Toxic-appearing patients must be aggressively treated with intravenous (IV) fluids and parenteral antibiotics.

№ 2

1. Urinary tract infection.
2. Ultrasonography.
3. Treatment: plentiful drinking, antibacterial therapy within 7–10 days, possibly in combination with uroseptic.

№ 3

1. Chronic Pyelonephritis
2. Intravenous urogram, voiding cystourethrogram, radioisotopic scanning with technetium dimercaptosuccinic acid, computed tomography (CT) scanning.
3. The penicillins (amoxicillin) and first-generation cephalosporins are the drugs of choice because of good activity against gram-negative rods and good oral bioavailability. In infants, the choice of antibiotics is either amoxicillin or a first-generation cephalosporin. In patients aged 3–6 months, therapy can be changed to sulfamethoxazole or nitrofurantoin. Older children and adults may be treated with trimethoprim-sulfamethoxazole (Bactrim).

№ 4

1. VUR Stages I and II on the left. Chronic Pyelonephritis.
2. Complications of obstruction with superimposed infection include hydronephrosis, pyonephrosis, urosepsis, and xanthogranulomatous pyelonephritis.
3. Correction of the obstruction. Long-term antibiotic therapy. Sometimes nephrectomy, sometimes followed by renal transplantation.

№ 5

1. Acute pyelonephritis.
2. Blood urea nitrogen (BUN) and/or creatinine, electrolyte measurements, Renal ultrasonography, doppler ultrasonography, voiding cystourethrography.
3. Supportive care, monitoring of urine and blood culture results, monitoring of comorbid conditions for deterioration, maintenance of hydration status with IV fluids until hydration can be maintained with oral intake, IV antibiotics until defervescence and significant symptomatic improvement occur; convert to an oral regimen tailored to urine or blood culture results.

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Навчальне видання

Диференційна діагностика запальних захворювань нирок у дітей

Методичні вказівки
для студентів V-VI курсів вищих медичних закладів освіти
III-IV рівнів акредитації, що навчаються англійською мовою

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Переклад І. С. Аленіна
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Формат А5. Ум. друк. арк. 1,5. Зам. № 19-33752.

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Свідоцтво про внесення суб'єкта видавничої справи до Державного реєстру видавництв, виготівників і розповсюджувачів видавничої продукції серії ДК № 3242 від 18.07.2008 р.