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Urinary tract infections in children with cancer and febrile neutropenia – single center experience

Infekcije mokraćnih puteva kod dece obolele od malignih tumora sa febrilnom neutropenijom – iskustvo jednog centra

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Abstract

Background/Aim. Urinary tract infection (UTI) in children with febrile neutropenia (FN) after receiving chemotherapy could be followed by atypical symptoms and signs. The absence of routine urine culture (UC) sampling for analysis could lead to undiagnosed disease and inadequate treatment of these patients. The aim of the study was to indicate the importance of sampling UC in children who have developed FN and to point out the most probable causative agents of UTI in children with FN and antibiotic sensitivity/resistance of the isolated strains. **Methods.** During a five-year observation period, 40 UTIs were registered in 30 patients with FN. In the study group of patients with FN, the number of UTIs, the number of recurrent UTIs, isolated pathogens, their sensitivity to antibiotics, characteristics of urine sediment, the presence of localized symptoms of UTI, and the presence of urosepsis were analyzed. The obtained results were compared with the control group which consisted of children who were healthy prior to hospitalization due to febrile urinary infection. **Results.** When compared to the control group, significant differences in the presence of symptoms of UTI and urine sediment findings in patients with FN were observed. A higher percentage of resistant strains of *Escherichia coli* isolated from UC of cancer patients with FN was noted when compared to the control group. Three UTI cases were followed by urosepsis. **Conclusion.** UC findings are important not only in establishing the diagnosis of UTI and detecting multi-resistant bacterial strains but also in choosing appropriate antibiotics and selecting a subgroup of patients with recurrent UTI who require further monitoring and detecting potential complications in a timely manner.

Key words:
bacteriological techniques; child; febrile neutropenia; medical oncology; urinary tract infection; urinalysis.

Apstrakt

Uvod/Cilj. Infekcije mokraćnih puteva (IMP) kod dece koja su razvila febrilnu neutropeniju (FN) nakon primene hemioterapije, mogu biti praćene atipičnim simptomima i znacima. Odsustvo rutinskog uzimanja uzorka urinokulture (UK) za analizu može dovesti do neprepoznavanja i neadekvatnog lečenja tih bolesnika. Cilj rada bio je da se ukaže na značaj uzimanja UK kod dece kod kojih se razvila FN, na najčešće uzročnike IMP kod ove dece, kao i da se ukaže na osetljivost/rezistenciju na antibiotike izolovanih sojeva uzročnika IMP. **Metode.** U posmatranom petogodišnjem periodu registrovano je 40 IMP kod 30 bolesnika sa FN. U grupi bolesnika sa FN analiziran je broj IMP, broj ponovljenih IMP, izolovani uzročnici infekcije, njihova osetljivost na antibiotike, karakteristike sedimenta urina, prisustvo lokalnih simptoma IMP i prisustvo urosepse. Dobijeni podaci su upoređivani sa kontrolnom grupom, koju su činila zdrava deca prethodno hospitalizovana zbog urinarne infekcije praćene febrilnošću. **Rezultati.** Kod bolesnika sa FN, u odnosu na kontrolnu grupu uočena je statistički značajna razlika povezana sa prisustvom simptoma IMP i nalazom sedimenta urina. Registrovan je viši procenat izolovanih rezistentnih sojeva *Escherichia coli* iz UK bolesnika sa FN, u odnosu na kontrolnu grupu. Tri bolesnika sa IMP imala su prateću urosepsu. **Zaključak.** Nalaz UK je značajan ne samo u postavljanju dijagnoze IMP i otkrivanju multirezistentnih bakterijskih sojeva, već i u pravilnom odabiru antibiotske terapije i selekciji onih bolesnika sa ponovljenim IMP, koji zahtevaju dalje praćenje i pravovremeno otkrivanje potencijalnih komplikacija.

Ključne reči:
bakteriološke tehnike; deca; neutropenija, febrilna; onkologija, medicinska; urinarni trakt, infekcije; mokraća, analiza.

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Introduction

Urinary tract infections (UTIs) present a significant cause of morbidity in children. They are characterized by significant bacteriuria in urine culture, clinical signs of infection (fever, dysuria, pollakiuria, hematuria, abdominal pain), as well as the presence of pyuria. Pyuria is defined by the presence of more than five leukocytes per high-power field in centrifuged urine, which is consistent with positive leukocyte esterase on dipstick. The presence of nitrites, microscopical findings of bacteria, and the occurrence of microscopic hematuria in urine sediment can indicate the presence of infection. UTIs can be divided into two types: upper (acute pyelonephritis – renal parenchyma infected) and lower UTIs (cystitis) [1].

While the above-mentioned characteristics can be implemented in patients with normal blood leukocyte counts, in cancer patients with febrile neutropenia (FN), fever could often be the only sign of infection. Frequently, the presence of leukocytes in urine sediment could fail due to the existing leukopenia. In these patients, infection is often asymptomatic with normal urine findings, and diagnosis of UTI is established by the presence of significant bacteriuria [2–4].

Considering the fact that these infections could be caused by bacterial strains that are resistant to empiric antibiotic therapy, the omission of urine sampling in patient work-up could lead to undiagnosed UTIs and inadequate treatment. Consequently, this could cause the occurrence of renal scarring and may give rise to complications such as hypertension and chronic renal insufficiency [1].

At the moment, a small number of studies focused on UTI in children with FN have been conducted. The lack of studies might be attributed to the fact that according to Infectious Diseases Society of America recommendations from 2010, sampling urine in febrile oncology patients was recommended only when symptoms of UTI are present, a urinary catheter is placed, or if ultrasound of urinary tract shows evidence of urinary tract pathology [5]. According to current guidelines, urinalysis and urine culture (UC) should be obtained routinely as part of the diagnostic evaluation.

The aim of this paper was to present the importance of UC sampling in children who have developed FN after a cycle of chemotherapy. The absence of localized symptoms of UTI and normal urine sediment findings cannot safely exclude the presence of UTI in these patients. The presence of fever and significant bacteriuria can be the only signs of UTI.

Methods

This retrospective study was conducted in the Department of Oncology of the Institute for Health Care of Children and Youth of Vojvodina, Serbia. Ethical approval was obtained from the local Ethics Committee (No. 1402-1, from April 01, 2022). During a five-year observation period (from January 1, 2016, to January 1, 2021), 40 UTIs were registered in 30 patients with FN. The patients were children aged 3 to 18 years diagnosed with malignant diseases that established normal urinary continence and developed FN after a cycle of chemotherapy. Patients without normal urinary continence and patients with fever of another known origin were excluded from this study.

The obtained results were compared to the control group which consisted of 40 previously healthy children, in the same age range (3 to 18 years; average 6.9 years) hospitalized due to febrile urinary infection. Patients with congenital anomalies of the urinary system were excluded. Children from both groups were hospitalized during the same five-year study period.

Diagnosis of UTI was established due to the presence of significant bacteriuria in patients with an unknown origin of infection. In patients who had a urinary catheter placed, UC samples were taken from the catheter, while in other cases, a sample of mid-stream urine was obtained in a sterile container after cleaning the perineal/genital area. Standard bacterial, chemical, and microscopic techniques were used to analyze the urine samples, which included the analysis of urine appearance, pH, specific gravity, and presence of proteins, ketones, bilirubin, urobilinogen, nitrites, leukocytes, erythrocytes, and bacteria. After urine sampling, uricult was cultured, and if positive, UC was also tested. Significant bacteriuria was > 100,000 colony forming unit (CFU)/mL isolated from a voided specimen. Moreover, a sample for blood culture from the peripheral vein was obtained in all patients, and in patients who had central venous (CVC) catheters placed, a sample from CVC was also obtained. Urosepsis is defined by the isolation of the same causative agent from UC and blood culture.

During the study, we analyzed demographic characteristics (age, gender), the number of UTIs in patients with FN, the number of recurrent UTIs, isolated causative agents, their sensitivity to antibiotics, characteristics of urine sediment, the presence of localized symptoms of UTI (dysuria, pollakiuria, hematuria, and abdominal pain), as well as the presence of urosepsis. Available data on complete blood count (leukocytes, hemoglobin, platelets) and the inflammatory marker C-reactive protein (CRP) were collected.

Statistical package SPSS 23.0 was used for data processing and analysis. Besides descriptive statistics, the Chi-squared test was also implemented in order to compare the differences between the groups.

Results

The gender distribution in patients was equal (male/female ratio 50% : 50%). The majority (83%) of patients had hematologic malignancies (leukemia and lymphoma) while a smaller number (17%) had solid tumors (neuroblastoma, nephroblastoma, rhabdomyosarcoma, brain and testicular tumors). One UTI was present in 22 (73.3%) patients, while recurrent UTI was present in 8 (26.7%) patients. In half of the patients, recurrent UTIs occurred one month after the first infection. The largest number (70%) of examined patients previously received trimethoprim/sulfamethoxazole (TMP/SMZ) prophylaxis against *Pneumocystis jirovecii* in-

fection, out of whom 28% had recurrent UTI. The patients who did not receive prophylactic therapy had recurrent UTIs in 40% of the cases. Statistically significant differences were detected in the presence of symptoms of UTI and urine sediment findings in patients with FN when compared to the control group (Table 1). The symptoms of UTI (dysuria, pollakiuria, haematuria, and/or abdominal pain) were present in only 3 (7.7%) patients, while other (92.3%) patients, besides fever, did not have any other symptoms. By examining the differences in clinical manifestation, statistically significant differences between the groups with FN and the control group were detected ($\chi^2 = 25.813$, $p < 0.001$). All patients in the control group had pyuria, 55% of them had microscopic hematuria, and 25% had positive nitrites in urine sediment. In contrast, the patients with FN did not have pyuria in urine sediment in 90% of UTI episodes. This difference was also statistically significant ($\chi^2 = 65.455$, $p < 0.001$). Patients with pyuria (10%) most commonly manifested mild pyuria (5–10 leukocytes). Microscopic hematuria was recorded in two cancer patients with UTI compared to 22 patients in the control group; the difference was statistically significant ($\chi^2 = 23.8095$, $p < 0.001$). The presence of nitrite was recorded in one patient in the study group, while it was recorded in 10 UTI episodes in the control group. These differences were statistically significant ($\chi^2 = 8.5375$, $p < 0.05$). Three cancer patients with UTI subsequently developed urosepsis (7.5%). In all three patients, fever was the only sign of infection – all of them had prolonged neutropenia, and one of them had a central venous line. In the above-mentioned patients, one patient manifested mild pyuria and positive nitrites in urine sediment, another patient had microscopic hematuria, and the third patient had completely normal urine sediment. The only isolated causative agent in the UC of the control group was *Escherichia (E.) coli* in patients with FN. Besides *E. coli* (70% of all isolates), infections caused by other bacterial strains (*Klebsiella* spp 12.5%, *Enterococcus* and *Enterobacter* spp 5%, *Proteus*, *Pseudomonas* and *Morganella morganii* 2.5%) were also noticed. *E. coli* was a causative agent of urosepsis in two patients, while one patient developed urosepsis caused by *Klebsiella*. All of the *Klebsiella* strains

Table 1

Differences in UTI presence and in urine sediment findings in patients with FN and children without FN

Parameter	Group		Total	χ^2	*p*-level
	FN	control			
Urine leucocytes					
no	36 (90.0)	0 (0.0)	36 (45.0)		
yes	4 (10.0)	40 (100.0)	44 (55.0)	65.455	0.000
total	40 (100.0)	40 (100.0)	80 (100.0)		
Urine erythrocytes					
no	38 (95.0)	18 (45.0)	56 (70.0)		
yes	2 (5.0)	22 (55.0)	24 (30.0)	23.809	0.000
total	40 (100.0)	40 (100.0)	80 (100.0)		
Urine nitrites					
no	39 (97.5)	30 (75.0)	69 (86.3)		
yes	1 (2.5)	10 (25.0)	11 (13.8)	8.537	0.009
total	40 (100.0)	40 (100.0)	80 (100.0)		
UTI symptoms					
no	36 (90.0)	14 (35.0)	50 (62.5)		
yes	4 (10.0)	26 (65.0)	30 (37.5)	25.813	0.000
total	40 (100.0)	40 (100.0)	80 (100.0)		

UTI – urinary tract infection; FN – febrile neutropenia.
All values are expressed as numbers (percentages).

Table 2

Difference in the percentage of resistant strains of *Escherichia coli* in urine culture findings in patients with FN and children without FN

Antibiotics	Group	
	FN	control
Ampicillin	89.65	29.50
Amoxicillin/clavulanic acid	55.17	14.30
Amikacin	30.00	6.25
Piperacillin/tazobactam	57.15	11.76
Cephalexin	58.62	14.30
Cefixime	48.00	15.15
Ceftriaxone	50.00	15.15
Ciprofloxacin	48.14	6.66
Trimethoprim/sulphamethoxazole	79.31	20.00
Meropenem	17.86	0.00
Imipenem	10.72	0.00

FN – febrile neutropenia.
All values are expressed as percentages.

were resistant to ampicillin, amoxicillin, cephalexin, and cefixime; 83% of the strains showed resistance to ceftriaxone, amoxicillin/clavulanic acid and TMP/SMZ, 66% showed resistance to piperacillin/tazobactam, 22% to amikacin, and 16% to meropenem and imipenem. A higher percentage of resistant strains of *E. coli* was isolated from UC of patients with FN when compared to the control group (Table 2).

By observing the inflammatory markers, we found that the average value of CRP in patients with FN was 47.5 mg/L [minimum (min) 0.5 mg/L, maximum (max) 359 mg/L; reference range (RR) 0–5 mg/L], while the control group had a higher average value of 122 mg/L. In most episodes of FN (71.8%), the average value of CRP was below 50 mg/L. Mean values of leukocyte count was 1.2×10^9/L (min 0.3×10^9/L, max 3.2×10^9/L; RR 4.0–10.4 $\times 10^9$), hemoglobin levels were 93 g/L (min 72 g/L, max 131 g/L; RR 110–165 g/L), and platelet count 106 x 10^9/L (min 11 x 10^9/L, max 350×10^9/L; RR $150–450 \times 10^9$).

Discussion

FN is one of the most common complications of chemotherapy. Since it presents the leading cause of morbidity and mortality in children with malignant diseases, it should be suspected in every febrile cancer patient who received chemotherapy in the past 14 days [6–9]. Chemotherapy damages the skin and mucous membranes, disrupts the cellular and humoral immune response, and causes inadequate production of antibodies and depletion of immunoglobulin subclasses. After chemotherapy, it takes months for B and T lymphocyte counts to recover, while it takes years for the recovery of their subclasses. The mucocutaneous junction can also be damaged by the presence of intravascular and urinary catheters. After the pathogens enter the bloodstream, tissue damage, and systemic inflammatory response occur, potentially leading to organic dysfunction. Coagulopathy, as well as both quantitative and qualitative platelet disorders, can occur [10–14]. During the period of this study, the largest number of patients developed pancytopenia after a cycle of chemotherapy and became prone to infection. The majority (90%) of patients presented with fever on hospital admission. Three patients developed urosepsis, and fever was the only sign of systemic infection in all of them.

In children who have developed FN after the chemotherapy cycle, fever over 38 °C could be the only sign of systemic infection. Moreover, the inflammatory response can be absent, and thus, in children who have developed sepsis, instead of fever, signs of hypothermia, hypotension, confusion, poor general condition, or signs coming from the site of the primary infection may be present. Furthermore, children with normal absolute neutrophil count might have occult infection due to qualitative disorder of white blood cells. Neutropenic sepsis development and other life-threatening infections pose a high risk to these patients. In up to 50% of patients with FN, the primary infection site remains unidentified, while a causative agent is cultivated from only 20–30% of blood cultures [9, 11, 15, 16]. Therefore, a meticulous search for the primary infection site is mandatory.

The presence of UTI in adult cancer patients with FN is estimated at around 5–30% [2]. The exact prevalence of UTI in children with FN is unknown. In previously conducted studies, the estimated risk of UTI was around 8% [3, 4, 17]. In a study conducted by Klaassen et al. [18], only 4% of the UTI episodes in children with FN were associated with pyuria in urine sediment. The data about the presence of nitrites and microscopic hematuria are missing. In this study, 10% of the UTI episodes were associated with pyuria, 5% with microscopic hematuria, and 2.5% with the presence of nitrites in urine sediment. Both studies are retrospective, and the data about the presence of vulvitis/balanitis, which could possibly cause pyuria, are missing. Rahman et al. [17] have reached a similar conclusion, the largest number of patients with analyzed UTI episodes had normal urine sediment (the absence of pyuria, negative urinary nitrite test, and leukocyte esterase test), and none of the patients had symptoms of localized UTI. In the mentioned study, all patients, except one, received *Pneumocystis jirovecii* prophylaxis with TMP/SMZ three days weekly, and only one patient had a UTI with *E. coli* sensitive to this antibiotic. Prophylactic use of TMP/SMZ caused the most common UTI causative agents to develop resistance to the mentioned antibiotic. Our research showed similar results – 79.31% of *E. coli* isolates, and 83% of *Klebsiella spp* isolates were resistant to TMP/SMZ. On the other hand, in the control group, resistance to this antibiotic was present in 20% of the cases. The largest number of patients with FN was previously treated with prophylactic antibiotic therapy; out of them, 28% had recurrent UTI. In 40% of the cases, patients who were not treated with prophylactic therapy had recurrent UTIs. In our research, all three study patients with FN and urosepsis had additional risk factors for infection. All of them had prolonged neutropenia, and two of them had a central venous line. One of these patients presented with pyuria and positive nitrites, the second had microscopic hematuria, and the third had completely normal urine sediment.

Growing antimicrobial resistance is becoming a considerable problem worldwide, and thus, the selection of adequate antibiotics for treating episodes of FN is also becoming limited. Due to the high morbidity and mortality rates, empirical antibiotic therapy is introduced to every patient with FN. For the initial treatment of children with FN and high risk for developing complications, empirical antipseudomonal penicillin monotherapy (piperacillin/tazobactam, ticarcillin/clavulanic acid), fourth-generation antipseudomonal cephalosporins monotherapy (cefepime) or carbapenem monotherapy (meropenem, imipenem) is recommended. Usage of other antibiotics efficient in the treatment of Gram-negative bacteria (aminoglycosides) or glycopeptide antibiotics efficient in the treatment of Gram-positive bacteria (vancomycin, teicoplanin) is reserved only for clinically unstable patients suspected of developing infections with resistant microorganisms and centers with high-frequency rates of antimicrobial resistance. A Korean study in pediatric patients with FN showed evidence of a growing number of infections caused by Gram-negative bacteria since 2010, with a special focus on strains of *E. coli* and *Klebsiella spp*, which produce extended-spectrum beta-

lactamase (ESBL) [19]. Higher frequencies of ESBL-producing strains (30.6%) were noted by comparison with a previously conducted study in the same center [20]. The main risk factors in patients with FN are previous treatment with antibiotics and former FN episodes treated with broad-spectrum antibiotics. In the study of Hirmas et al. [21], the most isolated causative agents of UTI in pediatric cancer patients were Gram-negative bacteria (84%) with *E. coli* (51%), *Klebsiella pneumoniae* (9%), and *Pseudomonas aeruginosa* (8%) being the most frequent. ESBL-producing strains were present in 37% of the cases, and multidrug-resistant bacterial strains were present in 3%. Our study showed similar results – the most frequently isolated bacteria in patients with FN were *E. coli* and *Klebsiella spp*. Strains of *E. coli* isolated from UC were resistant to carbapenem in 17.86% of the cases, while in 57.15% of the cases, strains were resistant to piperacillin/tazobactam. Strains of *Klebsiella spp* were resistant to carbapenem in 16% of the cases and piperacillin/tazobactam in 66% of the cases. Sensitivity to cefepime was not routinely analyzed. Concerning the above-mentioned facts, recommended empirical antibiotic therapy for the treatment of pediatric UTI is likely to be ineffective in FN patients due to increased resistance of causative microorganisms. Moreover, failing to obtain UC in these patients may finally lead to an undiagnosed disease and inadequate treatment of UTI.

Regarding the fact that FN is an emergency that requires urgent empirical antibiotic treatment, it is necessary to start treatment regardless of the urine findings [22].

Conclusion

The urine sampling is extremely important, not only in establishing the diagnosis of UTI but also in detecting multiresistant bacterial strains. Possible isolation of a causative agent will improve appropriate antibiotic choice and selection of patients with recurrent UTIs who require further monitoring and early detection of potential complications in a timely manner.

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