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Original Article

Bacterial Profile and Antibiotic Resistance Pattern among Children with Urinary Tract Infections in Dr. Soetomo Hospital, Surabaya, Indonesia

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ABSTRACT

Urinary tract infections (UTIs) are the most common infections in pediatric patients characterized by the growth of bacteria in the urine in significant numbers. Antibiotics remain the primary treatment of UTI in children. However, there has been an increase in antibiotic resistance to uropathogens worldwide due to their inappropriate and extensive uses. There is considerable geographical variation in the distribution of bacteria and antibiotic resistance pattern. Thus, to prevent further resistance and provide empirical antibiotic options, this study aims to determine the profile of bacteria and antibiotics resistance pattern among UTI pediatric patients in Dr. Soetomo Hospital. This study was performed by collecting data from the urine culture logbook at the Clinical Microbiology Laboratory of Dr. Soetomo Hospital in July-October 2019. The sample was UTI patients aged one day – 18 years due to bacterial infection with a colony count of ≥100,000 CFU/ml. In this study, 131 patients showed significant bacterial growth dominated by males and ages one month – 2 years. UTI were caused by gram-negative bacteria (74%) and gram-positive bacteria (26%), with the most bacteria found in each group were Escherichia coli and Enterococcus faecalis. E. coli showed ≥70% resistance to ampicillin, cefazoline, piperacillin, tetracycline, and trimethoprim-sulfamethoxazole. Comorbidities were dominated by hydronephrosis (10.98%), chronic kidney disease (9.79%) and hydrocephalus (8.09%). In conclusion, gram-negative bacteria were the leading cause of UTI in children with E. coli as the most common uropathogen, highly resistant to ampicillin and cefazolin. Gram-positive bacteria were less frequent with varied resistance patterns. Most common comorbidity was hydronephrosis.

Keywords: *antibiotic resistance; bacterial pathogen; urinary tract infection*

ABSTRAK

Infeksi saluran kemih (ISK) merupakan penyakit infeksi yang banyak dijumpai pada anak ditandai dengan pertumbuhan bakteri urin dalam jumlah yang signifikan. Pengobatan ISK anak utamanya dengan pemberian antibiotik. Namun, telah terjadi peningkatan resistensi antibiotik terhadap uropatogen di seluruh dunia akibat penggunaan yang kurang tepat dan terlalu ekstensif. Variasi geografis dalam distribusi bakteri penyebab ISK dan pola resistensi antibiotiknya juga cukup besar. Untuk mencegah

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resistensi lebih lanjut dan memberikan pilihan antibiotik empiris, penelitian ini diperlukan untuk mengetahui profil bakteri dan pola resistensi antibiotik pada pasien anak ISK di RSUD Dr. Soetomo. Penelitian ini dilakukan dengan menggunakan data sekunder berupa catatan hasil kultur urin di Laboratorium Mikrobiologi Klinik RSUD Dr. Soetomo pada bulan Juli-Oktober 2019 dengan sampel pasien ISK anak berusia 1 hari – 18 tahun akibat infeksi bakteri dengan hitung koloni sebanyak ≥100,000 CFU/ml. Dalam penelitian ini, 131 pasien menunjukkan pertumbuhan bakteri signifikan, yang didominasi oleh laki-laki dan usia 1 bulan – 2 tahun. ISK disebabkan oleh bakteri gram negatif (74%) dan gram positif (26%) dengan bakteri terbanyak yang ditemukan pada masing-masing kelompok adalah Escherichia coli dan Enterococcus faecalis. E. coli menunjukkan resistensi ≥70% terhadap ampisilin, sefazolin, piperasilin, tetrasiklin, dan trimetoprim-sulfametoksazol. Penyakit penyerta pada pasien ISK anak didominasi oleh hidronefrosis (10,98%), penyakit ginjal kronis (9,79%), dan hidrosefalus (8,09%). Sehingga dapat disimpulkan bahwa bakteri gram negatif merupakan penyebab utama ISK anak dengan E. coli sebagai uropatogen yang paling sering dijumpai, yang resisten terhadap ampisilin dan cefazolin. Sedangkan bakteri gram positif lebih jarang ditemukan dengan pola resistensi yang bervariasi. Penyakit penyerta pasien terbanyak adalah hidronefrosis.

Kata kunci: *bakteri patogen; infeksi saluran kemih; resistensi antibiotik*

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INTRODUCTION

Urinary Tract Infection (UTI) is the second most common infectious disease in children after respiratory tract infection characterized by the growth of bacteria in the urine in significant numbers.[1,2] Mostly, UTI in children are caused by gram-negative bacteria with *Escherichia coli* as the most common uropathogen.[3] UTI in children are often underdiagnosed due to their non-specific signs and symptoms, especially in neonates and infants[4], such as fever, decreased appetite, vomiting, diarrhea, jaundice, abdominal distension, weight loss, and failure to thrive.[2] In addition, pediatric UTIs are commonly associated with various congenital abnormalities of the urinary tract, such as posterior urethral valves, ureteropelvic junction obstruction, neurogenic bladder, urethral stricture, and vesicoureteral reflux, which can lead to recurrent UTIs.[5] If the patient is not treated promptly, complications such as renal scarring, hypertension, or chronic kidney disease, will develop progressively. Thus, it is necessary to give empirical antibiotics based on local antimicrobial susceptibility patterns as initial therapy before the urine culture results are available.[3]

Globally, UTI in pediatric are estimated around 150 million cases annually.[6] In the United States, there are an estimated 1.5 million cases of UTI in pediatric outpatients.[7] While at Dr. Soetomo Hospital Surabaya, Indonesia, it obtained 94 urine samples among children with UTI within two months.[8] The incidence of UTI in children is more common in girls (8%) than boys (2%).[9] Boys have a greater incidence of UTI than girls with a ratio of 2:1 to 5:1 in the neonatal period and early infancy.[3,10] In addition, the increasing prevalence of antimicrobial resistance among uropathogens over the past few decades also complicates UTI management.[3] The National Healthcare Safety Network (NHSN) in the United States reported that an increase in multidrug-resistant gram-negative bacteria was found in 2,039 hospitals.[11] A study from South India demonstrated that Extended-Spectrum Beta-Lactamase (ESBL) production was detected in 53% of isolates from patients with community-acquired bacteremia caused by *E. coli* and *Klebsiella* spp.[12]

In the recent years, the increasing trend of bacterial uropathogen resistance against commonly used antimicrobials has become a major concern worldwide. Antibiotic susceptibility patterns vary widely between different geographic areas. In a study in Ethiopia showed that *E. coli*, as the most common isolated uropathogen, was resistant

to ampicillin (100%) and nitrofurantoin (78.6%) whereas sensitive to ciprofloxacin (71.4%), norfloxacin (71.4%) and ceftriaxone (57.1%).[6] In Nepal, the percentage of sensitivity for *E. coli* were high for nitrofurantoin, ceftriaxone, amikacin, gentamicin, and ofloxacin, while a high level of resistance was observed for ampicillin and cotrimoxazole.[13] A study by Patwardhan et al. in North India reported that the incidence of resistance to ampicillin, amoxiclav, nitrofurantoin, co-trimoxazole, and norfloxacin increased significantly over a five-year period. This situation is certainly very concerning because the complexity of UTI treatment can increase the risk of long-term consequences in children.[14]

Given the high prevalence of antibiotic resistance worldwide with the diversity of resistance patterns between geographic areas that change easily over time, continuous monitoring of uropathogens and local antibiotic resistance patterns is needed as a basic consideration in selecting empiric pharmacotherapy which is important to optimize the initial management of pediatric UTIs to reduce risk of unexpected complications.[4] Studies recommend that policies for UTI treatment in children should be re-evaluated every five years according to local resistance levels.[15] Hence, this study was conducted to assess the prevalence of bacterial uropathogens and their susceptibility patterns to antibiotic agents amongst pediatric patients with UTI in Dr. Soetomo Hospital.

MATERIALS AND METHODS

Study Design

This descriptive retrospective study was conducted at the Clinical Microbiology Laboratory of Dr. Soetomo Hospital, Surabaya, from September 2020 to June 2021. Data on age, sex, urine culture, antibiotic sensitivity, and patient comorbidities were obtained from the urine culture logbook in July-October 2019. Samples were collected using consecutive sampling techniques from pediatric patients aged one day – 18 years with UTI (inpatient and outpatients). The diagnosis of UTI was established when the result of the bacterial colony count was >100,000 colony-forming units per millilitre (CFU/ml).[17] Bacterial identification and antibiotic susceptibility test were carried out using the automatic microdilution method, BD Pheonix and Vitek, validated and interpreted by Clinical Laboratory Standard International (CLSI). Patients with incomplete urine examination data and medical records were excluded from this study.

Statistical Analysis

The data were analyzed descriptively with Statistical Package for the Social Sciences (SPSS) 16.0 and Microsoft Excel resulted in the distribution of the number and percentage of each variable.

Ethical Approval

This research received ethical approval from the health research ethics committee of Dr. Soetomo Hospital on November 26, 2020, with the letter number 0225/LOE/301.4.2/XI/2020.

RESULTS AND DISCUSSION

Characteristics of pediatric UTI patients

Based on the urine culture logbook in pediatric UTI in July-October 2019, there were 211 data on patients aged one day – 18 years who performed urine culture examinations and antibiotic sensitivity tests at the Clinical Microbiology Laboratory of Dr. Soetomo Hospital. However, significant bacterial growth (≥100,000 CFU/ml) was found in 131 patients and was dominated by boys (54.2%). Based on age, the results showed that UTI in children mainly occurred in the age group of one month – 2 years.

If we look at the distribution of age by sex (Table 1), the results show that most boys are found in the age group of one month – 2 years, while most girls are found in the age group of 6–12 years.

Table 1. Age and Sex Distribution

Age	Sex		Total n (%)
	Girl	Boy	
	n (%)	n (%)	
0-30 days	0(0.00)	2(1.53)	2(1.53)
1 month - 2 years	15(11.45)	23(17.56)	38(29.01)
2-6 years	8(6.11)	18(13.74)	26(19.85)
6-12 years	19(14.50)	15(11.45)	34(25.95)
12-18 years	18(13.74)	13(9.92)	31(23.66)
Total	60(45.80)	71(54.20)	131(100.00)

Bacteria Isolation

Bacteria causing UTI were dominated by gram-negative bacteria (74%) followed by gram-positive bacteria (26%). The most common gram-negative bacteria were *E. coli* (30.5%) while the most common gram-positive bacteria were *E. faecalis* (8.4%). All the data are shown in Figure 1. In this study, there were 17 isolates of *E. coli* and eight isolates of *K. pneumoniae* ESBL-producing gram-negative bacteria.

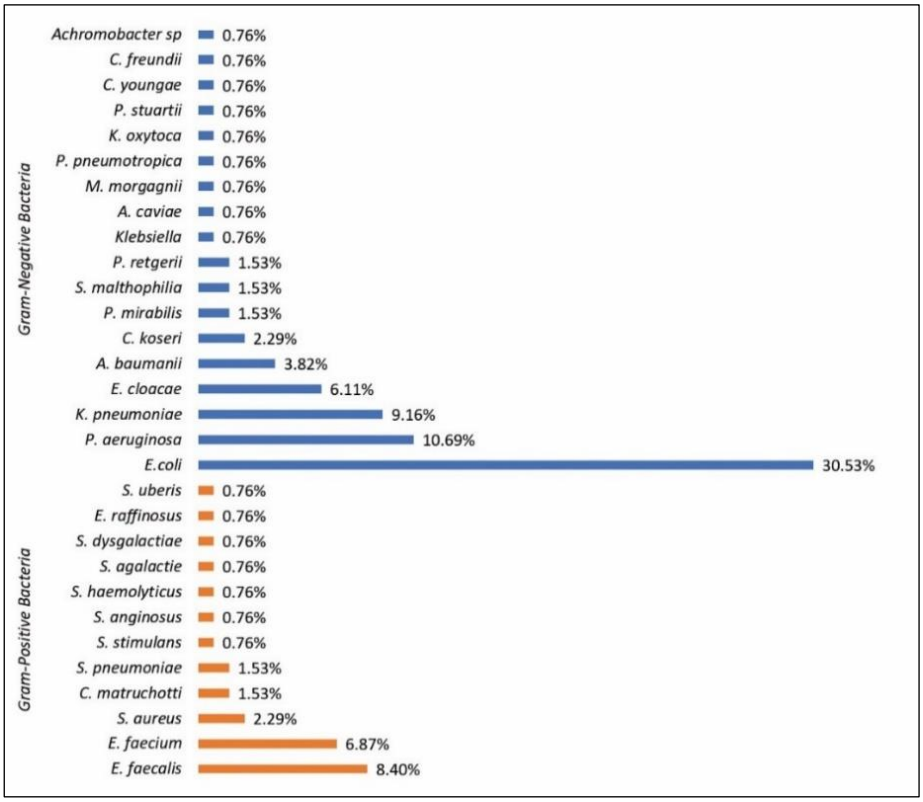

Figure 1. Distribution of Bacteria Causing UTI

Gram-Negative Bacteria Resistance Pattern

In this study, *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *E. cloacae*, and *A. baumannii*, showed resistance to ampicillin and cefazolin. *E. coli* was found to be resistant to ampicillin, cefazolin, piperacillin, sulfamethoxazole, trimethoprim- and tetracycline for about more than 70%. In contrast to *P. aeruginosa* which was resistant to more antibiotics such as ampicillin, cefazolin, amoxicillin-clavulanate, ampicillin-sulbactam, chloramphenicol, cefotaxime, nitrofurantoin, tetracycline, tigecycline, trimethoprim-sulfamethoxazole and ceftriaxone (Table 3).

In addition, the five most common gram-negative bacteria showed high sensitivity to amikacin, imipenem, meropenem, and piperacillin-tazobactam, as shown in Table 3. *E. coli* was also sensitive to tigecycline, nitrofurantoin, gentamicin, and cefoperazone-sulbactam, while *P. aeruginosa* was also found to be sensitive to piperacillin, gentamicin, and ceftazidime.

Table 3. Distribution of Antibiotic Resistance in Gram-Negative Bacteria

Antibiotic		*E. coli* (N=40)	*P. aeruginosa* (N=14)	*K. pneumoniae* (N=12)	*E. cloacae* (N=8)	*A. baumanii* (N=5)
Amikacin	R (%)	0/40 (0.00)	1/14 (7.14)	2/12 (16.67)	4/8 (50.00)	0/5 (0.00)
	I (%)	0/40 (0.00)	1/14 (7.14)	1/12 (8.33)	0/8 (0.00)	0/5 (0.00)
	S (%)	40/40 (100.00)	12/14 (85.71)	9/12 (75.00)	4/8 (50.00)	5/5 (100.00)
Amoxicillin-clavulanate	R (%)	13/40 (32.50)	14/14 (100.00)	4/12 (33.33)	8/8 (100.00)	5/5 (100.00)
	I (%)	10/40 (25.00)	0/14 (0.00)	3/12 (25.00)	0/8 (0.00)	0/5 (0.00)
	S (%)	17/40 (42.50)	0/14 (0.00)	5/12 (41.67)	0/8 (0.00)	0/5 (0.00)
Ampicillin	R (%)	36/39 (92.31)	13/13 (100.00)	12/12 (100.00)	8/8 (100.00)	5/5 (100.00)
	I (%)	0/39 (0.00)	0/13 (0.00)	0/12 (0.00)	0/8 (0.00)	0/5 (0.00)
	S (%)	3/39 (7.69)	0/13 (0.00)	0/12 (0.00)	0/8 (0.00)	0/5 (0.00)
Ampicillin-sulbactam	R (%)	21/40 (52.50)	13/13 (100.00)	7/12 (58.33)	8/8 (100.00)	0/5 (0.00)
	I (%)	9/40 (22.50)	0/13 (0.00)	1/12 (8.33)	0/8 (0.00)	0/5 (0.00)
	S (%)	10/40 (25.00)	0/13 (0.00)	4/12 (33.33)	0/8 (0.00)	5/5 (100.00)
Aztreonam	R (%)	17/40 (42.50)	8/14 (57.14)	8/12 (66.67)	4/8 (50.00)	5/5 (100.00)
	I (%)	3/40 (7.50)	3/14 (21.43)	0/12 (0.00)	0/8 (0.00)	0/5 (0.00)
	S (%)	20/40 (50.00)	3/14 (21.43)	4/12 (33.33)	4/8 (50.00)	0/5 (0.00)
Cefazolin	R (%)	26/26 (100.00)	14/14 (100.00)	8/8 (100.00)	8/8 (100.00)	5/5 (100.00)
	I (%)	0/26 (0.00)	0/14 (0.00)	0/8 (0.00)	0/8 (0.00)	0/5 (0.00)
	S (%)	0/26 (0.00)	0/14 (0.00)	0/8 (0.00)	0/8 (0.00)	0/5 (0.00)
Cefepime	R (%)	18/40 (45.00)	7/14 (50.00)	8/12 (66.67)	4/8 (50.00)	1/5 (20.00)
	I (%)	1/40 (2.50)	0/14 (0.00)	0/12 (0.00)	0/8 (0.00)	0/5 (0.00)
	S (%)	21/40 (52.50)	7/14 (50.00)	4/12 (33.33)	4/8 (50.00)	4/5 (80.00)
Cefotaxime	R (%)	18/40 (45.00)	14/14 (100.00)	8/12 (66.67)	4/8 (50.00)	1/5 (20.00)
	I (%)	1/40 (2.50)	0/14 (0.00)	0/12 (0.00)	0/8 (0.00)	3/5 (60.00)
	S (%)	21/40 (52.50)	0/14 (0.00)	4/12 (33.33)	4/8 (50.00)	1/5 (20.00)
Gentamicin	R (%)	8/40 (20.00)	2/14 (14.29)	5/12 (41.67)	4/8 (50.00)	2/5 (40.00)
	I (%)	0/40 (0.00)	1/14 (7.14)	0/12 (0.00)	0/8 (0.00)	0/5 (0.00)
	S (%)	32/40 (80.00)	11/14 (78.57)	7/12 (58.33)	4/8 (50.00)	3/5 (60.00)
Ceftazidime	R (%)	17/40 (42.50)	2/14 (14.29)	8/12 (66.67)	4/8 (50.00)	1/5 (20.00)
	I (%)	2/40 (5.00)	1/14 (7.14)	0/12 (0.00)	0/8 (0.00)	0/5 (0.00)
	S (%)	21/40 (52.50)	11/14 (78.57)	4/12 (33.33)	4/8 (50.00)	4/5 (80.00)
Ceftriaxone	R (%)	22/39 (56.41)	11/13 (84.62)	8/12 (66.67)	4/8 (50.00)	2/5 (40.00)
	I (%)	1/39 (2.56)	2/13 (15.38)	0/12 (0.00)	0/8 (0.00)	2/5 (40.00)
	S (%)	16/39 (41.03)	0/13 (0.00)	4/12 (33.33)	4/8 (50.00)	1/5 (20.00)
Chloramphenicol	R (%)	1/3 (33.33)	12/12 (100.00)	1/1 (100.00)	4/4 (100.00)	5/5 (100.00)
	I (%)	0/3 (0.00)	0/12 (0.00)	0/1 (0.00)	0/4 (0.00)	0/5 (0.00)
	S (%)	2/3 (66.67)	0/12 (0.00)	0/1 (0.00)	0/4 (0.00)	0/5 (0.00)
Ciprofloxacin	R (%)	12/39 (30.77)	3/13 (23.08)	2/12 (16.67)	4/8 (50.00)	1/5 (20.00)
	I (%)	1/39 (2.56)	1/13 (7.69)	2/12 (16.67)	0/8 (0.00)	0/5 (0.00)
	S (%)	26/39 (66.67)	9/13 (69.23)	8/12 (66.67)	4/8 (50.00)	4/5 (80.00)
Ertapenem	R (%)	0/1 (0.00)	-	-	-	-
	I (%)	0/1 (0.00)	-	-	-	-
	S (%)	1/1 (100.00)	-	-	-	-
Fosfomycin	R (%)	0/11 (0.00)	1/3 (33.33)	0/1 (0.00)	-	2/2 (100.00)
	I (%)	0/11 (0.00)	1/3 (33.33)	0/1 (0.00)	-	0/2 (0.00)
	S (%)	11/11 (100.00)	1/3 (33.33)	1/1 (100.00)	-	0/2 (0.00)
Imipenem	R (%)	0/38 (0.00)	1/12 (8.33)	1/12 (8.33)	4/8 (50.00)	0/5 (0.00)
	I (%)	3/38 (7.89)	1/12 (8.33)	0/12 (0.00)	1/8 (12.50)	0/5 (0.00)
	S (%)	35/38 (92.11)	10/12 (83.33)	11/12 (91.67)	3/8 (37.50)	5/5 (100.00)
Levofloxacin	R (%)	11/40 (27.50)	3/12 (25.00)	2/12 (16.67)	4/8 (50.00)	1/5 (20.00)
	I (%)	2/40 (5.00)	3/12 (25.00)	0/12 (0.00)	0/8 (0.00)	0/5 (0.00)
	S (%)	27/40 (67.50)	6/12 (50.00)	10/12 (83.33)	4/8 (50.00)	4/5 (80.00)
Meropenem	R (%)	0/40 (0.00)	1/14 (7.14)	1/12 (8.33)	4/8 (50.00)	0/5 (0.00)
	I (%)	0/40 (0.00)	1/14 (7.14)	0/12 (0.00)	0/8 (0.00)	0/5 (0.00)
	S (%)	40/40 (100.00)	12/14 (85.71)	11/12 (91.67)	4/8 (50.00)	5/5 (100.00)

Moxalactam	R (%)	-	-	-	0/1 (0.00)	-
	I (%)	-	-	-	0/1 (0.00)	-
	S (%)	-	-	-	1/1 (100.00)	-
Moxifloxacin	R (%)	13/38 (34.21)	-	2/12 (16.67)	4/7 (57.14)	-
	I (%)	0/38 (0.00)	-	2/12 (16.67)	1/7 (14.29)	-
	S (%)	25/38 (65.79)	-	8/12 (66.67)	2/7 (28.57)	-
Nitrofurantoin	R (%)	4/39 (10.26)	14/14 (100.00)	7/12 (58.33)	6/8 (75.00)	5/5 (100.00)
	I (%)	1/39 (2.56)	0/14 (0.00)	3/12 (25.00)	0/8 (0.00)	0/5 (0.00)
	S (%)	34/39 (87.18)	0/14 (0.00)	2/12 (16.67)	2/8 (25.00)	0/5 (0.00)
Piperacillin	R (%)	31/38 (81.58)	2/12 (16.67)	9/12 (75.00)	5/8 (62.50)	1/5 (20.00)
	I (%)	4/38 (10.53)	0/12 (0.00)	1/12 (8.33)	1/8 (12.50)	1/5 (20.00)
	S (%)	3/38 (7.89)	10/12 (83.33)	2/12 (16.67)	2/8 (25.00)	3/5 (60.00)
Piperacillin-tazobactam	R (%)	4/40 (10.00)	3/14 (21.43)	1/12 (8.33)	4/8 (50.00)	1/5 (20.00)
	I (%)	1/40 (2.50)	0/14 (0.00)	1/12 (8.33)	0/8 (0.00)	0/5 (0.00)
	S (%)	35/40 (87.50)	11/14 (78.57)	10/12 (83.33)	4/8 (50.00)	4/5 (80.00)
Tetracycline	R (%)	27/38 (71.05)	13/13 (100.00)	5/12 (41.67)	5/8 (62.50)	1/5 (20.00)
	I (%)	0/38 (0.00)	0/13 (0.00)	0/12 (0.00)	0/8 (0.00)	1/5 (20.00)
	S (%)	11/38 (28.95)	0/13 (0.00)	7/12 (58.33)	3/8 (37.50)	3/5 (60.00)
Tigecycline	R (%)	1/39 (2.56)	14/14 (100.00)	1/12 (8.33)	2/7 (28.57)	1/5 (20.00)
	I (%)	1/39 (2.56)	0/14 (0.00)	1/12 (8.33)	2/7 (28.57)	1/5 (20.00)
	S (%)	37/39 (94.87)	0/14 (0.00)	10/12 (83.33)	3/7 (42.86)	3/5 (60.00)
Trimethoprim-sulfamethoxazole	R (%)	28/39 (71.79)	13/13 (100.00)	6/12 (50.00)	6/8 (75.00)	1/5 (20.00)
	I (%)	0/39 (0.00)	0/13 (0.00)	0/12 (0.00)	0/8 (0.00)	0/5 (0.00)
	S (%)	11/39 (28.21)	0/13 (0.00)	6/12 (50.00)	2/8 (25.00)	4/5 (80.00)
Sefoperazon-sulbaktam	R (%)	0/38 (0.00)	0/14 (0.00)	1/12 (8.33)	4/8 (50.00)	0/5 (0.00)
	I (%)	8/38 (21.05)	5/14 (35.71)	3/12 (25.00)	0/8 (0.00)	0/5 (0.00)
	S (%)	30/38 (78.95)	9/14 (64.29)	8/12 (66.67)	4/8 (50.00)	5/5 (100.00)

Gram-Positive Bacterial Resistance Pattern

The five most common gram-positive bacteria, are *E. faecalis, E. faecium, S. aureus, C. matruchotii*, and *S. pneumoniae* showed varied resistance patterns. *E. faecalis* showed resistance to ceftriaxone, oxacillin, quinupristin-dalfopristin, tobramycin, trimethoprim, trimethoprim-sulfamethoxazole, gentamicin, clindamycin, cefotaxime, amikacin, cefoxitin, fusidic acid, tetracycline, and ciprofloxacin for about more than 70%. Meanwhile, *E. faecium* was resistant to amikacin, ampicillin, cefotaxime, gentamicin, ceftriaxone, clindamycin, erythromycin, penicillin, trimethoprim-sulfamethoxazole, levofloxacin, ciprofloxacin, and nitrofurantoin. In contrast to *S. aureus, C. matruchotii*, and *S. pneumoniae*, which were only resistant to one or two types of antibiotics (Table 4).

For the sensitivity pattern, these five bacteria were sensitive to vancomycin and linezolid (Table 4). *E. faecalis* is also sensitive to ampicillin, nitrofurantoin, and teicoplanin, while for *E. faecium*, another antibiotic sensitivity was only found in teicoplanin. In contrast to their resistance, *S. aureus, C. matruchotii*, and *S. pneumoniae* were found to be sensitive to many types of antibiotics.

Table 4. Distribution of Antibiotic Resistance in Gram-Positive Bacteria

Antibiotic		*E. faecalis* (N=11)	*E. faecium* (N=9)	*S. aureus* (N=3)	*C. matruchotti* (N=2)	*S. pneumoniae* (N=2)
Amikacin	R (%)	6/7 (85.71)	4/4 (100.00)	-	-	0/1 (0.00)
	I (%)	0/7 (0.00)	0/4 (0.00)	-	-	0/1 (0.00)
	S (%)	1/7 (14.29)	0/4 (0.00)	-	-	1/1 (100.00)
Amoxicillin-clavulanate	R (%)	0/1 (0.00)	-	1/3 (33.33)	-	-
	I (%)	0/1 (0.00)	-	0/3 (0.00)	-	-
	S (%)	1/1 (100.00)	-	2/3 (66.67)	-	-
Ampicillin	R (%)	2/11 (18.18)	6/6 (100.00)	3/3 (100.00)	-	-
	I (%)	0/11 (0.00)	0/6 (0.00)	0/3 (0.00)	-	-
	S (%)	9/11 (81.82)	0/6 (0.00)	0/3 (0.00)	-	-
Cefotaxime	R (%)	7/8 (87.50)	9/9 (100.00)	-	0/2 (0.00)	0/2 (0.00)
	I (%)	0/8 (0.00)	0/9 (0.00)	-	0/2 (0.00)	0/2 (0.00)
	S (%)	1/8 (12.50)	0/9 (0.00)	-	2/2 (100.00)	2/2 (100.00)
Gentamisin	R (%)	10/11 (90.91)	9/9 (100.00)	1/3 (33.33)	1/1 (100.00)	0/2 (0.00)
	I (%)	0/11 (0.00)	0/9 (0.00)	0/3 (0.00)	0/1 (0.00)	0/2 (0.00)
	S (%)	1/11 (9.09)	0/9 (0.00)	2/3 (66.67)	0/1 (0.00)	2/2 (100.00)
Cefoxitin	R (%)	6/7 (85.71)	3/3 (100.00)	1/2 (50.00)	-	-
	I (%)	0/7 (0.00)	0/3 (0.00)	0/2 (0.00)	-	-
	S (%)	1/7 (14.29)	0/3 (0.00)	1/2 (50.00)	-	-
Ceftriaxone	R (%)	9/9 (100.00)	8/8 (100.00)	-	0/2 (0.00)	0/2 (0.00)
	I (%)	0/9 (0.00)	0/8 (0.00)	-	0/2 (0.00)	0/2 (0.00)
	S (%)	0/9 (0.00)	0/8 (0.00)	-	2/2 (100.00)	2/2 (100.00)
Chloramphenicol	R (%)	0/1 (0.00)	0/1 (0.00)	-	1/2 (50.00)	-
	I (%)	0/1 (0.00)	1/1 (100.00)	-	0/2 (0.00)	-
	S (%)	1/1 (100.00)	0/1 (0.00)	-	1/2 (50.00)	-
Ciprofloxacin	R (%)	8/10 (80.00)	5/6 (83.33)	2/3 (66.67)	-	0/1 (0.00)
	I (%)	0/10 (0.00)	1/6 (16.67)	0/3 (0.00)	-	0/1 (0.00)
	S (%)	2/10 (20.00)	0/6 (0.00)	1/3 (33.33)	-	1/1 (100.00)
Clindamycin	R (%)	10/11 (90.91)	8/8 (100.00%)	-	0/2 (0.00)	1/2 (50.00)
	I (%)	0/11 (0.00)	0/8 (0.00)	-	0/2 (0.00)	0/2 (0.00)
	S (%)	1/11 (9.09)	0/8 (0.00)	-	2/2 (100.00)	1/2 (50.00)
Erythromycin	R (%)	6/9 (66.67)	9/9 (100.00)	-	0/2 (0.00)	1/2 (50.00)
	I (%)	2/9 (22.22)	0/9 (0.00)	-	1/2 (50.00)	0/2 (0.00)
	S (%)	1/9 (11.11)	0/9 (0.00)	-	1/2 (50.00)	1/2 (50.00)
Fusidic Acid	R (%)	6/7 (85.71)	3/3 (100.00)	-	-	-
	I (%)	0/7 (0.00)	0/3 (0.00)	-	-	-
	S (%)	1/7 (14.29)	0/3 (0.00)	-	-	-
Levofloxacin	R (%)	6/9 (66.67)	7/8 (87.50)	2/3 (66.67)	0/2 (0.00)	1/2 (50.00)
	I (%)	1/9 (11.11)	1/8 (12.50)	0/3 (0.00)	0/2 (0.00)	0/2 (0.00)
	S (%)	2/9 (22.22)	0/8 (0.00)	1/3 (33.33)	2/2 (100.00)	1/2 (50.00)
Linezolid	R (%)	2/11 (18.18)	1/9 (11.11)	0/3 (0.00)	0/2 (0.00)	0/2 (0.00)
	I (%)	6/11 (54.55)	1/9 (11.11)	0/3 (0.00)	0/2 (0.00)	0/2 (0.00)
	S (%)	3/11 (27.27)	7/9 (77.78)	3/3 (100.00)	2/2 (100.00)	2/2 (100.00)
Moxalactam	R (%)	0/1 (0.00)	-	-	-	-
	I (%)	0/1 (0.00)	-	-	-	-
	S (%)	1/1 (100.00)	-	-	-	-
Moxifloxacin	R (%)	2/3 (66.67)	-	-	0/2 (0.00)	0/1 (0.00)
	I (%)	0/3 (0.00)	-	-	0/2 (0.00)	0/1 (0.00)
	S (%)	1/3 (33.33)	-	-	2/2 (100.00)	1/1 (100.00)
Nitrofurantoin	R (%)	2/11 (18.18)	7/9 (77.78)	0/3 (0.00)	-	1/2 (50.00)
	I (%)	0/11 (0.00)	1/9 (11.11)	0/3 (0.00)	-	0/2 (0.00)
	S (%)	9/11 (81.82)	1/9 (11.11)	3/3 (100.00)	-	1/2 (50.00)
Oxacillin	R (%)	5/5 (100.00)	2/2 (100.00)	1/3 (33.33)	-	-
	I (%)	0/5 (0.00)	0/2 (0.00)	0/3 (0.00)	-	-
	S (%)	0/5 (0.00)	0/2 (0.00)	2/3 (66.67)	-	-
Penicillin	R (%)	4/10 (40.00)	8/8 (100.00)	3/3 (100.00)	0/2 (0.00)	1/2 (50.00)
	I (%)	0/10 (0.00)	0/8 (0.00)	0/3 (0.00)	0/2 (0.00)	0/2 (0.00)
	S (%)	6/10 (60.00)	0/8 (0.00)	0/3 (0.00)	2/2 (100.00)	1/2 (50.00)

Quinupristin-dalfopristin	R (%)	11/11 (100.00)	1/6 (16.67)	1/3 (33.33)	-	-
	I (%)	0/11 (0.00)	3/6 (50.00)	0/3 (0.00)	-	-
	S (%)	0/11 (0.00)	2/6 (33.33)	2/3 (66.67)	-	-
Rifampin	R (%)	-	-	0/3 (0.00)	0/2 (0.00)	-
	I (%)	-	-	0/3 (0.00)	0/2 (0.00)	-
	S (%)	-	-	3/3 (100.00)	2/2 (100.00)	-
Streptomycin	R (%)	0/2 (0.00)	1/2 (50.00)	-	-	-
	I (%)	0/2 (0.00)	0/2 (0.00)	-	-	-
	S (%)	2/2 (100.00)	1/2 (50.00)	-	-	-
Teicoplanin	R (%)	2/11 (18.18)	0/6 (0.00)	0/3 (0.00)	-	-
	I (%)	0/11 (0.00)	0/6 (0.00)	0/3 (0.00)	-	-
	S (%)	9/11 (81.82)	6/6 (100.00)	3/3 (100.00)	-	-
Tetracycline	R (%)	9/11 (81.82)	2/6 (33.33)	2/3 (66.67)	0/2 (0.00)	0/1 (0.00)
	I (%)	0/11 (0.00)	0/6 (0.00)	0/3 (0.00)	0/2 (0.00)	0/1 (0.00)
	S (%)	2/11 (18.18)	4/6 (66.67)	1/3 (33.33)	2/2 (100.00)	1/1 (100.00)
Tigecycline	R (%)	-	-	-	0/2 (0.00)	-
	I (%)	-	-	-	0/2 (0.00)	-
	S (%)	-	-	-	2/2 (100.00)	-
Tobramycin	R (%)	7/7 (100.00)	3/3 (100.00)	-	-	-
	I (%)	0/7 (0.00)	0/3 (0.00)	-	-	-
	S (%)	0/7 (0.00)	0/3 (0.00)	-	-	-
Trimethoprim	R (%)	6/6 (100.00)	3/3 (100.00)	-	-	-
	I (%)	0/6 (0.00)	0/3 (0.00)	-	-	-
	S (%)	0/6 (0.00)	0/3 (0.00)	-	-	-
Trimethoprim-sulfamethoxazole	R (%)	11/11 (100.00)	9/9 (100.00)	1/3 (33.33)	1/2 (50.00)	1/1 (100.00)
	I (%)	0/11 (0.00)	0/9 (0.00)	0/3 (0.00)	0/2 (0.00)	0/1 (0.00)
	S (%)	0/11 (0.00)	0/9 (0.00)	2/3 (66.67)	1/2 (50.00)	0/1 (0.00)
Vancomycin	R (%)	2/11 (18.18)	1/9 (11.11)	0/3 (0.00)	0/2 (0.00)	0/2 (0.00)
	I (%	0/11 (0.00)	0/9 (0.00)	0/3 (0.00)	0/2 (0.00)	0/2 (0.00)
	S (%)	9/11 (81.82)	8/9 (88.89)	3/3 (100.00)	2/2 (100.00)	2/2 (100.00)

Co-morbidities

In this study, children with UTI were diagnosed with more than one disease. The patient's comorbidities were dominated by hydronephrosis, chronic kidney disease, and hydrocephalus (Figure 2).

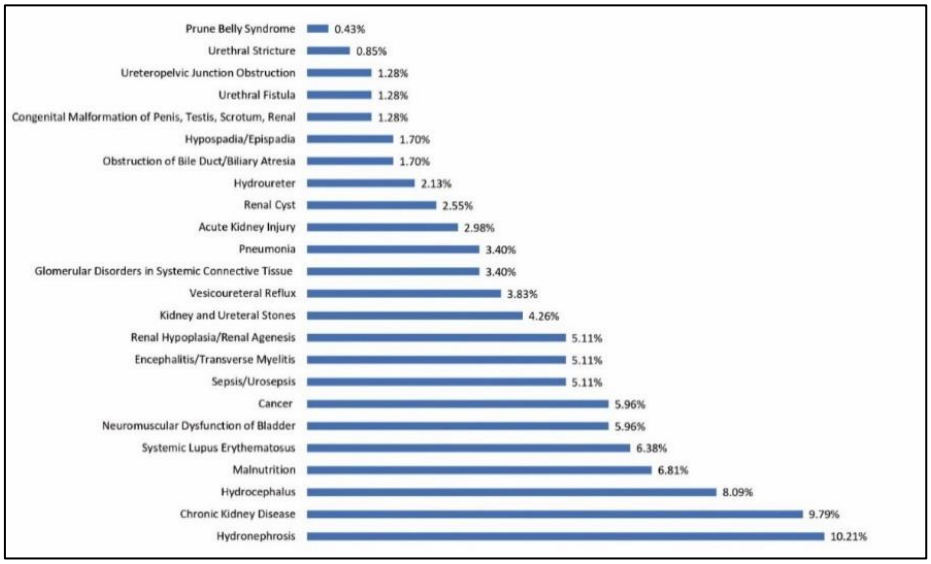

Figure 2. Distribution of Comorbidities

DISCUSSION

UTI is one of the most common bacterial infectious diseases in children with non-specific symptoms. Epidemiologically, it is estimated that Emergency Department visits by children diagnosed with UTI reach more than 500,000 visits and 50,000 hospitalizations.[18] The incidence of UTI is influenced by two important interrelated variables, namely age and gender.[19] According to the American Academy of Pediatrics, the highest prevalence of UTI in children is found at the age of two months - two years, which is about 5% of children with fever complaints.[20] Similar to this study, which found that there were 54.2% of 131 children with UTI were male, dominated by one month – 2 years. Similar with Mirsoleymani et al in their study in Bandar Abbas, South Irian, UTI incidence in boys reached 54.9%.[21] The high incidence of UTI in boys at this age may be due to their uncircumcised status, so that uropathogens colonize the foreskin and cause ascending infection.[22] Poor diaper hygiene during infancy is also an important predisposition to UTI.[23]

In addition, the incidence of UTI in boys in early life is also possible because males have a higher risk of Congenital Anomalies of The Kidney and Urinary Tract (CAKUT) than females, so boys are more prone to UTI.[24]

Based on gender, the tendency of UTI among children will change with age. The dominance of uncircumcised male of UTI in infants will change to female preponderance in older children.[17] At the age of 7 years, it is estimated that approximately 7.8% of girls and 1.7% of boys are diagnosed with UTI.[25] This study found that boys were most commonly found at the age of one month – 2 years, while girls were most commonly found at the age of 6-12 years. UTI in girls is due to the relatively shorter urethral structure of girls so that bacteria more easily cause ascending infection to the bladder. It could also be due to heavy colonization of enteric bacteria in the perineal uropathogens.[22]

In the majority, UTIs in children are caused by gram-negative bacteria from the intestinal flora that colonize the perineum and cause ascending infection to the urinary tract. It is estimated that approximately 80% of pediatric UTIs are caused by *E. coli*.[3] In concordance with this study, which found a predominance of gram-negative bacteria (74%) with *E. coli* as the most common gram-negative bacteria, followed by *P. aeruginosa, K. pneumoniae, E. cloacae,* and *A. baumannii*. *E. coli* has various virulence factors, namely P fimbriae, a type of surface fimbriae that induces attachment to host-specific receptors on the uroepithelium. In addition, flagella, lipopolysaccharide, capsule polysaccharide, and hemolysin are also important virulence factors in infecting the host. Most uropathogenic *Escherichia coli* (UPEC) can produce aerobactin, a high affinity iron-binding protein that causes acute pyelonephritis.[2] While the gram-positive bacteria were only found in 26%, dominated by *E. faecalis*, followed by *E. faecium, S. aureus, C. matruchotii*, and *S. pneumoniae*. Similar to Benachinmardi et al in their study in India where 82.22% gram-negative bacteria were found, with *E. coli* (52.9%) as the most common bacterial isolate followed by *K. pneumoniae* (7.6%) while gram-positive bacteria were only found in 16% of isolates dominated by *Coagulase negative Staphylococcus* (9.8%) followed by *Enterococcus spp.* (5.8%).[4]

Currently, the management of UTI is becoming more difficult as various resistance mechanisms emerge, such as members of the *Enterobacteriaceae* family including *E. coli* and *K. pneumoniae* that produce ESBL. Kitagawa et al stated that ESBL-producing *E. coli* and *K. pneumoniae* were found to be more dominant than non-ESBL-producing isolates[8], in contrast to this study which found non-ESBL-producing *E. coli* and ESBL-producing *K. pneumoniae* strains are more dominant. This difference can be attributed to risk factors for ESBL infection including comorbidities, frequent use of health resources for a long time, previous use of antibiotics, experiencing recurrent UTI, older age, and male gender.[26]

To reduce the risk of acute and chronic complications in pediatric UTIs, prompt and appropriate initial treatment with empirical antibiotics plays an important role.

Unfortunately, an increase in resistant strains

has been widely reported, especially in developing countries due to the habit of consuming over-the-counter antibiotics without a prescription and prior consultation.[14] Antimicrobial resistant pattern varies by geographic area. Therefore, local antimicrobial susceptibility patterns are needed in selecting empirical antibiotics for initial treatment of pediatric UTIs considering potential side effect and economic consequences.[4] This study showed that the most resistant antibiotics to *E. coli, P. aeruginosa, K. pneumoniae, E. cloacae,* and *A. baumannii*, were ampicillin and cefazolin, similar with Kitagawa et al in their study of UTI patients in Surabaya.[8] The high resistance to these two antibiotics may be due to their frequent use considering that UTI management in Indonesia generally uses ampicillin, cephalosporins, and fluoroquinolones.[27]

Carbapenems are the broadest spectrum beta-lactam antibiotics that have become the gold standard for treating infections caused by ESBL-producing *Enterobacteriaceae*. They have high stability against hydrolysis reactions by beta-lactamase enzymes[28], however, its use should be limited to avoid irresponsible prescribing, resulting in the emergence of carbapenem-resistant organisms.[29] In contrast to amikacin, Poey et al explain that amikacin monotherapy can be used as the first line of empirical treatment in febrile UTI among pediatric patients so that amikacin may be a more appropriate empiric therapy option.[30] However, this still requires further research in the form of randomized controlled trials (RCT).[31] This study showed that the five most common gram-negative bacteria were sensitive to carbapenems (imipenem, meropenem), amikacin, and piperacillin-tazobactam, similar to Rahmadi in his research on UTI patients at the Department of Internal Medicine Dr. Soetomo Hospital.[32]

In Taiwan, Wu et al reported that *E. coli* was resistant to ampicillin, piperacillin, trimethoprim-sulfamethoxazole, and sensitive to amikacin, imipenem, ceftazidime, ceftriaxone, and cefuroxime, gentamicin.[33] Similar to this study in which *E. coli* was also resistant to ampicillin, cefazolin, piperacillin, trimethoprim-sulfamethoxazole, tetracycline exceeded 70%, and sensitive to amikacin, imipenem, meropenem, and piperacillin-tazobactam, tigecycline, nitrofurantoin, gentamicin, cefoperazone-sulbactam. A study in India stated that trimethoprim-sulfamethoxazole resistance increased significantly over a five-years period.[14] The increasing resistance of trimethoprim-sulfamethoxazole in various regions has resulted in this antibiotic being no longer recommended as empiric therapy unless it is proven to be sensitive according to local antibiogram data.[31] Meanwhile, cefoperazone-sulbactam showed a sensitivity of more than 90% in ESBL-producing *Enterobacteriaceae*.[34] Tigecycline is well tolerated in cases of serious Extensively Drug-Resistant (XDR) gram-negative bacterial infections[35], but should not be used as monotherapy in pediatric UTIs because of its limited excretion and some side effects, enamel hypoplasia.[36] According to the American Academy of Pediatrics, nitrofurantoin is not recommended for febrile infants because serum and parenchymal concentrations may be insufficient to treat urosepsis or pyelonephritis. In addition, nitrofurantoin is contraindicated in cases of decreased renal function with creatinine clearance <60 millilitre per minute (ml/min).[37]

The second largest gram-negative bacteria, *P. aeruginosa* was also found to be resistant to amoxicillin-clavulanate, ampicillin-sulbactam, cefotaxime, chloramphenicol, nitrofurantoin, tetracycline, tigecycline, trimethoprim-sulfamethoxazole, ceftriaxone and sensitive to piperacillin, gentamicin, ceftazidime. In previous studies, *P. aeruginosa* was reported to be highly resistant to trimethoprim-sulfamethoxazole, nitrofurantoin, cefotaxime, ampicillin, amoxicillin/clavulanate, cephalexin, cefuroxime, ceftriaxone, nalidixic acid[38,39] and more sensitive to piperacillin-tazobactam, ceftazidime, imipenem, ciprofloxacin, gentamicin, and tobramycin.[40]

It is different with gram-positive bacteria, which show high sensitivity to vancomycin and linezolid with varying resistance patterns. Both of *E. faecalis* and *E. faecium* showed resistance

to ceftriaxone, trimethoprim-sulfamethoxazole, gentamicin, cefotaxime, amikacin, ciprofloxacin for about more than 70%, and sensitive to vancomycin, linezolid, teicoplanin. This is in accordance with Hameed et al and Benachinmardi et al which showed that *Enterococcus spp*. resistant to trimethoprim-sulfamethoxazole (100%), amikacin (71.43%), gentamicin (85%), erythromycin (76.92%), and ciprofloxacin (60%) and completely sensitive to vancomycin, linezolid, and teicoplanin.[4,41] Enterococci are resistant to antibiotics because they are naturally resistant to low levels of aminoglycosides, cephalosporins, clindamycin and trimethoprim/sulfamethoxazole. Beta-lactams have also been reported to have limited clinical efficacy on enterococci due to the low affinity Penicillin-binding proteins (PBPs).[42]

In pediatric UTI, urinary tract abnormalities contribute to increasing recurrent UTI and resulting in the development of multi drug resistance organisms.[43] In this study, comorbidities in pediatric UTI patients were dominated by hydronephrosis (10.98%) followed by chronic kidney disease (9.79%), and hydrocephalus (8.09%). According to Coelho et al, the increasing severity of hydronephrosis leads to an increased risk of UTI due to urinary tract dilatation.[44] Hydronephrosis or dilation of the renal collecting system can be caused by partial or complete obstruction of urine flow caused by vesicoureteral reflux, posterior urethral valves, ureteropelvic junction obstruction, ureterocele, or duplication of the collecting system.[45] The most severe long-term sequelae as a complication of UTI is renal scarring that may progress to end-stage renal disease.[46] On the other hand, chronic kidney disease can also be a contributing factor to UTI due to oxidative stress and inflammatory cytokines, which can result in impaired immunity and increase susceptibility to various infections, especially UTI.[47]

Non-urinary disorders that can also increase the risk of UTI is hydrocephalus. Hydrocephalus is generally caused by myelomeningocele, the most common form of open spina bifida that can increase the incidence of UTI in children.[48,49] Hydrocephalus has an additional effect at the central level on the micturition process controlled by the pons, brain stem, and cerebral cortex which can aggravate the neurogenic bladder which results in impaired bladder emptying and increases the risk of UTI.[50]

The limitations found in this study are related to the instruments used. In this study, the researcher used secondary data in the form of a urine culture logbook, so that there could be bias because the researcher was not directly involved during the examination process and some of the data were found to be incomplete. However, this study is essential to evaluate the antibiotic resistance pattern among uropathogens in Dr. Soetomo Hospital, who could be considered in selecting the appropriate empirical antibiotics to optimize initial UTI therapy.

CONCLUSIONS

This study revealed gram-negative bacteria isolates as the preponderance uropathogen, with *E. coli* as the most common bacteria found. Gram-negative bacteria are highly resistant to ampicillin and cefazoline, while gram-positive bacteria showed varied antibiotics resistance. UTI comorbidities are dominated by hydronephrosis, chronic kidney disease, and hydrocephalus. This research can be useful for health workers, especially in Dr. Soetomo Hospital, Surabaya, as an initial consideration in selecting empirical antibiotics before culture results are available. In addition, this study can be used as a reference for further research on children with UTI in order to develop public health services.

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CONFLICT OF INTEREST

All authors declared that they do not have any conflict of interest.

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