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ORIGINAL RESEARCH
Pediatrics Emergency

Extended-spectrum beta-lactamase-producing gram-negative urinary tract infections in children: A retrospective children's hospital experience

Nihan Uygur Kulcu,[1] Merve İşeri Nepesov[2]

[1]Department of Pediatrics, University of Health Sciences, Zeynep Kamil Maternity and Children's Training and Research Hospital, İstanbul, Türkiye
[2]Department of Pediatric Infectious Diseases, University of Health Sciences, Zeynep Kamil Maternity and Children's Training and Research Hospital, İstanbul, Türkiye

ABSTRACT

Objective: Extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacteria are an increasing concern in pediatric urinary tract infections (UTIs), contributing to antimicrobial resistance, limited treatment options, and higher recurrence rates. This study aimed to identify the risk factors associated with ESBL-positive Gram-negative UTIs in children and evaluate antimicrobial susceptibility patterns.

Material and Methods: Medical records of pediatric patients aged 1 month to 18 years with culture-confirmed ESBL-producing Gram-negative UTIs were retrospectively reviewed between January 2015 and December 2020 at a tertiary pediatric hospital in Istanbul. Both inpatient and outpatient cases were included. Data extracted from electronic records included demographic characteristics, clinical presentation, comorbidities, recent antibiotic use, prior hospitalization or surgery, intensive care unit (ICU) admission, use of urinary or central venous catheters, and total parenteral nutrition (TPN).

Results: Among 4,722 positive pediatric urine cultures, ESBL-producing Gram-negative organisms were identified in 215 cases (4.6%). After applying the inclusion criteria, 184 patients were analyzed. The cohort showed a female predominance (80.4%), with a median age of 57 months. Presentations included cystitis (60.9%) and pyelonephritis (39.1%). Common risk factors were recent antibiotic use (44%) and prior hospitalization (12.5%). Antimicrobial susceptibility testing demonstrated high in vitro activity for meropenem, fosfomycin, and amikacin (>90%). No treatment failure or urosepsis occurred during the initial episode. Recurrent UTIs were observed in 10.3% of cases.

Conclusion: ESBL-producing Gram-negative UTIs highlight the need for risk-based evaluation and antimicrobial stewardship. Fosfomycin and nitrofurantoin may be suitable oral options pending culture results, while meropenem remains effective for severe infections.

Keywords: Antibiotic resistance; children; *Enterobacteriaceae*; extended-spectrum beta-lactamases; urinary tract infections.

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Correspondence (İletişim): Dr. Nihan Uygur Kulcu. Sağlık Bilimleri Üniversitesi, Zeynep Kamil Kadın Doğum ve Çocuk Eğitim ve Araştırma Hastanesi, Pediatri Kliniği, İstanbul, Türkiye.
Phone (Tel): +90 532 686 46 75 **e-mail (e-posta):** nihanped@hotmail.com

Genişlemiş spektrumlu beta-laktamaz üreten gram-negatif idrar yolu enfeksiyonları olan çocuklar: Retrospektif bir çocuk hastanesi deneyimi

ÖZET

Amaç: Genişlemiş spektrumlu beta-laktamaz (ESBL) üreten Gram-negatif bakteriler, pediatrik idrar yolu enfeksiyonlarında (İYE) giderek artan bir sorun olup antimikrobiyal direnç, sınırlı tedavi seçeneklerine ve daha yüksek nüks oranlarına katkıda bulunmaktadır. Bu çalışmanın amacı, çocuklarda ESBL pozitif Gram-negatif İYE ile ilişkili risk faktörlerini belirlemek ve antimikrobiyal duyarlılık paternlerini değerlendirmektir.

Gereç ve Yöntemler: İstanbul'daki üçüncü basamak bir çocuk hastanesinde Ocak 2015 ile Aralık 2020 tarihleri arasında kültürle doğrulanmış ESBL üreten Gram-negatif İYE tanısı alan 1 ay–18 yaş arası pediatrik hastaların tıbbi kayıtları retrospektif olarak incelendi. Hem yatan hem de ayaktan başvuran hastalar çalışmaya dahil edildi. Elektronik kayıtlardan elde edilen veriler; demografik özellikler, klinik başvuru şekli, komorbiditeler, yakın zamanda antibiyotik kullanımı, önceki hastaneye yatış veya cerrahi öyküsü, yoğun bakım ünitesi (YBÜ) yatışı, üriner veya santral venöz kateter kullanımı ve total parenteral beslenme (TPN) durumunu içermektedir.

Bulgular: Toplam 4.722 pozitif pediatrik idrar kültürü arasında ESBL üreten Gram-negatif mikroorganizmalar 215 olguda (%4,6) saptandı. Dahil edilme kriterlerinin uygulanmasının ardından 184 hasta analiz edildi. Kohortta kadın cinsiyet baskındı (%80,4) ve medyan yaş 57 aydı. Klinik başvurular sistit (%60,9) ve piyelonefrit (%39,1) şeklindeydi. En sık risk faktörleri yakın zamanda antibiyotik kullanımı (%44) ve önceki hastaneye yatış (%12,5) idi. Antimikrobiyal duyarlılık testleri, meropenem, fosfomisin ve amikasin için yüksek in vitro etkinlik göstermiştir (>%90). İlk enfeksiyon epizodu sırasında tedavi başarısızlığı veya ürosepsis gözlenmemiştir. Olguların %10,3'ünde tekrarlayan İYE gelişmiştir.

Tartışma: ESBL üreten Gram-negatif İYE'ler, risk temelli değerlendirme ve antimikrobiyal yönetimin önemini vurgulamaktadır. Kültür sonuçları beklenirken fosfomisin ve nitrofurantoin uygun oral tedavi seçenekleri olabilirken ağır enfeksiyonlarda meropenem etkinliğini korumaktadır.

Anahtar Kelimeler: Antibiyotik direnci; çocuklar; *Enterobacteriaceae*; genişlemiş spektrumlu beta-laktamazlar; idrar yolu enfeksiyonları.

ORCID ID

NUK: 0000-0001-8771-5292; MİN: 0000-0003-4584-1818

[1]Sağlık Bilimleri Üniversitesi, Zeynep Kamil Kadın ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi, Çocuk Sağlığı ve Hastalıkları Kliniği, İstanbul, Türkiye
[2]Sağlık Bilimleri Üniversitesi, Zeynep Kamil Kadın ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi, Çocuk Enfeksiyon Hastalıkları Kliniği, İstanbul, Türkiye

INTRODUCTION

Urinary tract infections (UTIs) are among the most common bacterial infections in children and are most frequently caused by *Enterobacteriaceae* species such as *Escherichia coli* and *Klebsiella* spp. Over recent decades, resistance to β-lactam antibiotics among Gram-negative bacteria has significantly increased, largely due to the emergence of extended-spectrum β-lactamases (ESBLs) (1, 2). ESBL-producing *Enterobacteriaceae* (ESBL-PE) are now increasingly prevalent worldwide, affecting both adults and children and posing a serious therapeutic challenge in both community and hospital settings (3–6). With the World Health Organization warning about a "post-antibiotic era," healthcare providers must carefully balance the effective treatment of ESBL-PE infections with efforts to prevent further antibiotic resistance (7).

While a recent meta-analysis reported a pooled ESBL-UTI prevalence of 14% in children (8), findings from individual studies vary substantially, with reported rates ranging from 3.8% to 15.5%, depending on local epidemiology, patient demographics, and healthcare practices (9, 10).

Despite the growing body of research on ESBL-PE in pediatric populations, knowledge gaps remain, particularly regarding the identification of clinical and demographic risk factors. A summary of the identified risk factors for ESBL-positive infections, categorized by study, population, and reported determinants, is presented in Table 1.

However, findings vary significantly across populations and settings, and the consistency and predictive value of these risk factors remain uncertain. Understanding these predictors is essential for guiding empirical treatment and infection control strategies. Although multiple recent studies have examined similar risk factors in pediatric populations, data from different regions remain limited. Therefore, the primary aim of this study was to identify the risk factors associated with pediatric ESBL-positive UTIs, while the secondary aim was to evaluate antibiotic susceptibility patterns in urine cultures of affected children, thereby contributing region-specific evidence to the existing literature.

MATERIAL AND METHODS

A single-center retrospective study was conducted using medical records collected between January 1, 2015, and December 31, 2020. The study included children aged 1 month to 18 years who were either hospitalized or presented to the pediatric outpatient

Table 1. Summary of risk factors for ESBL-positive infection categorized by study, population, and the major risk factors reported

Study	Population	Significant risk factors for ESBL-positive infection
Çelebi (Türkiye, 2009) (17)	Pediatric	PICU stay, hospital-acquired infection broad/prolonged antibiotic use, immunosuppressive therapy, blood transfusion, central venous catheter, TPN, prolonged hospitalization
Dayan (Israel, 2013) (31)	Pediatric	Longer hospital stay, recent hospitalization, previous UTI, urinary tract anomalies, cephalexin prophylaxis, *Klebsiella* spp. infection
Biehl (2016) (32)	Mixed (adult and pediatric)	Prior antimicrobial use, recent hospitalization, recent/repeated surgery
Flokas (USA, 2016) (8)	Pediatric	Prior antibiotic use, hospitalization, surgical interventions, healthcare contact
Park (Korea, 2017) (26)	Pediatric	Previous hospitalization, high recurrence rate, prolonged pre-onset hospitalization
Tüzün (Türkiye, 2019) (33)	Adult/mixed	Healthcare-associated UTI, antibiotics in past 6 months
Lu (China, 2022) (34)	Pediatric	Age <12 months, urological anomalies (VUR), urodynamic changes, neurologic disorders, undernutrition, recent antibiotic use (past 3 months), previous UTI (past 3 months)
Collingwood (2023) (4)	Adult	Male sex, history of urology care, previous antibiotic exposure
Bousseta (Tunisia, 2023) (19)	Pediatric	Antibiotic use (past 3 months), prophylaxis, hospitalization (past year), outpatient care (past 6 months), age >6 years
Bursal (Türkiye, 2025) (14)	Pediatric	Blood in urine, high CRP

ESBL: Extended spectrume beta lactamases; PICU: Pediatric intensive care unit; UTI: Urinary tract infection; VUR: Vesicourethral reflux.

clinics of our tertiary referral hospital in Istanbul. All cases involved urinary tract infections (UTIs) caused by ESBL-producing Gram-negative bacteria, confirmed by urine culture. Both inpatient and outpatient cases were analyzed. No additional follow-up was conducted beyond the documented clinical encounter. The study was approved by the Institutional Research Ethics Committee of the hospital (05.05.2021/108). As this study was conducted retrospectively using previously recorded data, obtaining informed consent from participants was not required.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) age between 1 month and 18 years, (2) diagnosis of UTI confirmed by a positive urine culture, and (3) isolation of ESBL-producing Gram-negative bacteria.

The exclusion criteria included the following: (1) urine samples collected using urine bags, (2) polymicrobial growth in cultures, (3) bacterial counts below diagnostic thresholds, and (4) missing key clinical or laboratory data in patient records.

Data Collection

The following variables were analyzed: patient demographic data, type of clinical encounter (inpatient or outpatient), presence of systemic or urinary tract comorbidities, and underlying conditions such as congenital or acquired urogenital system anomalies, chronic endocrine or congenital diseases, and immunodeficiency. Additional variables included recent antibiotic use (within the previous 30 days), use of nasogastric tubes (NGTs), presence of indwelling urinary catheters or central venous lines, and presenting symptoms (e.g., fever, vomiting, diarrhea, anorexia, dysuria, lumbar or flank pain, and urinary incontinence). Physical examination findings (e.g., costovertebral angle tenderness and suprapubic pain), ICU (intensive care unit) admission, total parenteral nutrition (TPN) administration, and duration of hospitalization were also recorded.

Definitions

Acute pyelonephritis and cystitis were defined based on standard clinical guidelines (11, 12). Acute upper UTI was defined as bacteriuria accompanied by either fever ≥38°C or a lower-grade fever with flank pain or tenderness. Lower UTI (cystitis) was defined as bacteriuria without systemic symptoms. The diagnosis of UTI was confirmed via urine culture, with thresholds defined as $\geq 10^3$ CFU/mL for suprapubic aspiration, $\geq 10^4$ CFU/mL for bladder catheterization, and $\geq 10^5$ CFU/mL for clean-catch midstream samples (12).

Microbiological Analysis

Urine samples were incubated on 5% blood agar plates (BAPs) and chromogenic plates for ESBL (CPSE, ChromID® ESBL Agar; bioMérieux, Hazelwood, MO, USA) at 37°C for 18–24 hours. Urinary pathogen identification and antimicrobial susceptibility testing were performed using the VITEK® 2 Compact automated system (bioMérieux).

ESBL production was confirmed by the hospital microbiology laboratory in accordance with EUCAST guidelines (13). The diagnosis of comorbidities and device usage was validated through clinical documentation and imaging reports.

Table 2. Risk factors associated with ESBL-positive urinary tract infections

Risk factors	n (%)
History of hospitalization in last 3 months	23 (12.5)
History of antibiotic use in last 3 months	81(44)
History of surgery in last months	6 (3.3)
Immunosuppression	1 (0.5)
Malnutrition	1 (0.5)
Presence of gastrostomy	1 (0.5)
Presence of a central venous catheter	2 (1.1)
Presence of indwelling urinary catheters	3 (1.6)

ESBL: Extended spectrume beta lactamases.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). Numerical variables are presented as mean±standard deviation (SD), as well as median, minimum, and maximum values. Categorical variables are expressed as frequencies (n) and percentages (%).

RESULTS

During the study period, 4,722 urine cultures from children aged between 1 month and 18 years were positive. ESBL-positive Gram-negative microorganisms were isolated in 215 cultures (4.6%). Of the 215 cases initially identified, 31 were excluded due to incomplete medical records. The final study population comprised 184 patients with culture-confirmed ESBL-producing Gram-negative urinary tract infections, of whom 148 (80.4%) were female and 36 (19.6%) were male. The median age at diagnosis was 57 months (range: 1–203 months).

Urine culture samples were obtained during hospitalization in 13.0% (n=24) of patients and during outpatient clinic visits in 87.0% (n=160). Among the hospitalized patients, 20 were managed in pediatric wards and 4 were admitted to the intensive care unit. The median length of hospital stay among inpatients was 9 days (range: 4–48 days).

According to the retrospective chart review, the most frequently reported reasons for urine sample collection included dysuria (46.2%), fever (39.1%), nausea or vomiting (28.3%), hematuria (16.3%), suprapubic pain (10.3%), increased urinary frequency (3.8%), urinary incontinence (3.3%), flank pain (2.2%), restlessness (2.2%), and constipation (1.1%). In terms of risk factors, 12.5% of patients had a prior history of hospitalization, 44.0% had received antibiotics within the previous three months, and 3.3% had undergone surgery in recent months. These risk factors are summarized in Table 2.

Urinary system comorbidities among the patients included vesicoureteral reflux (4.9%), neurogenic bladder (4.3%), spina bifida (4.3%), enuresis (2.7%), hydronephrosis (2.2%), perineal fissure (1.6%), posterior urethral valves (1.1%), nephrolithiasis (0.5%), solitary kidney (0.5%), horseshoe kidney (0.5%), and hypospadias (0.5%). Additionally, 19 patients (10.3%) had a documented history of recurrent urinary tract infections.

The most commonly isolated ESBL-producing pathogen was *Escherichia* spp., identified in 158 cases (85.8%), followed by *Klebsiella* spp. in 21 cases (11.4%), *Proteus* spp. in 2 cases (1.1%), *Morganella morganii* in 2 cases (1.1%), and *Citrobacter* spp. in 1 case (0.5%). A total of 115 patients (62.5%) were diagnosed with cystitis, while 72 (39.1%) were diagnosed with pyelonephritis.

The antibiotic susceptibility profiles of *E. coli* and *Klebsiella* spp. isolates were analyzed based on the available data and are summarized in Table 3.

DISCUSSION

The increasing prevalence of antimicrobial resistance in ESBL-producing *Enterobacteriaceae* (ESBL-PE) represents a significant global health concern. This issue is driven by the transmission of resistance mechanisms and the widespread, often inappropriate, use of antimicrobials (14). In Türkiye, ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* have been identified as significant causative agents of both hospital-acquired and community-acquired (CA) infections. It has been reported that over half of hospital-acquired UTIs and approximately one-fourth of CA infections are attributable to ESBL-producing strains (15, 16).

Table 3. Susceptibility patterns of *E. coli* and *Klebsiella* spp. to commonly used antibiotics

Antibiotic	*Escherichia coli*		*Klebsiella* spp.	
	Sensitive	Resistant	Sensitive	Resistant
TMP-SMX (n=176)[1]	87	68	8	13
Piperacillin-tazobactam (n=144)	92	36	8	8
Amikacin (n=176)	146	9	18	3
Nitrofurantoin (n=143)	123	8	9	3
Fosfomycin (n=139)	127	0	11	1
Ciprofloxacin (n=169)	95	53	14	7
Meropenem (n=141)	123	0	18	0

1: Not all total number equal to 184 in each column because not all isolates had all the antibiotic susceptibility result; TMP-SMX: Trimethoprim-sulfamethoxazole.

A five-year surveillance study conducted among hospitalized pediatric patients reported an *E. coli* infection rate of 15.3 per 1,000 hospitalizations, with 62.5% of the isolates derived from urine samples. Among these, 54.4% were ESBL-producing *E. coli* strains, and notably, 83.7% (62 out of 74) of them were hospital-acquired infections (17). In our cohort, most ESBL-positive urine cultures (87%) were obtained during outpatient clinic visits, with the remaining samples collected from inpatients.

In the study by Akgül et al. (18), which evaluated pediatric patients aged 1 month to 18 years with UTIs over a three-year period, ESBL production was detected in approximately half of both *E. coli* and non-*E. coli* isolates. While their analysis assessed the proportion of ESBL positivity within each microorganism group, our study examined the distribution of pathogens among ESBL-producing isolates. In our cohort, *E. coli* accounted for 85.8% of ESBL-PE strains, followed by *Klebsiella* species (11.4%).

Upon examining the risk factors in children diagnosed with ESBL-positive UTIs (mean age, 57 months), we identified a high prevalence of recent antibiotic use and hospitalization within the past three months (antibiotic use: 44%; hospitalization: 12.5%). Additionally, 3.3% of the patients had undergone surgery in the last month. In our cohort, 62.5% of patients presented with acute cystitis and 37.5% with pyelonephritis. Hospitalization was required in 13% of the cases, with a median length of stay of 9 days. Consistent with our findings, Collingwood et al. (4) reported that children with ESBL-producing *E. coli* UTIs are more likely to experience prolonged hospital admissions. Understanding the epidemiological profile and risk factors for ESBL-producing UTIs, including ESBL-producing *E. coli*, in the pediatric population could improve the therapeutic approach (19).

Recent antibiotic exposure was the most prominent risk factor identified in our cohort, supporting previous evidence that inappropriate or repeated antimicrobial use contributes to the emergence of ESBL-producing organisms through selective pressure. This finding further emphasizes the importance of antimicrobial stewardship programs aimed at reducing unnecessary broad-spectrum antibiotic exposure, particularly in pediatric outpatient settings, where most of our cases were identified (20).

Although our study did not evaluate treatment practices or clinical outcomes, the antibiotic susceptibility patterns observed in our cohort highlight the importance of considering local resistance profiles when selecting empirical therapy. The wide regional variation in the detection rates of ESBL-producing *E. coli* makes it essential to consider local epidemiological data and institutional surveillance reports when determining initial treatment strategies. In regions with a high ESBL prevalence, empirical therapy may need to consider the possibility of ESBL-producing organisms, particularly in children with recognized risk factors such as recent antibiotic exposure or prior hospitalization (20). However, while carbapenems are regarded as the first-line treatment for serious and invasive ESBL-PE infections, their use may contribute to the emergence of carbapenem-resistant strains and should be avoided unless clearly indicated (5).

A multicenter study from Japan investigating febrile UTIs in children reported similar clinical outcomes in patients with ESBL-producing organisms. The study recommended postponing the use of broad-spectrum antibiotics until culture results are available (21, 22) and suggested that cephalosporins may remain effective for initial empirical therapy (21–24). Aminoglycosides, despite their variable efficacy, may serve as second-line agents when third-generation cephalosporins fail to provide bactericidal activity in ESBL-related UTIs, with amikacin showing the most promising results (25–27).

Several studies from Türkiye have assessed antibiotic resistance in *E. coli* and *Klebsiella* spp. isolates (14, 28). In general, *Klebsiella* spp. exhibited higher resistance levels compared with *E. coli*. Among Gram-negative isolates, the lowest resistance rates were observed for amikacin, meropenem, piperacillin, and oral nitrofurantoin (28).

Furthermore, fosfomycin has demonstrated higher susceptibility rates than nitrofurantoin against ESBL-PE and appears to be clinically comparable to intramuscular ertapenem. Nonetheless, it is not recommended for the treatment of pyelonephritis, as it does not achieve sufficient serum or renal tissue concentrations (27, 29, 30). The high susceptibility rates observed for fosfomycin, nitrofurantoin, and amikacin support the potential role of carbapenem-sparing strategies in selected patients, particularly in uncomplicated lower UTIs without systemic involvement (27). Culture-guided de-escalation and selective carbapenem use may help preserve the effectiveness of last-resort antibiotics while reducing selective pressure for further resistance development (20, 27).

At our institution, antibiotic usage patterns and resistance trends are closely monitored. In our study of pediatric patients with urine cultures growing ESBL-PE, 100% of the isolates were susceptible to meropenem. This antibiotic is administered under strict clinical oversight and in accordance with our institutional antibiogram guidelines, taking into account the patient's age and clinical condition.

Importantly, our study also revealed that ESBL-PE strains were highly susceptible to orally administered nitrofurantoin and fosfomycin. This suggests that these agents may represent potential oral treatment alternatives in selected cases of suspected lower UTI pending culture results (20, 27).

Although this study has certain limitations, including its retrospective design, possible gaps in medical documentation, and the risk of underestimating some cases due to prior antibiotic exposure or low bacterial loads, it also has notable strengths. Most importantly, urine samples were collected under strict aseptic conditions, ensuring the reliability of the microbiological findings. No formal sample size calculation was performed due to the retrospective nature of the study. However, selection bias was mitigated by including only microbiologically confirmed cases with comprehensive clinical documentation.

CONCLUSION

Our findings highlight the growing clinical relevance of ESBL-producing *Enterobacteriaceae* in pediatric UTIs and emphasize the importance of local epidemiological surveillance and careful risk assessment. Recent antibiotic exposure emerged as a major associated factor, underscoring the need for strengthened antimicrobial stewardship strategies.

Ethics Committee Approval: This study followed the Declaration of Helsinki, and the University Faculty of Medicine Local Ethics Committee approved the study (Decision protocol no: 05.05.2021/108 Date: 05.05.2021).

Informed Consent: As this study was conducted retrospectively using previously recorded data, obtaining informed consent from participants was not required.

Conflict of Interest: The author declare that there is no conflict of interest.

Use of AI for Writing Assistance: The authors declared that artificial intelligence was not used in the study.

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Authorship Contributions: Concept – NUK, MİN; Design – MİN, NUK; Supervision – NUK, MİN; Data Collection and/or Processing – MİN, NUK; Analysis and/or Interpretation – NUK, MİN; Literature Search – MİN, NUK; Writing – NUK, MİN; Critical Reviews – MİN, NUK.

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Hasta Onamı: Bu çalışma, daha önce kaydedilmiş veriler kullanılarak retrospektif olarak yürütüldüğünden, katılımcılardan bilgilendirilmiş onam alınması gerekli görülmemiştir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

Yazma Yardımı için Yapay Zeka Kullanımı: Bu makale için yapay zekadan herhangi bir destek alınmamıştır.

Yazarlık Katkıları: Fikir – NUK, MİN; Tasarım – MİN, NUK; Denetlemeler – NUK, MİN; Veri toplanması ve/veya işleme – MİN, NUK; Analiz ve/veya yorumlama – NUK, MİN; Literatür araştırması – TC, FKC, EES, NH; Yazım – NUK, MİN; Eleştirel incelemeler – MİN, NUK.

Hakemli inceleme: Harici olarak hakemli.

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