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IS IT SAFE TO USE LEVOFLOXACIN FOR TREATING RESISTANT GRAM-NEGATIVE BACTERIAL INFECTIONS IN THE PEDIATRIC INTENSIVE CARE UNIT?

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ABSTRACT

Objective: Hospital-associated multidrug-resistant infections are currently on the rise. Widespread resistance to antibiotics and limited therapeutic options make it a challenge to eradicate these infections. Therefore, the use of different antibiotics was increased in pediatric intensive care (PICU). Fluoroquinolones belong to a class of broad-spectrum antimicrobials, and their use in children has not been associated with any known clinical complications. In this single-centre retrospective study, we aimed to evaluate the effects, results, and safety of levofloxacin treatment.
Materials and Methods: A retrospective, single-center study was conducted at a local tertiary hospital involving 22 patients who were treated with levofloxacin in the PICU from July to December 2021. Levofloxacin was initiated at a dose of 10mg/kg twice daily intravenously for 14-21 days. The study examined and evaluated various factors related to the patients, including their demographic characteristics, medical history, comorbidities, length of stay, need for mechanical ventilation support, laboratory results, type of infection/microorganism, duration of treatment, treatment response and adverse effects, morbidity and mortality.
Results: Stenotrophomonas maltophilia13(59.1%) and Pseudomonas aeruginosa9(40.9%) were detected in included patients who had levofloxacin treatment 20(90.9%) of their infections were eradicated. The mortality rate was found to be 13.6%, and 19 patients (86.4%) were successfully treated. No complications related to levofloxacin were detected during the treatment period. The duration of levofloxacin treatment in patients with eradication of gram negative bacteria was 21 days (range: 14-27 days), compared to 12 days (range: 10-14 days) in patients without eradication. This difference was found to be statistically significant (p=0.007).
Conclusion: Due to the challenge of eradicating infections and the rising antibiotic resistance, it may be necessary to use antibiotics that are not typically prescribed to children or to develop new drug categories. Therefore, there is a need for more multicenter, randomized controlled, and long-term observational studies to evaluate the efficacy of different and new groups of antibiotics, including levofloxacin, in treating gram-negative bacterias.

Keywords: Pediatrics, Intensive care unit, Resistant, Antibiotic, Gram negative bacterias, Levofloxacin.

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ÖZET

Amaç: Günümüzde hastane ilişkili ve dirençli enfeksiyonlar artmaktadır. Bunların eradikasyonu, artmış antibiyotik direnci ve dar tedavi seçenekleri nedeniyle zordur. Bu nedenle çocuk yoğun bakımlarda farklı antibiyotiklerin kullanımı artmıştır. Florokinolonlar, geniş spektrumlu bir antimikrobiyal türüdür. Çocuklarda klinik olarak kullanımlarına ilişkin bildirilen belirli bir komplikasyon yoktur. Çalışmamız tek merkezli retrospektif olup levofloksasin tedavisinin etkileri, sonuçları ve güvenliği açısından değerlendirilmesini amaçlanmıştır.
Materyal ve Metot: Üçüncü basamak olan hastanemizde Temmuz-Aralık 2021 tarihleri arasında çocuk yoğun bakımda levofloksasin ile tedavi edilen 22 hastanın dahil edildiği retrospektif tek merkezli bir çalışma yapıldı. Hastaların demografik özellikleri, tıbbi öyküleri, komorbiditeleri, yatış süreleri, mekanik ventilasyon ihtiyacı, laboratuvar tetkikleri, enfeksiyon/mikroorganizma tipi ve tedavi süresi, tedaviye yanıtı ve yan etkileri, morbidite ve mortaliteleri incelendi.
Bulgu: Levofloksasin kullanılan hastalarda Stenotrophomonas maltophilia 13 (%59,1) ve Pseudomonas aeruginosa 9 (%40,9) hastada saptandı. Bu hastalarından 20 (%90,9)'sinin enfeksiyonları eradike edilmişti. Çalışmanın mortalite oranı %13,6 olup 19 hasta (%86,4) başarılı şekilde tedavi edildi. Bu tedavi süresince levofloksasine bağlı herhangi bir komplikasyona rastlamadık. Eradike olan hastalarda levofloksasin 14-27 (21) gün, eradike edilemeyenlerde tedavi 10-14(12) gün verilmişti. Bu tedavi süresi istatistiksel olarak anlamlı bulunmuştur (p=0.007).
Sonuç: Enfeksiyonların eradikasyonunun zorluğu ve artan antibiyotik direnci nedeniyle, genellikle pediatrik grupta kullanılmayan antibiyotiklerin veya yeni ilaç kategorilerinin geliştirilmesi gereklidir. Bu nedenle levofloksasin de dahil, yeni antibiyotik gruplarının gram negatif bakterilerin tedavisindeki etkinliğini değerlendirecek çok merkezli, randomize kontrollü ve uzun süreli gözlemsel çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Pediatri, Yoğun bakım ünitesi, Direnç, Antibiyotik, Gram negatif bakteriler, Levofloksasin.

INTRODUCTION

Due to advancements in technology and healthcare services, the length of hospital stays for patients has increased, resulting in an increase in hospital-associated multi-drug resistant infections (MDRI). In pediatrics, MDRIs are difficult to treat and can lead to increased mortality (1). Common causes of healthcare-associated infections (HAI) are gram-negative bacteria (GNB) such as Pseudomonas spp, Stenotrophomonas spp, Enterobacteriaceae spp, Acinetobacteriaceae spp, Salmonella spp, Moraxella spp, Helicobacter spp, and Legionella spp (2, 3, 4). For this reason, paediatric intensive care units (PICUs) are increasingly using combination and different antibiotics. In PICU high rates of using broad-spectrum antibiotics caused nosocomial infections with multidrug-resistant, pan-drug-resistant, and extensively drug-resistant. Another study of the hospital where this study was conducted on ventilator-associated pneumonia in the PICU found that drug-resistant GNB was much more common than drug-sensitive pneumonia (5). Many different types of diseases are treated by using immunosuppressive drugs in the PICU. Although isolation measures are taken, nosocomial infection rates remain high, especially in developing countries, with an increasing prevalence of drug-resistant GNB infections. Therefore, in paediatric age groups, previously unused or rarely used drugs are now being utilised, and there is a need for the development of new antibiotics. Additionally, drugs that are commonly used in the adult population are now being used in children due to increased antibiotic resistance. It is crucial to develop new antibiotics to combat this issue. Fluoroquinolone group drugs are a group of antibiotics that are known to be effective in GNB and are frequently used in the adult age group the most well-known are ciprofloxacin and levofloxacin. Additionally, there is no certain evidence for causing cartilage toxicity in children and clinically usually these antibiotics are used without any complications for multiresistant GNBs (6). In the age of pediatrics, levofloxacin is not approved by the U.S. Food and Drug Administration (FDA). However, in data from use in the past, fluoroquinolones had similar adverse effects as adults (7). In addition, the use of these agents can lead to the development of resistant bacteria against fluoroquinolone groups. Therefore, it is important to take precautions for rational antibiotic use and to develop new antibiotic groups. In this single-center retrospective study, we aim to evaluate levofloxacin treatment in GNB infections against its effects, results, and safety in PICU. Additionally, this study investigated the types of microorganism agents, effective dose and duration of treatment, eradication status, impact on length of stay, and development of secondary organ dysfunction in patients receiving levofloxacin.

MATERIALS AND METHODS

Patients

We performed a retrospective single-center study, in a local tertiary hospital, including in patients treated with levofloxacin for the periods of July and December 2021 in PICU. The study included patients aged between 1 month and 18 years who had blood and/or endotracheal aspirate cultures positive for GNB and were treated with levofloxacin during the 6-month period. The patients who had GNB infections initiated levofloxacin for 14-21 days with 10 mg/kg/dose twice doses intravenously (8). During the study period, the patients received identical clinical treatment from the same group of physicians. Patients with GNB infection who were found to be non-sensitive to levofloxacin in the culture sensitivity test were excluded from the study. During this period, the demographic characteristics, medical histories, comorbidities, length of stay in PICU, need for mechanical ventilation supports, lab-

oratories, type of infection and treatment periods, treatment response and adverse effects, morbidities, and mortalities of patients examined and evaluated. All data of the study were obtained by retrospectively investigating the electronic files of patients with GNB growth. Previous histories of the patients were learned from their families for their predisposing conditions of resistant GNB, and patients with comorbid diseases but not diagnosed with definitive immunodeficiency were also included in the immunosuppressed group. Recommended procedures for controlled and effective antibiotic use were done to our patients in accordance with the recommendations of the infection control committee and current guidelines. In PICU patients, in patients with suspected infection and/or sepsis based on symptoms, clinical and laboratory examinations, empirical broad-spectrum antibiotics were started, firstly, based on the findings and the sources that were predicted to be infection sources. Then, in those with GNB growth signal in endotracheal and/or blood culture within 24-48 hours after the culture taken before antibiotic therapy, more frequently used antibiotics such as empiric cephalosporin, aminoglycoside, and carbapenem were ordered, taking into account the flora of the unit. After reporting the exact microorganism that was growing in all our patients and giving us the culture and antibiogram sensitivity results, treatment was given based on the causative agent (9). The levofloxacin treatment was initiated for the patients included in the study according to the same procedure. Levofloxacin was chosen due to its availability in the hospital pharmacy and its inclusion in the fluoroquinolone group of the culture antibiogram against GNB during the study. Control cultures (endotracheal and peripheral/catheter blood) were taken 48-72 hours after each patient started levofloxacin treatment, and in case of continued GNB growth, control cultures were repeated at 3-day intervals. If the patient's culture without growth was detected within the first 10 days, the treatment was continued until 14 days, and if it was detected in 10-14 days or later, the treatment was continued until 21 days. Patients who demonstrated clinical and laboratory improvement during follow-up but continued to show growth in culture and/or a decreased number of detected colonies were considered to be colonized, and their treatment was discontinued after 21 days. Nosocomial infection was diagnosed in these patients if GNB infection was detected 48 hours after hospitalization. The microbiological culture sensitivity results of patients with GNB growth in the culture sample were also examined for carbapenem and ciprofloxacin resistance. The success of levofloxacin treatment was evaluated in these patients. All data were obtained from their electronic and archived files and thus recorded as patient data. The ethics committee approval for the study was obtained by the clinical research ethics committee in our city (22/05/01) before the study began.

Statistical Analysis

Statistical analysis was performed with SPSS statistical package (IBM® SPSS® 26 (SPSS Inc., Chicago, IL, ABD) for Windows 22.0. The conformity of the variables to the normal distribution was analyzed by analytical methods (Kolmogorov-Smirnov test). Descriptive analyzes were given as minimum-maximum, median and IQR (interquartile range) for continuous data. Descriptive statistics were made by giving frequency and percentage values of categorical variables belonging to sociodemographic and clinical information. Pearson's Chi-Square or Fisher's Exact Chi-Square test was used to compare categorical variables. Significance was considered when the p-value was less than 0.05.

RESULTS

In a retrospective, local single-center study, 22 (4.58%) patients were included who had GNB infections treated with levofloxacin between July and December 2021 in the PICU, during this period, there were approximately 480 new admissions. Of the patients, 40.9% were male and 59.1% were female. 31.8% of the patients did not have any comorbidities, while the remaining 68.2% had at least one chronic disease. These included genetic syndromes (36.4%), cerebral palsy (18.2%), congenital heart disease (9.1%), and spinal muscular atrophy (4.5%). Respiratory failure was the most common cause of PICU hospitalization with 20 (90.9%) patients. Apart from these patients, only 2 (9.1%) were admitted due to status epilepticus. 21 patients (95.5%) were transferred from our hospital's emergency department. The remaining 1 (4.5%) was transferred from the general pediatric service of our hospital due to increased respiratory failure. At the first evaluations of patients the Glasgow coma scale (GKS) under 8 points were 16 (72.7%) patients. At the time of admission, the first respiratory supports were evaluated 14 (63.6%) of them were intubated, others 8 (36.4%) had a high flow nasal cannulas oxygen (HFNC) and bilevel positive airway pressure (BIPAP) support. Table.I displays the patient's age, length of stay, PRISM III score, the initial time of GNB infections, duration of antibiotic use, and first laboratory results at the time of admission. All the patients had a long PICU stay, which is a predisposing factor to antibiotic-resistant GNB infection. CVC use (p= 0.005) and length of stay PICU (p= 0.009), which are predisposing conditions, were found to be statistically significantly associated with the development of GNB infection and levofloxacin use. Table II presents the distribution of TPN, steroid and CVC use, immunosuppression status, mechanical ventilation, and statistical analysis of the patients. Levofloxacin treatment indications were 4 (18.18%) catheter-associated bloodstream infections and 18 (81.82%) ventilator-associated pneumonia. Table. III displays the distribution of treatment for patients with GNB infection who received levofloxacin treatment, categorized by types of bacteria and infections. Upon consideration of the reasons that predispose to GNB infection in the PICU, 18 (81.8%) pneumonia and 4 central venous catheter (CVC) infections were identified. Among the patients who received levofloxacin treatment, 17 (77.3%) were treated for nosocomial infection due to the time of infection detection. When the GNB types were identified, two distinct bacteria were grown in cultures. These were 13 (59.1%) Stenotrophomonas maltophilia and 9 (40.9%) Pseudomonas aeruginosa. In all these GNBs,

Table 1: On admission, the age of the patient, the length of stay, the PRISM III score, the time of the first GNB infection, the duration of antibiotic use and the first laboratory results

	Minimum	**Maximum**	**Median**	**IQR**
Patients age (month)	2	180	28.89	51.64
Lenght of stay (day)	16	376	87.6	81.23
PRISM III	4	80	27.0	23.73
Infection time (day)	3	350	47.18	78.83
Antibiotic time (day)	10	27	20.59	13.68
Hemoglobin (g/dL)	7	13	9.59	11.79
Hematocrit (%)	22	40	29.14	25.26
White blood cell (103/uL)	1800	29000	11229.09	7142.71
Platelets (103/uL)	8000	346000	147909.09	90134.24
C- reaktive protein (mg/L)	9	452	114.09	107.88

**PRISM III: Pediatrik Risk of Mortality Score III*

Table 2: Distribution of factors and microorganisms predisposing to the development of resistant gram-negative infection, and statistical analysis of predisposing causes

Predisposing Factors	**Patient**	**Pseudomonas aeruginosa**	**Stenotrophomonas maltophilia**	**P value**
	n (%)	**n (%)**	**n (%)**	
TPN	2 (9.09%)	2 (100%)	0 (0%)	0.355
Steroid	0 (0%)	0 (0%)	0 (0%)	-
Immunosuppression	15 (68.18%)	4 (26.66%)	11 (73.33%)	0.474
CVC	21 (95.45%)	9 (42.85%)	12 (57.14%)	0.005
Increased length of stay	22 (100%)	9 (40.9%)	13 (59.1%)	0.009
Mechanical ventilation	14 (63.63%)	5 (35.71%)	9 (64.28%)	0.236

CVC: Central Venous Catheter, TPN: Total Parenteral Nutrition

21 (95.5%) carbapenem and 14 (63.6%) ciprofloxacin resistance (in studied samples) were observed. All the patients had same treatment strategy levofloxacin treatment 10-27 (median: 20.59; IQR: 13.68) days and 20 (90.9%) of their GNBs were eradicated. The 2 (9.1%) exitus patients' characteristics: 8-month-old male patient developed colonization after 21 days of GNB treatment but exitus due to progression of his primary comorbid disease; A 2-month-old girl with congenital syndromic appearance died in the septic shock clinic on the 14th day of GNB treatment. In this study, the mortality rate was detected at 13.6% (3 patients), and successfully we treated 19 patients (86.4%). During this treatment period, we did not detect any complications related to levofloxacin as renal, cardiac, hepatic failures, and/or ion imbalances. After treatment, they had no sequels in the central nervous and skeletal systems. In this study, we detected that nosocomial infections were significantly correlated with length of stay time (p= 0.009). The levofloxacin treatment strategy was examined for Stenotrophomonas maltophilia and Pseudomonas aeruginosa infections, there was no significant difference (p=0.739). Examining the duration of levofloxacin treatment, it was found that those who eradicated GNS received 14-27 (21) days of treatment, while those who could not eradicate GNS received 10-14 (12) days of treatment. This situation was found to be statistically significant (p=0.007) as is shown in Table.IV. However, there was no significant difference in carbapenem and ciprofloxacin resistance between patients whose GNS infection was eradicated and was not (p=1.000).

Table 4: The duration of levofloxacin treatment and the success of eradication

	Treatment time (day)			**P value**
	Minimum	**Maximum**	**Mean**	
Eradication (+)	14	27	21	0.007
Eradication (-)	10	14	12	

DISCUSSION

Fluoroquinolones are a type of broad-spectrum antimicrobials widely used to treat multi-resistant infections in adults. The use of these drugs was not recommended because of previous evidence of cartilaginous toxicity, although no clinical complications were reported in children. The rise in multidrug resistance resulted from the increase in clinical trials conducted in laboratories. It is worth noting that there were no clinically evident toxicities observed in young animals using florokinolone in the 1990s. These clinical trials provided for supported initiating FDA sanctioned, comparative efficacy, prospective, and safety clinical trials (10, 11). In the age of pediatrics, levofloxacin is not approved by the FDA. However, in data from use in the past, fluoroquinolones had similar adverse effects as adults (7). In 2014, a large population of pediatric age published a clinical trial for the assessment of musculoskeletal toxicity on levofloxacin for 5 years. It was reported that there was no significant complication because of using levofloxacin on musculoskeletal systems

Table 3: The distribution of treatment for patients with GNB infection who received levofloxacin treatment, categorized by types of bacteria and infections

Type of bacteria	Type of infection	Treatment period	Eradication status
	n (%)	(day)	n (%)
Stenotrophomonas maltophilia	VAP: 10 (76.92%)	Median: 21.81 IQR:21.00	Yes: 10 (100%) No: 0(0%)
	CLABSI: 3 (23.08%)	Median: 22.00 IQR: 22.17	Yes: 3 (100%) No: 0 (0%)
Pseudomonas aeruginosa	VAP: 6 (75%)	Median: 17.42 IQR: 18.52	Yes: 4 (66.7%) No: 2(33.3%)
	CLABSI: 3 (25%)	Median: 24.00 IQR: 23.35	Yes: 3 (100%) No:0 (0%)

VAP: Ventilator-associated pneumonia, CLABSI: Catheter-associated bloodstream infections

(6). In this single-center retrospective study, our aim is to assess the effects, results, and safety of levofloxacin treatment in the PICU for all systems. The study was conducted at a local tertiary hospital and included patients who were treated with levofloxacin between July and December 2021. During the six-month period, we included patients aged between one month and 18 years who had growth of GNB in their blood and/or endotracheal aspirate cultures and were treated with levofloxacin. We did not observe any complications, allergic reactions or deaths due to drug use in our study of a heterogeneous population over 6 months. It has been reported that in animal studies of fluoroquinolone toxicity of the skeletal system, adverse effects on cartilage are related to the dosage of the drug and the duration of treatment (12). The treatment effects of levofloxacin for community-acquired pneumonia in children are contained in a randomized controlled study in 2008. According to this study, the utilisation of levofloxacin is considered secure and efficacious for treating infections. It is observed that levofloxacin is 90% curable to community-acquired pneumonia as standard antibiotics (amoxicillin-clavulanate, ceftriaxone, macrolide) in children age (7). In our study, like the referenced, patients within the identical age group were administered intravenous levofloxacin treatment twice, at a dose of 10 mg/kg/dose. The duration of treatment was not scheduled for a fixed 10 days, which was the only difference. Levofloxacin was administered to all patients in the study as part of their infection treatment. Culture controls were intermittently taken from the patients during the treatment. The antibiotic treatment regimen was modified for patients who continued to grow GNB for more than 14 and/or 21 days, developed levofloxacin resistance in control cultures, or experienced clinical deterioration. These patients were deemed resistant to levofloxacin treatment. Examining the duration of levofloxacin treatment, it was found that those who eradicated GNS received 14-27 (21) days of treatment, while those who could not eradicate GNS received 10-14 (12) days of treatment. This situation was found to be statistically significant (p=0.007). Therefore, based on our study, we can recommend at least 14 days and possibly 21 days of treatment for eradication in the use of levofloxacin against GNB. Furthermore, it is deemed suitable to administer levofloxacin at a dosage of 20 mg/kg/day due to the absence of any adverse reactions. In a retrospective, multicenter, and observational study, in adults, the levofloxacin treatment for nosocomial infection in critically ill patients is reported 500 mg twice a day for 9 days. Levofloxacin was chosen at the rate of 77.8% in combination therapy. The clinical success rate was detected at 67.4% in all studies (13). Additionally, in the adult age group, the recommendation of the Infectious Diseases Society of America and the American Thoracic Society group for hospital-acquired or ventilator-associated pneumonia is to first start empirical treatment and, if necessary, add levofloxacin as a combination. In terms of dosage, 750 mg daily as a single dose orally or intravenously is generally recommended for 7 days, depending on the severity of the disease or treatment response (14). According to the recommendation of the Committee on Infectious Diseases in 2016, the dosage for susceptible infections is peroral or intravenous 8 to 10 mg/kg/dose twice daily, and after 5 years oral or intravenous 10 mg/kg/dose once daily (maximum dose: 750 mg/day) is recommended (8). A study on the risk factors and effects of gram-negative bacilli infections that resist treatment in adult patients receiving intensive care reveals that there is no direct connection between antibiotics and the deaths caused by such infections. However, age and comorbidities are found to be related (15). In our study, 13 (59.1%) Stenotrophomonas maltophilia and 9 (40.9%) Pseudomonas aeruginosa are detected, 21 (95.5%) carbapenem and 14 (63.6%) ciprofloxacin resistance was observed. All patients received levofloxacin treatment for 21 days, with 20 (90.9%) achieving eradication. On the contrary, in our study, which included a small pediatric patient population, the group in which GNB eradication was not detected covered ventilator-associated pneumonia patients who grow Pseudomonas aeruginosa bacteria. The duration of levofloxacin treatment in these patients is shorter than Stenotrophomonas maltophilia growth (ventilator-associated pneumonia and catheter-associated bloodstream infections) and catheter-associated bloodstream infections with Pseudomonas aeruginosa infection detected. (median: 17.42; IQR: 18.52 days). The remaining 2 (9.1%) patients died before completing 14 days of treatment. The study identified a mortality rate of 13.6% (3 patients), with successful treatment of 19 patients (86.4%). All patients included in the study had a comorbid chronic disease. In a randomized controlled study conducted to evaluate levofloxacin given in addition to high-dose rifampicin

in cases of tuberculous meningitis in the childhood age group, functional outcome was generally found to be good (16). Additionally, the relationship of levofloxacin use in the induction phase with Enterobacteriaceae colonization, Clostridioides difficile diarrhea, and other adverse events in newly diagnosed acute lymphoblastic leukemia patients was investigated. In this Brazilian multicenter, randomized controlled study, prophylactic use of levofloxacin during the induction phase was found to be safe in patients with acute lymphoblastic leukemia (17). A crossover pharmacokinetic study covering 25 patients in children under 5 years of age was conducted by Van der Laan LE, et al. For pharmacokinetic evaluation, 15-20 mg/kg/dose levofloxacin treatments, 100 mg dispersible and crushed and 250 mg non-dispersible levofloxacin types were used. Although bioavailability was more improved in the use of dispersible formulation than in the non-dispersible formulation, it was found to be lower than in adults. It has been reported that the use of a dispersible formulation may be appropriate when used in accordance with age and weight (18). Throughout, although this study is retrospective and covers only a small number of patients from a single center, we may conclude that treating GNB-resistant bacteria with a strategy lasting at least 14 days and preferably 21 days, along with the intravenous administration of 10 mg/kg/dose twice a day to combination therapies, might be an efficient treatment option. The limitations of our study include the fact that it was conducted retrospectively in a small heterogeneous population in a short period of 6 months. Furthermore, we lacked a laboratory capable of testing the effectiveness of levofloxacin in serum in terms of its pharmacokinetic, pharmacodynamic effects, and bioavailability. During the study, there was no pediatric infection specialist in our hospital, and there was a period when levofloxacin sensitivity was studied in culture antibiogram but ciprofloxacin sensitivity was not. Although the data of these studies were found to be supportive of levofloxacin treatment, the study has lots of limitations including the small sample size, lack of a control group, potential for selection bias, and inability to assess long-term safety.

CONCLUSION

Due to the challenge of eradicating infections and the rising antibiotic resistance, it may be necessary to use antibiotics that are not typically prescribed to children or to develop new drug categories. Therefore, there is a need for more multicenter, randomized controlled, and long-term observational studies to evaluate the efficacy of different and new groups of antibiotics, including levofloxacin, in treating GNB.

Ethics

The ethics committee approval for the study was obtained Harran University Clinical Research Ethics Committee (22/05/01).

Authorship Contributions:

H.F.A. (1) and U. A. (3) conceived the idea, and were involved in clinical care/following of the patients. M. A. (2) performed statistical analyzes of the data. H. F. A. (1) and M. A. (2) wrote the first draft of the manuscript which was critically revised by all the authors. All authors read and approved the final version of the manuscript.

Declaration of competing interest:

The authors declare that they have no competing interests.

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The authors report no conflicts of interest.

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