ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Accompanying Infections in Hospitalized Children with Neurological Disease

Hastaneye Yatırılan Nörolojik Hastalığı Olan Çocuklarda Eşlik Eden Enfeksiyonlar

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Abstract

Introduction: Infections in children with neurological disease often require hospitalization and are treated with antibiotics. In this study, it was aimed to determine the accompanying infections, antibiotics used and pathogenic microorganisms grown in cultures in hospitalized children with neurological disease.

Materials and Methods: Digital medical files of patients between one month and 18 years old admitted to the pediatric neurology service were retrospectively analyzed. Diagnoses of neurological and infectious disease, antibiotics and antiepileptics used, and culture antibiogram results were recorded.

Results: The most common infectious disease in children with neurological disease was lower respiratory tract infections (50%). Antibiotic use rate in children with neurological diseases was 51.9% (32.4% single and 19.4% combined). Lower respiratory tract infections (50%) were the leading antibiotic indications. Third generation cephalosporins (46%) were the most used in mono antibiotherapy, carbapenems (26.6%), gylicopeptides (26.6%) and broad-spectrum penicillins (10%) were used at higher rates in combined antibiotherapy. Pathogenic microorganisms such as *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Morganella morganii* and *Enterococcus raffinosus* were grown in urine cultures, *Staphylococcus aureus* and *Enterococcus faecium* in blood cultures. 59.3% of the children with neurological diseases were receiving antiepileptic treatment. Valproic acid 24.6%, levetiracetam 20.0%, phenobarbital and carbamazepine were used at 10.8% frequency.

Conclusion: The most common infectious disease in hospitalized children with neurological disease is lower respiratory tract infections. Although cephalosporin is mostly preferred in mono-antibiotherapy, carbapenem and glycopeptides come to the fore in combined therapy. It is important to know the infections that may develop in the follow-up of this group of patients and the possible causative pathogens for rapid and effective treatment and to reduce health costs.

Keywords
Antiepileptics, antibiotics, children, pediatric, treatment

Öz

Giriş: Nörolojik hastalığı olan çocuklarda ortaya çıkan enfeksiyonlar sıklıkla hastaneye yatış gerektirmekte ve antibiyotiklerle tedavi edilmektedir. Bu çalışmada hastaneye yatırılan nörolojik hastalığı olan çocuklarda eşlik eden enfeksiyonların, kullanılan antibiyotiklerin ve kültürlerde üreyen patojenik mikroorganizmaların belirlenmesi amaçlanmıştır.

Anahtar kelimeler
Antiepileptikler, antibiyotikler, çocuklar, pediatrik, tedavi

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Gereç ve Yöntem: Çocuk nörolojisi servisine yatırılan 1 ay-18 yaş arası hastaların dijital tıbbi dosyaları retrospektif olarak incelendi. Nörolojik ve enfeksiyon hastalığı tanıları, kullanılan antibiyotik ve antiepileptikler ve kültür antibiyogram sonuçları kaydedildi.
Bulgular: Nörolojik hastalığı olan çocuklarda en sık görülen enfeksiyon hastalığı alt solunum yolu enfeksiyonlarıydı (%50). Antibiyotik kullanım oranı %51,9 (%32,4 mono ve %19,4 kombine) idi. Tekli antibiyotik tedavisinde en çok üçüncü kuşak sefalosporinler (%46) kullanılmıştı. Çoklu antibiyotik tedavisinde ise karbapenemler (%26,6), glikopeptidler (%26,6) ve geniş spektrumlu penisilinler (%10) daha yüksek oranlarda kullanılmıştı. İdrar kültürlerinde *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Morganella morganii* ve *Enterococcus raffinosus*, kan kültürlerinde ise *Staphylococcus aureus* ve *Enterococcus faecium* patojenleri üredi. Nörolojik hastalığı olan çocukların %59,3'ü antiepileptik tedavi almaktaydı. Valproik asit %24,6, levetirasetam %20,0, fenobarbital ve karbamazepin %10,8 sıklıkta kullanılmıştı.
Sonuç: Hastaneye yatırılan nörolojik hastalığı olan çocuklarda en sık görülen enfeksiyon alt solunum yollarına aittir. Mono antibiyoterapide çoğunlukla sefalosporinler tercih edilse de kombine tedavide karbapenem ve glikopeptitler öne çıkmaktadır. Bu grup hastaların takiplerinde gelişebilecek enfeksiyonların ve neden olan olası patojenlerin bilinmesi hızlı ve etkin tedavi ve sağlık maliyetlerinin azaltılması için önemlidir.

Introduction

Since the discovery of sulfonamide and penicillin, antibiotics have become indispensable treatment tools in modern medicine (1). They are at the top of prescription rankings in developed and developing countries in the world at present and are the most commonly prescribed medication in the childhood period in Turkey (2-4). To date, many antibiotics have been developed; however, this situation had led to problems like antibiotic resistance development and additional financial load (5).

Antibiotic use rates in special units like pediatric/neonatal intensive care units (PICU/NICU), pediatric surgery, and hematology-oncology are high compared to other pediatric units (6). Due to antimicrobial stewardship programs (ASPs) developed in these special units, the target is prevention of antibacterial resistance development and reduction of costs (7).

There are many beneficial microorganisms preventing colonization of pathogens in a healthy human body. People with chronic neurological disease experience changes in oropharyngeal, gastrointestinal and urinary tract flora over time (8). Antiepileptic (AED), myorelaxant, immunomodulatory drugs and ketogenic diet used for treatment of neurological diseases in the childhood period contribute to variation in the microbiota (9-11). For example, it is known that the respiratory tract of children with cerebral palsy is colonized by *Pseudomonas aeruginosa (P. aeruginosa)* and other gram-negative bacteria, while the urinary systems of children with meningomyelocele and neurogenic bladder are colonized by antibiotic resistant *Escherichia coli (E. coli)*, *Enterobacteriaceae* and *Klebsiella* (12,13). When we examine the literature, there are very few studies on the change of microbiota in children with chronic neurological disease, pathogenic microorganisms grown in cultures and appropriate use of antibiotics. Unfortunately, currently there are no guidelines such as ASP for children with neurological diseases. In our study, it was aimed to reveal common infectious diseases, antibiotics used for treatment and pathogens grown in cultures in children hospitalized in the pediatric neurology service in order to contribute to this gap in the field.

Materials and Methods

Patient Selection

This study was designed as a retrospective and cross-sectional study in a tertiary level university hospital. The files of patients with neurological disease who were hospitalized and treated with antibiotics were retrospectively reviewed. Diagnosis of neurological diseases was made by the pediatric neurology division and monitoring of inpatients was completed by the same unit. In necessary situations, consultations were made with other units led by infectious diseases specialists.

The study inclusion criteria; a- children admitted to the pediatric neurology ward from 01. January 2018-31. December 2019, b- to be between 1 month and 18 years old, c- having a neurological disease such as epilepsy, cerebral palsy, demyelinating disease, meningomyelocele, hydrocephalus, muscle and peripheral nervous system diseases, d- having received at least 3 days of antibiotic treatment during hospitalization in the pediatric neurology ward.

The study exclusion criteria; children with prophylactic antibiotic use due to reasons like surgery or burns were not included in the study. Additionally,

children monitored by intensive care or hematology clinics were not included in the study. Cases whose treatment was referred to other units were excluded from the study.

Age, sex, primary neurological disease, comorbid infectious disease, empirical or therapeutic antibiotic use and hospitalization durations were retrospectively collected from digital medical files. Culture and antibiogram results were documented in line with reports from the microbiology laboratory serving in our hospital.

Statistical Analysis

Age, primary neurological disease, infectious diseases, antibiotics, AEDs and hospitalization duration had mean ± SD, median (minimum-maximum) and percentages calculated. Culture and antibiogram results were presented from the available reports.

Ethical Statement

Ethical approval was received for this study from the local ethics committee of Çanakkale Onsekiz Mart University Faculty of Medicine (approval number: 2011-KAEK-27/2019-E.1900186491, date: 15.01.2020).

Results

Within the determined dates, 171 digital medical files suitable for the study were investigated. Cases were divided into two groups as those given and not given antibiotic treatment.

Group receiving antibiotics; A total of 93 cases were detected. Of these, two patients transferred to intensive care, one transferred to hematology, and one patient receiving burn treatment were excluded from the study. Nine cases with similar infection diagnoses and recurrent hospitalizations were also excluded from the study (Figure 1).

A total of 80 cases (51.9%) who were treated with antibiotics that met the study criteria were identified. The mean age in this group was 6.0±4.5 years, median 4.5 years (range: 1.2-17.6) and sex ratio boy/girl 44/36. Hospitalization duration was mean 7.3±4.1 days and median 6.0 days (minimum: 3.0-maximum: 24.0). Among those administered antibiotic treatment, 25 had epilepsy, 21 had cerebral palsy, 18 had cerebral palsy + epilepsy, four had myelomeningocele, two had acute disseminated encephalomyelitis, two had hydrocephalus, two had Guillain-Barre syndrome (GBS), four had meningomyelocele + hydrocephalus + epilepsy, one had leukoencephalopathy (vanishing white matter disease) and one had Wilson disease (Table 1).

Group not receiving antibiotics; A total of 78 cases who did not receive antibiotic treatment were identified. Those who received treatment for different reasons such as hypotension (1), urticaria (2) and angioedema (1) were not included in the study (Figure 1).

There were 74 cases (48.1%) not administered antibiotics with mean age 4.7±3.8 years, median 5.8 years (minimum: 1.1-maximum: 17.8), sex ratio boy/girl 39/35 and hospitalization duration mean 5.1±2.1 days, and median 6.3 days (minimum: 1-maximum: 13). Of these, 27 had epilepsy, 21 had febrile seizure, 12 had cerebral palsy + metabolic disturbance or malnutrition, 11 had neurometabolic and other undiagnosed diseases, two had hydrocephalus and one had GBS diagnosis (Table 1).

Among the 80 cases with neurological disease administered antibiotics, antibiotic treatment was given for the following diagnoses: 50% had lower respiratory tract infection (LRTI), 23.8% had lower urinary tract infection (LUTI), 11.3% had central nervous system infection (CNSI), 7.5% had gastrointestinal system infection (GISI), 5% had skin and soft tissue infection (SSTI) and 2.5% had occult bacteriemia (OB). A total of 127 cultures from these patients were studied comprising 71 blood samples, 33 urine samples, 11 cerebrospinal fluid (CSF) samples, nine stool samples, two wound samples and one sputum sample (Table 2).

There was grown in 18 urine cultures, eight blood cultures and the two wound cultures. According to urine culture results, *E. coli* (6), *Proteus mirabilis (P. mirabilis)* (4), *P. aeruginosa* (3), *Klebsiella pneumoniae (K. pneumoniae)* (2), *Morganella morganii* (1) and *Enterococus raffinosus* (1) were accepted as pathogenic microorganisms. *Streptococcus parasanguinis* (1) was not accepted as pathogen with proliferation below 100,000 CFU/mL. According to blood culture results, microorganisms accepted as pathogenic were *Staphylococcus aureus* (2) and *Enterococcus faecium* (1). However, as *Staphylococcus aureus* was not resistant to methicillin

and *Enterococcus faecium* was not resistant to ampicillin and vancomycin, antibiogram results are not presented. *Streptococcus mitis* (2), Coagulase-negative *Staphylococci* (2), and *Staphylococcus epidermidis* (1) proliferating in blood cultures were not accepted as pathogenic. One of the wound cultures produced *Provetella* spp. (1); however, antibiogram results were not given as significant antibiotic resistance was not identified. The other wound culture produced Staphylococcus hominis (1); however, this microorganism was not accepted as pathogenic (Table 2). The antibiogram results for gram-negative microorganisms accepted as being pathogenic are also presented in Table 3.

The general antibiotic use rate among children admitted to hospital for neurological disease was 51.9% (80/154). Within the total study population, the monotherapy rate was 32.4% (50/154) and combined treatment rate was 19.4% (30/154). In empirical or pathogen-specific monotherapy were used third generation cephalosporins most at 46%. This was followed by ampicillin-sulbactam at 32%, second generation cephalosporins at 12% and aminoglycosides at 6%. For combined antibiotic therapy, it was observed that broad spectrum antibiotics like carbapenem (26.6%), glycopeptides (26.6%), aminoglycosides (20%) and broad-spectrum penicillin (100%, fourth generation) were used. Nearly all antivirals (30% acyclovir and oseltamivir) were used within combined therapy (Graphic 1a, b).

It was identified that 59.3% of children with neurological disease administered antibiotic treatment were also receiving antiepileptic treatment. Among these, 33.9% were receiving mono and 25.4% were receiving combined antiepileptic treatment. When we examine the frequency of AED use individually, the order was valproic acid 24.6%, levetiracetam 20.0%, phenobarbital and carbamazepine 10.8%, clobazam 9.2%, topiramate 6.2%, clonazepam, vigabatrin 4.6% and others (lamotrigine, phenytoin, zonisamide, stiripentol) 9.2% (Graphic 2a, b). Little used treatments such as tizanidine, trihexyphenidyl, intravenous immunoglobulin, and steroids were not recorded.

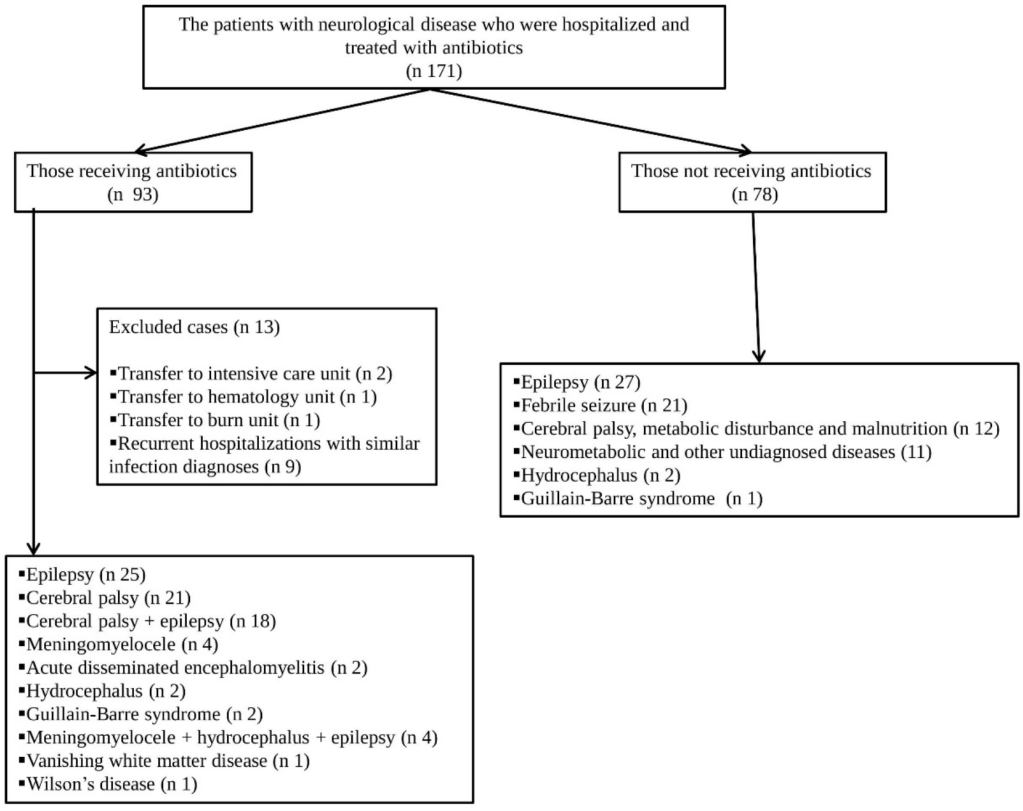


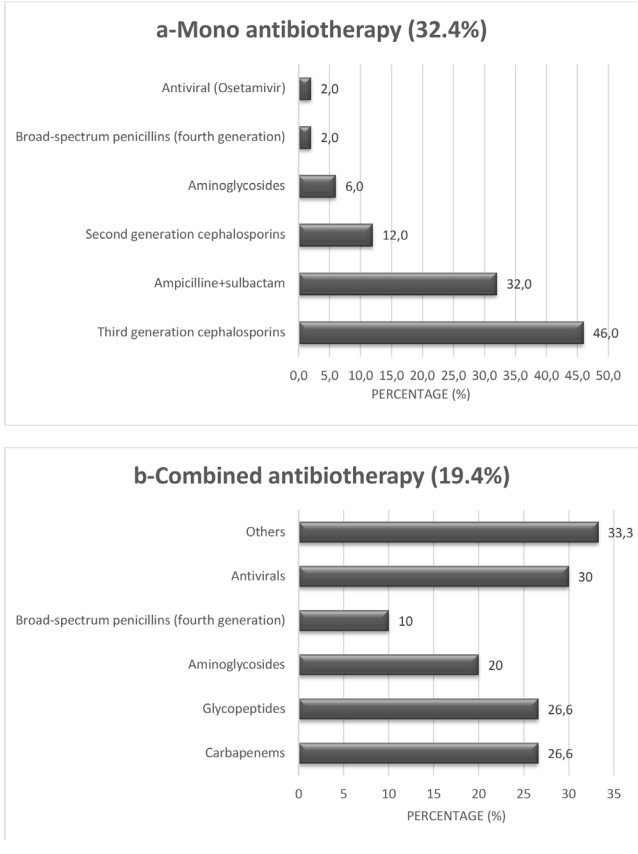
Figure 1. Patients and disease groups included in the study.

Discussion

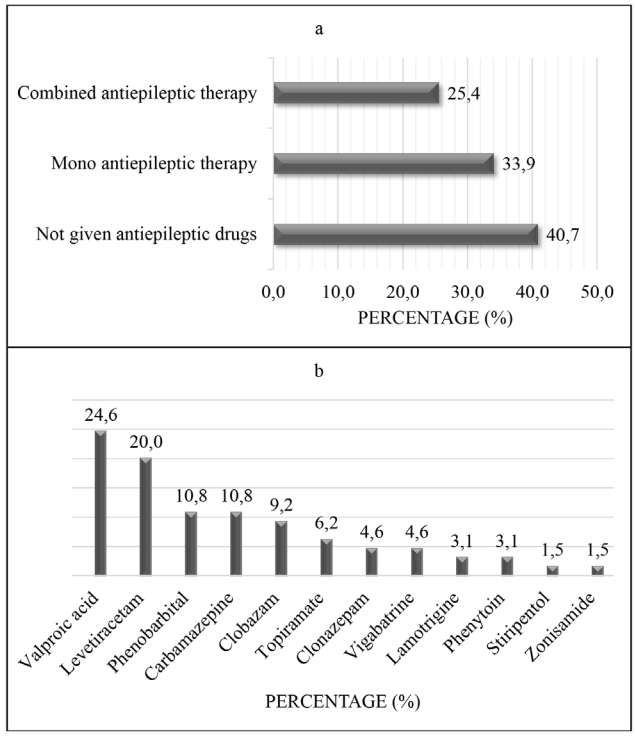
In many neurological diseases, especially CP, respiratory tract diseases are seen due to multiple factors such as impaired airway clearance, breathing mechanics, non-effective coughing and oropharyngeal dysphagia (14). Vomiting and occult aspirations seen in other neurological diseases, especially seizures (postictal stage), also facilitate the development of respiratory diseases (15). In addition to these factors, malnutrition also causes deterioration of general health and susceptibility to respiratory infections (16).

In our study, the majority of children with neurological disease were hospitalized for LRTI. In point prevalence surveys (PPSs) LRTI lead the indications for antibiotic use (17). In our study, respiratory, urinary and gastrointestinal tract infections led the list of antibiotic indications. Differently in our study, the rate was 11.3% for CNSI in terms of antibiotic use indications (Table 2). This rate is higher than rates reported by Versporten et al. (18) (2010) and Amadeo et al. (19) (2016). This elevation may be due to diseases like encephalitis, meningitis or meningoencephalitis naturally being included in pediatric neurology compared to general pediatrics. However, the lack of pathogen proliferation in CSF cultures indicates deficiencies in technical topics like taking cultures and sending to the laboratory or perhaps a tendency toward overdiagnosis of CNSI.

In our study, the antibiotic use rate for children with neurological diseases hospitalized for treatment was 51.9% (Table 1). This rate is a little higher than antibiotic use rates reported in outpatient PPSs (20). PPSs are also applied in inpatient clinics and antibiotic use rates are reported according to ward (e.g., general pediatrics, PICU/NICU, surgery and hematology-oncology) (21). However, to date, there is no data about antibiotic use in children hospitalized with neurological diseases. Versporten et al. (18) (2016) reported 36.7% antibiotic use in hospitalized children in a multinational PPS, while Gharbi et al. (22) reported 40.9% in multicenter studies, Amadeo et al. (19) (2010) reported 32% and Gerber et al. (23) reported 60%. Antibiotic use rates in special units like the PICU/NICU, surgery and hematology-oncology increase further to reach 60-90% (24).



Graphic 1. Antibiotic use rates in children hospitalized with neurological diseases; (a) frequency of antibiotics used in monotherapy, (b) frequency of antibiotics used in combined therapy.



Graphic 2. Antiepileptic drugs used by children with neurological diseases; (a) mono and combined antiepileptic treatment rates, (b) frequency of antiepileptic drugs.

Table 1. Demographic characteristics of the study group	
Children with primary neurological disease undergoing antibiotherapy (n 80), %51.9	
Age (years)	Mean 6.0±4.5, median 4.5 (minimum: 1.2-maximum: 17.6)
Gender; male/female (%)	44 (55.0%)/36 (45.0%)
Hospitalization lenght (days)	Mean 7.3±4.1 median 6.0 (minimum: 3-maximum: 24)
Neurological diagnoses (n)	
	Epilepsy (n=25)
	Cerebral palsy (n=21)
	Cerebral palsy + epilepsy (n=18)
	Meningomyelocele (n=4)
	ADEM (n=2)
	Hydrocephalus (n=2)
	GBS (n=2)
	Meningomyelocele + hydrocephalus + epilepsy (n=4)
	VWM (n=1)
	Wilson's disease (n=1)
Children with primary neurological disease not receiving antibiotherapy (n=74), 48.1%	
Age (years)	Mean 4.7±3.8, median 5.8 (minimum: 1.1-maximum: 17.8)
Gender; male/female (%)	39 (52.7%)/35 (47.2%)
Hospitalization lenght (days)	Mean 5.1±2.1 median 6.3 (minimum: 1-maximum: 13)
Neurological diagnoses (n)	
	Epilepsy (n=27)
	Febrile seizure (n=21)
	Cerebral palsy, metabolic disturbance and malnutrition (n=12)
	Neurometabolic and other undiagnosed diseases (11)
	Hydrocephalus (n=2)
	GBS (n=1)
n: number of cases, ADEM: Acute disseminated encephalomyelitis, GBS: Guillain-Barre syndrome, VWM: Vanishing white matter disease	

Due to developed ASPs, the target is to treat infections in a short time and effective way. Additionally, one of the important aims of ASPs is to prevent development of antibiotic resistance (25). Due to ASPs developed for PICU/NICU, surgery and hematology-oncology wards, antibiotic resistance development has been brought partially under control. However, the presence of infections with neurological diseases and AED use makes antibiotic treatment very complex. It is necessary to consider the choice of suitable antibiotic and reaching effective blood levels, keeping AED at effective blood levels, effects on liver, kidney and other organ functions, drug-drug interactions (DDIs) and adverse drug reactions that may develop (26). Unfortunately, in practice we see these parameters are not always considered. This situation makes a range of difficulties in treatment of both infectious disease and neurological disease unavoidable.

The basic target for treatment of infectious diseases is to administer the most effective antibiotic for the possible or identified infectious agent. However, a natural problem like possible antibiotic-AED interaction occurs. For solution of this paradox, paying attention to culture and antibiogram results may provide a guide. Thorbum et al. (27) (2009) reported *P. aeruginosa*, *Klebsiella* and *Enterobacter* species proliferated in throat cultures from children with CP admitted to the PICU and on mechanical ventilation. In our study, CP cases were followed in

Table 2. Infectious diseases using antibiotics in children with neurological diseases and pathogenic microorganisms growing in their cultures				
Files reviewed (n=80)				
Infectious diseases		**(%)**		
	LRTI	50.0		
	LUTI	23.8		
	CNSI	11.3		
	GISI	7.5		
	SSTI	5.0		
	OB	2.5		
Cultures studied		**(n)**	**(n)**	**Production**
	Blood	71	8	*Staphylococcu saureus* (2)* *Streptococcus mitis* (2) Coagulase-negative *Staphylococci* (2) *Enterococcus faecium* (1)* *Staphylococcus epidermi*dis (1)
	Urine	33	18	*Escherichia coli* (6)* *Proteus mirabilis* (4)* *Pseudomonas aeruginosa* (3)* *Klebsiella pneumoniae* (2)* *Enterococcus raffinosus* (1)* *Morganella morganii* (1)* *Streptococcus parasanguis* (1)
	CSF	11	0	
	Sputum sample	1	0	
	Wound	2	2	*Staphylococcus hominis* (1) *Prevotella* spp (1)*
	Gaita	9	0	

LRTI: Lower respiratory tract infection, LUTI: Lower urinary tract infection, CNSI: Central nervous system infection, GISI: Gastrointestinal system infection, SSTI: Skin and soft tissue infection, OB: Occult bacteriemia, *: Microorganisms considered pathogenic, CSF: Cerebrospinal fluid

the ward and mechanical ventilation was not applied. Most pathogens like *E. coli*, Pseudomonas aeruginosa, *K. pneumoniae* and *P. mirabilis* were identified in the urine cultures of myelomeningocele cases. These pathogens were observed to have multiple antibiotic resistance. Gram negative pathogens easily colonize susceptible hosts due to pili and fimbriae creating chaperone-usher pathway (28). Additionally, another situation which eases pathogen colonization is degradation of mucosal fibronectin by elastase secreted by macrophages with stimulation of chronic diseases and the resulting disruption of the robustness of muco-ciliary clearance (29).

In our study, the majority of children with neurological disease (59.3%) were observed to receive antiepileptic treatment. AEDs with elimination through the liver like valproic acid, phenobarbital, carbamazepine and benzodiazepine were mostly used (Graphic 2). Levetiracetam with elimination via the renal route was used at 20% levels. In this context, we can say that first generation antiepileptics are more commonly used for epilepsy treatment. AEDs in this group, especially carbamazepine, valproic acid, phenobarbital and phenytoin, may affect the efficacy and safety of medications when used together (30). In our study, it was observed that cephalosporins, ampicillin + sulbactam, aminoglycosides, glycopeptides and carbapenem were frequently chosen for antibiotic treatment (Graphic 1). The frequent use of potent seizurogenic antibiotics like cephalosporin, penicillin and carbapenem in children with neurological disease indicates that infection treatment was prioritized due to identification of resistant pathogens and unfortunately, antibiotic-antiepileptic interactions were ignored.

Table 3. Pathogenic microorganisms produced in cultures of children with neurological diseases and their antibiotic susceptibility

Antibiotics/ Microorganisms	*E. coli*						*K. pneumoniae*		*P. aeruginosa*			*P. mirabilis*				*M. morganii*
	1	2	3	4	5	6	1	2	1	2	3	1	2	3	4	1
Amoxicilin/Cl	S	S	R	R	R	S	S	R	R			S	R	R	R	R
Ampicillin	S	S	R			R	R	R	R			S	R			
Cefixime	S	S	S	S	S	S	S					S		S	R	R
Ceftriaxone	S	S	S	S	S	S	S	R	R				S			
Cetfazidim				S	I		S	R	S	S	S		S	S	R	R
Cefepime				S	R		S	R	R		R		R	S	R	S
Gentamicin	S	S	S	R	S	S	S	S	R	S	R	I	R	R	R	S
Amikacin				S	S		S	S	I	S	I	S	I	S	R	S
Piperacillin/Tz	S	S	S	S	S	S	S	I	S	S	S		R	S	S	S
Meropenem				S			S		S	S	S			S	S	S
Ertapenem				S					R							S
Ciprofloxacin	S	S	S	R	S		S	S	S	S	R	R	R	R	R	S
Trimethoprim/Slf	S	S	S	R	S	S	S	R				S	R		S	S
Colistin											S			S		

Cl: Clavulonic acid, Tz: Tazobactam, Slf: Sulfamethooxazole, I: Intermediate susceptibility, R: Resistant, S: Susceptible

One of the important limitations of our study is that plasma levels of AEDs could not be measured. If we had been able to perform these measurements, we could make clearer interpretations about antibiotic-AED pharmacokinetic interactions and proconvulsant character of antibiotics. However, this was not part of our study design and we noted no serious variation in epileptic seizure frequency among children with neurological disease undergoing antibiotic treatment during investigation of the files.

Children receiving antiepileptic treatment and with chronic neurological disease have more variability in microbiota and susceptibility to infectious agents compared to healthy children (31). This situation naturally means that these children are more easily and frequently exposed to infectious diseases. Unfortunately, it is still a complex issue to consider drug interactions between AEDs and antibiotics and to avoid proconvulsive antibiotics. Measurement of the therapeutic plasma levels of both antibiotics and AEDs will bring extra financial load to health expenditure. Important situations that should be recalled are that macrolide, carbapenem and antituberculotic medications affect AED blood levels and especially carbapenem significantly lowers the plasma concentration of valproic acid (32). Additionally, care should be taken that factors like underlying neurological disease, infection, age and nutrition may negatively contribute to DDIs (33).

Conclusion

In this study, a situation determination was made about common infection diseases, antibiotics used, and pathogenic microorganisms produced in cultures in children with neurological disease who were hospitalized in the pediatric neurology ward. Neurological diseases such as epilepsy, CP, hydrocephalus and meningomyelocele are among the diseases that require hospitalization and antibiotic treatment. Upper respiratory tract infections are detected most frequently in this group of patients and they are mostly treated with cephalosporins. Gram-positive cocci such as staphylococci and streptococci grow in blood cultures, and gram-negative pathogens such as *E. coli*, *P. aeruginosa* and *P. mirabilis* in urine cultures. In parallel with technological and pharmacological developments, currently children with epilepsy, CP and other neurological diseases have

longer duration of survival. Knowing the common infection diseases in children with neurological diseases and predicting possible pathogens can provide serious benefits in important issues such as establishing an effective antibiotic treatment strategy and reducing health costs.

Ethics

Ethics Committee Approval: Ethical approval was received for this study from the local ethics committee of Çanakkale Onsekiz Mart University Faculty of Medicine (approval number: 2011-KAEK-27/2019-E.1900186491, date: 15.01.2020).

Conflict of Interest: No conflict of interest was declared by the authors.

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