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Researh Article / Araştırma Makalesi

Prevalence and Pattern of Antibiotic Susceptibility of Gram-negative Bacteria Isolated from Pediatric Blood Culture

Pediatrik Kan Kültüründen İzole Edilen Gram Negatif Bakterilerin Prevalansı ve Antibiyotik Duyarlılık Paterni

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Abstract: It was aimed to evaluate the antibiotic susceptibilities of Gram-negative bacteria isolated from blood samples taken from pediatric patients. The samples were evaluated with the Bactec 9120 automation system bacteria were identified by the Gram-Negative ID panel using the Vitek 2 Compact (Biomerieux France) device performed with the AST N090 panel, and the results were evaluated according to The Clinical and Laboratory Standards Institute (CLSI) recommendations. Antibiotic resistance results: Ceftriaxone was the most resistant antibiotic (71.4%). *Salmonella spp*. it was mostly resistant to levofloxacin and ciprofloxacin (100%). While *E. coli* strains were the most resistant to ticarcillin and piperacillin (71.4%), the most effective antibiotics against this bacterium were imipenem and meropenem (100%). Resistance rates to all tested antibiotics were significantly higher in ESBL-producing *Klebsiella spp* and *E coli* strains than in non-ESBL-producing strains ($p<0.05$). Considering this information, it is vital to evaluate the current resistance profiles in the application of empirical treatment in premature and newborn patients.

Keywords: Child , Blood culture, Gram-negative, Antibiotic resistance, Vitek 2..

Öz: Pediatrik hastalardan alınan kan örneklerinden izole edilen Gram negatif bakterilerin antibiyotik duyarlılıklarının değerlendirilmesi amaçlandı. Örnekler Bactec 9120 otomasyon sistemi ile değerlendirildi. AST N090 paneli ile gerçekleştirilen Vitek 2 Compact (Biomerieux Fransa) cihazı kullanılarak Gram-Negatif ID paneli ile bakteriler tanımlandı ve sonuçlar Klinik ve Laboratuvar Standartları Enstitüsü (CLSI) tavsiyelerine göre değerlendirildi. Antibiyotik direnci sonuçları: Seftriakson en dirençli antibiyotik (%71,4) oldu. *Salmonella spp*. çoğunlukla levofloksasin ve siprofloksasine (%100) dirençliydi. *E. coli* suşları tikarsilin ve piperasilin'e en dirençli (%71,4) iken, bu bakteriye karşı en etkili antibiyotikler imipenem ve meropenem (%100) oldu. Test edilen tüm antibiyotiklere karşı direnç oranları, ESBL üreten *Klebsiella spp* ve *E coli* suşlarında, ESBL üretmeyen suşlara göre anlamlı derecede yüksekti ($p<0,05$). Bu bilgiler göz önüne alındığında prematüre ve yenidoğan hastalarda ampirik tedavinin uygulanmasında mevcut direnç profillerinin değerlendirilmesi hayati önem taşımaktadır.

Anahtar Kelimeler: Çocuk, Kan kültürü, Gram negatif, Antibiyotik direnci, Vitek 2..

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Introduction

Increasing antimicrobial resistance in bacteria continues to be an important health problem in our country as well as all over the world. Accordingly, in addition to the increase in mortality and morbidity, the increase in the cost of treatment is also growing day by day. Gram Negative Bacteria (GNB) are especially important in nosocomial infections, and these bacteria are often isolated from community-acquired infections (Jain et al., 2021). With the spread of broad-spectrum antibiotics in recent years, the development of antibiotic resistance has increased and this resistance is transferred between bacterial species through genes. Therefore, the choice of antibiotics is important. Antibiotic resistance follow-up should be done regularly in the relevant

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center to determine the ideal treatment option. In empirical antibiotic selection, the change in antibiotic resistance patterns should be evaluated locally (He et al., 2019; Meng et al., 2022). The results of antibiotic susceptibility may vary from region to region, from hospital to hospital, and even between units of the same hospital. In addition, the rates change over the years according to the principles of antibiotic use. Therefore, regional antibiotic resistance patterns should be determined by performing susceptibility tests at regular intervals (Prestinaci et al, 2015). Gram-negative bacteria are one of the most important causes of hospital and community-acquired infections. Enterobacteriaceae (*Escherichia coli, Citrobacter, Klebsiella, Serratia, Proteus, Morganella, Providencia, and Enterobacter species, Pseudomonas aeruginosa, Acinetobacter* species, *Stenotrophomonas maltophilia*) are gram-negative nosocomial agents commonly encountered in children (Gajdács et al., 2020). Most infections caused by these organisms occur in neonatal and pediatric intensive care unit patients. Underlying diseases such as malignancy, immunosuppressive diseases, burns, prematurity, intravascular and/or central nervous system catheter, mechanical ventilation, and urinary catheterization are the main risk factors for developing these organism infections. Due to multidrug resistance among GNB, the number of antibiotics that can be used in treatment is gradually decreasing, the development of resistance sometimes creates problems during treatment, and almost incurable infections occur (Atay et al., 2019; de Oliveira Costa et al., 2015).

This study, aimed to evaluate antibiotic sensitivity against Gram-negative bacteria isolated from blood samples.

Materials and Methods

Study criteria

Blood samples taken from pediatric patients hospitalized in Diyarbakır Children's Hospital were analyzed. Study criteria; it was determined that the isolates grew easily on media such as blood agar and EMB, were Gram-negative and did not have colonization, contamination, or relapse disease.

Reproductive and Results Evaluation

Blood culture bottles [BACTECTM PLUS+ Aerobic/F and BACTECTM PEDS PLUS/F blood culture bottles (aerobic and pediatric bottles)] taken from the clinics were placed in the BACTEC 9120 automatic system. After the bottles with positive signals were removed from the device, they have inoculated on blood agar and EMB (Eosin Methylene Blue) media. All media were evaluated after incubation at 35°C for 18-24 hours. Colony morphology and reproductive characteristics were examined. Gram staining was done. To identify these bacteria and ensure antibiotic sensitivity, 3.0 ml of saline was first transferred from the dispenser to the tubes. Similar colonies were selected from fresh plates (medium) and suspended in ID (Identification) tubes. ID tubes were mixed with vortex and left in the Mcfarland device Those of the suspended ID tubes adjusted according to Mcfarland 0.5-0.63 were placed in the cassette and pipetted 145 µl from the ID tube to the AST (Antibiotic Susceptibility Test) tube. Then, the ID and AST cards were placed in the prepared tubes, and the cassette was identified with the Gram-negative ID panel in the Vitek 2 Compact (Biomerieux France) device in accordance with the manufacturer's instructions, and antibiotic susceptibility was tested with the AST N090 panel. Then, antibiotic susceptibility results in accordance with CLSI (Clinical and Laboratory Standards Institute) criteria were recorded using Vitek 2 device software with different options. These data were transferred to SPSS Statistics 17.0 program and evaluated statistically.

Data analysis

The data obtained in this study were expressed as frequencies and percentages, and statistical analyzes of the data were used to compare the difference in antibiotic susceptibility between

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ESBL-positive and ESBL-negative and other resistant strains, Statistical Package for the Social Sciences (SPSS) 17.0 (SPSS Inc., Chicago). IL, USA) using the $\chi 2$ test. The level of significance was accepted as $p<0.05$ in all statistical analyses.

Ethical consideration

This study received approval from the non-invasive research ethics committee (Date: 03.10.2022, Decision No: HRU/22.19.34, Session No: 19). Consent forms were obtained from the relatives of the patients included in the study it was carried out at Diyarbakır Children's Hospital.

Results

In the study, 23 *Klebsiella spp*., 21 *Acinetobacter spp*., 15 *Salmonella spp*., 14 *E. coli*, 8 *Enterobacter spp*.,6 *Sphingomonas spp*., 4 *Pseudomonas spp*., 3 *Serratia spp*., 3 *Burkholderia spp*., 2 *Stenotrophomonas maltophilia*, 1 Proteus mirabilis, and 1 Pantoea agglomerans, a total of 101 strains were analyzed. Distribution of these bacteria according to clinics and other demographic information is given in Table 1.

Table 1: Distribution of bacteria by clinics

CLINICS	PİC	GİC	HEM	PED	İNT	NN	OC	EME	ONC.	TOTAL
BACTERIA										
Klebsiella spp.	4	3	1	8	1	4	1	0	1	**23**
Acinetobacter spp.	13	0	0	3	2	1	1	1	0	**21**
Salmonella spp.	0	0	2	3	3	0	7	0	0	**15**
E. coli	4	2	0	3	2	3	0	0	0	**14**
Serratia spp.	1	0	0	0	0	2	0	0	0	**3**
E. cloacae	1	0	0	1	1	4	1	0	0	**8**
S. paucimobilis	0	0	0	1	0	3	2	0	0	**6**
Burkholderia spp.	0	0	0	2	1	0	0	0	0	**3**
Pseudomonas spp.	2	0	0	0	1	0	0	0	1	**4**
S. maltophilia	1	1	0	0	0	0	0	0	0	**2**
Proteus mirabilis	0	1	0	0	0	0	0	0	0	**1**
Pantoea agglomerans	0	0	0	0	0	1	0	0	0	**1**
TOTAL (n / %)	**26/25,8**	**7/6,9**	**3/2,9**	**21/20,8**	**11/10,9**	**18/17,9**	**12/11,8**	**1**	**2**	**101/100**

PIC: Premature Intensive Care, **GIC:** General Intensive Care, **HEM:** Hematology, **PED:** Pediatrics, **INT:** Intania (İnfection), **NN:** Neonatal, **OC:** Older Child, **EME:** Emergency**, ONC:** Oncology, **T:** Total.

In our study, 26 (25.8%) isolates were from the premature intensive care unit, 21 (20.8%) from pediatric clinics, 18 (17.9%) from the neonatal service, and 12 (11.8%) from the old children's service. 11 (10.9%) were recruited from the infection service, 7 (6.6%) from the general intensive care service, 3 (2.9%) from the hematology service, 2 (2%) from the oncology service, and 1 from the emergency Table 2. 12 (11.9%) girls and 39 (38.6%) boys, totally 51 (50.5%) of our patients whose blood cultures were taken are 0-3 months old, 9 (8.9%) A total of 32 (31.7%) 4-60 months old, 5 (4.9%) girls, 4 (4%) boys, 23 girls (22.8%) boys 9 (8.9%) were in the 5-10 age group, 5 (4.9%) girls, 4 (4%) boys, a total of 9 (8.9%) 11-18 in the age group.

Klebsiella spp. when the susceptibilities of the strains to antibiotics were examined, resistance developed against Cefepime, Ceftriaxone, and Ceftazidime at a rate of 56.5%, except Ticarcillin and Piperacillin, which were naturally resistant (100%). No resistance developed against Colistin, Tigecycline, Amikacin, Meropenem, Imipenem. Of the 23 examined Klebsiella spp. 13 of the strains were found to be ESBL positive. When the antibiotic resistance patterns of ESBL positive and ESBL negative *Klebsiella spp* strains were examined, it was

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seen that ESBL negative Klebsiella strains were naturally resistant to all antibiotics except Ticarcillin and Piperacillin. ESBL-positive *Klebsiella* strains were found to be resistant to Ampicillin/Sulbactam with the highest rate of 61.5% Table 3.

Table 2: Distribution of bacteria by age/gender characteristics.

	AGE/GENDER								
BACTERIA	**0-3 Month**		**4-60 Month**		**5-10 Years**		**11-18 Years**		**TOTAL/ (%)**
	K	E	K	E	K	E	K	E	
Klebsiella spp.	3	10	3	5	1	-	1	-	23 / 22,7
Acinetobacter spp.	4	12	2	3	-	-	-	-	21 / 20,8
Salmonella spp.	-	-	-	3	2	3	4	3	15 / 14,8
E. coli	2	5	4	3	-	-	-	-	14 / 13,9
Serratia spp.	-	2	-	1	-	-	-	-	3 / 3
Enterobacter cloacae	-	5	-	2	1	-	-	-	8 / 7,9
Sphingomonas paucimobilis	1	2	-	1	1	1	-	-	6 / 5,9
Burkholderia spp.	-	-	-	3	-	-	-	-	3 / 3
Pseudomonas spp.	1	1	-	1	-	-	-	1	4 / 4
Stenotrophomonas maltophilia	1	1	-	-	-	-	-	-	2 / 2
Proteus mirabilis	-	-	-	1	-	-	-	-	1 / 1
Pantoea agglomerans	-	1	-	-	-	-	-	-	1 / 1
TOTAL (n / %)	12	39	9	23	5	4	5	4	101 /100

Acinetobacter spp. When the susceptibility of the strains to antibiotics is examined, the most resistant antibiotic is CRO with 71.4%. CL, TGC, and CN seem to be the least resistant antibiotics with 4.8% Table 4.

Salmonella spp. when we look at the susceptibility of the strains to antibiotics, it is seen that they are 100% resistant to LEV and CIP, 2 (13.3%) strains are resistant to TC and PIP, and there is no resistance in all the remaining strains. In ESBL-producing Klebsiella spp strains, resistance rates against all tested antibiotics were found to be significantly higher than in non-Klebsiella spp-producing strains ($p<0.05$). (Table 4). When we look at the susceptibility of *Enterobacter cloacea* strains to antibiotics, they are naturally resistant (100%) and resistant to 25% CPZ/SUL PIP, TC, CRO, and CAZ except for TE, SAM, CIP, LEV, IPN, TOB, CN, AK, MEM and there is no resistance against FEP Table 4.

Considering the antibiotic susceptibility of *E. coli* strains, it is seen that the highest resistance against TK and PIP is 71.4%, followed by CAZ with 64.3%. It is seen that the least resistant strains are against LEV, CL, CIP, and TOB with 7.1%, while there is no resistance against AK, TGC, MEM, and IPN. Antibiotic susceptibility of ESBL-positive *E. coli* strains was investigated. It has been determined that it is resistant to TK and PIP at most 100%. Then 87.5% SAM and 50% SXT and TE were resistant. When the susceptibility of ESBL-negative *E. coli* strains to antibiotics was examined, it was found that the highest rate was 33.3% resistant to TC, PIP, and TE. In ESBL-producing *E. coli* strains, resistance rates against all tested antibiotics were found to be significantly higher than in non-ESBL-producing strains ($p<0.05$) Table 5.

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Tablo 3. *Klebsiella spp.,* Resistance rates of *Klebsiella* ESBL positive*, Klebsiella* ESBL Negative strains to various antibiotics.

Klebsiella spp							**ESBL positive** ***Klebsiella spp***						**ESBL negative** ***Klebsiella spp***					
Antibiotic	S		I		R		S		I		R		S		I		R	
	n	%	N	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
TK	0	0	0	0	23	100*	0	0	0	0	13	100*	0	0	0	0	10	100*
PIP	0	0	0	0	23	100*	0	0	0	0	13	100*	0	0	0	0	10	100*
SXT	16	69,6	0	0	7	30,4	6	46,2	0	0	7	53,8	10	100	0	0	0	0
CL	23	100	0	0	0	0	13	100	0	0	0	0	10	100	0	0	0	0
TGC	23	100	0	0	0	0	13	100	0	0	0	0	10	100	0	0	0	0
TE	21	91,3	0	0	2	8,7	11	84,6	0	0	2	15,4	10	100	0	0	0	0
LEV	22	95,7	0	0	1	4,3	11	84,6	0	0	2	15,4	10	100	0	0	0	0
CIP	22	95,7	0	0	1	4,3	11	84,6	0	0	2	15,4	10	100	0	0	0	0
TOP	18	78,3	1	4,3	4	17,4	8	61,5	1	7,7	4	30,8	10	100	0	0	0	0
GN	19	82,6	0	0	4	17,4	9	69,2	0	0	4	30,8	10	100	0	0	0	0
AK	20	87	3	13	0	0	10	76,9	3	23,1	0	0	10	100	0	0	0	0
MEM	23	100	0	0	0	0	13	100	0	0	0	0	10	100	0	0	0	0
İPN	23	100	0	0	0	0	13	100	0	0	0	0	10	100	0	0	0	0
FEP	10	43,5	0	0	13	56,5	0	0	0	0	13	100	10	100	0	0	0	0
CPZ/SUL	18	78,3	1	4,3	4	17,4	9	69,2	2	15,4	2	15,4	10	100	0	0	0	0
CRO	10	43,5	0	0	13	56,5	0	0	0	0	13	100	10	100	0	0	0	0
CAZ	10	47,8	0	0	13	56,5	0	0	0	0	13	100	10	100	0	0	0	0
PTZ	16	69,6	2	8,7	2	21,7	7	53,8	1	7,7	5	38,5	9	90	1	10	0	0
SAM	11	47,8	3	13	9	39,2	3	23,1	2	15,4	8	61,5	8	80	1	10	1	10
TOTAL	n: 23/100						n: 13/100						n: 10/100					

p<0.01 (SD±) ; * : Intrinsically Resistant

(n: Strain number, S: Susceptible, I: Intermediate, R: Resistant, TC: Ticarcillin, PIP: Piperacillin, SXT: Sulphamethox-Trimethoprim, CL: Colistin, TGC: Tigecycline, TE: Tetracycline, LEV: Levofloxacin, CIP : Ciprofloxacin, TOB: Tobramycin, CN: Gentamicin, AK: Amikacin, MEM: Meropenem, IPN: Imipenem, FEP: Cefepime, CTX: Cefotaxime, CPZ/SUL: Cefoperazone/Sulbactam, CRO: Ceftriaxone, CAZ: Ceftazidime, PTZ-Taz-Piperacillin : Ampicillin-Sulbactam, SAM : Ampicillin/Sulbactam).

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Tablo 4. Various antibiotics resistance rates of *Acinetobacter spp., Salmonella spp., Enterobacter cloacae* strains.

	Acinetobacter spp						***Salmonella spp***						***Enterobacter cloacae***					
Antibiotic	S		I		R		S		I		R		S		I		R	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
TK	8	38,1	0	0	13	61,9	13	86,7	0	0	2	13,3	6	75	0	0	2	25
PIP	7	33,3	1	4,8	13	61,9	13	86,7	0	0	2	13,3	6	75	0	0	2	25
SXT	9	42,9	0	0	12	57,1	15	100	0	0	0	0	7	87,5	0	0	1	12,5
CL	20	95,2	0	0	1	4,8	15	100	0	0	0	0	7	87,5	0	0	1	12,5
TGC	23	100	0	0	1	4,8	15	100	0	0	0	0	7	87,5	0	0	1	12,5
TE	10	47,6	1	4,8	10	47,6	15	100	0	0	0	0	7	87,5	1	12,5	0	0
LEV	9	42,6	7	33,3	5	23,8	0	0	0	0	15	100	8	100	0	0	0	0
CIP	8	38,1	2	9,5	11	52,4	0	0	0	0	15	100	8	100	0	0	0	0
TOP	10	47,6	7	33,3	4	19,1	15	100	0	0	0	0	8	100	0	0	0	0
GN	18	85,7	2	9,5	1	4,8	15	100	0	0	0	0	8	100	0	0	0	0
AK	19	90,5	0	0	2	9,5	15	100	0	0	0	0	8	100	0	0	0	0
MEM	10	47,6	0	0	11	52,4	15	100	0	0	0	0	8	100	0	0	0	0
İPN	10	47,6	0	0	11	52,4	15	100	0	0	0	0	8	100	0	0	0	0
FEP	8	38,1	0	0	13	61,9	15	100	0	0	0	0	8	100	0	0	0	0
CPZ/SUL	8	38,1	1	4,8	12	57,1	15	100	0	0	0	0	6	75	0	0	2	25
CRO	5	23,8	1	4,8	15	71,4	15	100	0	0	0	0	6	75	0	0	2	25
CAZ	6	28,6	1	4,8	14	66,6	15	100	0	0	0	0	6	75	0	0	2	25
PTZ	7	33,3	1	4,8	13	61,9	15	100	0	0	0	0	6	75	1	12,5	1	12,5
SAM	10	47,6	1	4,8	10	47,6	15	100	0	0	0	0	0	0	0	0	8	100*
TOTAL	n: 21/100						n: 15/100						n: 8/100					

(n: Strain number, S: Susceptible, I: Intermediate, R: Resistant, TC: Ticarcillin, PIP: Piperacillin, SXT: Trimethoprim /Sulfamethoxazole -, CL: Colistin, TGC: Tigecycline, TE: Tetracycline, LEV: Levofloxacin, CIP: Ciprofloxacin, TOB: Tobramycin, CN: Gentamicin, AK: Amikacin, MEM: Meropenem, IPN: Imipenem, FEP: Cefepime, CTX: Cefotaxime, CPZ/SUL: Cefoperazone/Sulbactam, CRO: Ceftriaxone, CAZ: Ceftazidime, PTZ-Taz-Piperacillin: Ampicillin-Sulbactam, SAM : Ampicillin/Sulbactam).

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Tablo 5: Resistance rates of *E coli., E coli* ESBL positive, *E coli* Negative strains to various antibiotics.

E coli							**ESBL positive *E. coli***						**ESBL negative *E. coli***					
Antibiotic	S		I		R		S		I		R		S		I		R	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
TK	4	28,6	0	0	10	71,4	0	0	0	0	8	100	4	66,7	0	0	2	33,3
PIP	4	28,6	0	0	10	71,4	0	0	0	0	8	100	4	66,7	0	0	2	33,3
SXT	10	71,4	0	0	4	28,6	4	50	0	0	4	50	6	100	0	0	0	0
CL	13	92,9	0	0	1	7,1	8	100	0	0	0	0	5	83,4	0	0	1	16,7
TGC	14	100	0	0	0	0	8	100	0	0	0	0	6	100	0	0	0	0
TE	8	57,1	0	0	6	42,9	4	50	0	0	4	50	4	66,7	0	0	2	33,3
LEV	13	92,9	0	0	1	7,1	7	87,5	0	0	1	12,5	6	100	0	0	0	0
CIP	13	92,9	0	0	1	7,1	7	87,5	0	0	1	12,5	6	100	0	0	0	0
TOP	13	92,9	0	0	1	7,1	7	87,5	0	0	1	12,5	6	100	0	0	0	0
GN	11	78,6	1	7,1	2	14,3	6	75	0	0	2	25	5	83,3	1	16,7	0	0
AK	13	92,9	1	7,1	0	0	7	87,5	1	12,5	0	0	6	100	0	0	0	0
MEM	14	100	0	0	0	0	8	100	0	0	0	0	6	100	0	0	0	0
İPN	14	100	0	0	0	0	8	100	0	0	0	0	6	100	0	0	0	0
FEP	6	42,9	0	0	8	57,1	0	0	0	0	8	100	6	100	0	0	0	0
CPZ/SUL	6	42,9	6	42,9	2	14,2	1	12,5	5	62,5	2	25	5	83,3	1	16,7	0	0
CRO	6	42,9	0	0	8	57,1	0	0	0	0	8	100	6	100	0	0	0	0
CAZ	5	35,7	0	0	9	64,3	0	0	0	0	8	100	5	83,3	0	0	1	16,7
PTZ	11	78,6	0	0	3	21,4	5	62,5	0	0	3	37,5	6	100	0	0	0	0
SAM	6	42,9	0	0	8	57,1	1	12,5	0	0	7	87,5	5	83,3	0	0	1	16,7
TOTAL	n: 14/100						n: 8/100						n: 6/100					

(n: Strain number, S: Susceptible, I: Intermediate, R: Resistant, TC: Ticarcillin, PIP: Piperacillin, SXT: Sulphamethox-Trimethoprim, CL: Colistin, TGC: Tigecycline, TE: Tetracycline, LEV: Levofloxacin, CIP: Ciprofloxacin, TOB: Tobramycin, CN: Gentamicin, AK: Amikacin, MEM: Meropenem, IPN: Imipenem, FEP: Cefepime, CTX: Cefotaxime, CPZ/SUL: Cefoperazone/Sulbactam, CRO: Ceftriaxone, CAZ: Ceftazidime, PTZ-Taz-Piperacillin tazobactem, Ampicillin-Sulbactam, SAM : Ampicillin/Sulbactam).*: The bacterium that is naturally resistant to these antibiotics is *P. aeruginosa.* The susceptible bacterium is *P. luteola.*

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Tablo 6: Resistance rates of *Sphingomonas paucim, Pseudomonas spp., Serratia spp* strains to various antibiotics.

Sphingomonas paucim							***Pseudomonas spp***						***Serratia spp***					
Antibiotic	S		I		R		S		I		R		S		I		R	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
TK	5	83,3	1	16,7	0	0	4	100	0	0	0	0	3	100	0	0	0	0
PIP	6	100	0	0	0	0	4	100	0	0	0	0	3	100	0	0	0	0
SXT	6	100	0	0	0	0	1	25	0	0	3	75*	0	0	0	0	0	0
CL	2	33,3	0	0	4	66,7	3	75	0	0	1	25	2	66,7	0	0	3	100*
TGC	6	100	0	0	0	0	1	25	0	0	3	75	3	100	1	33,3	0	0
TE	6	100	0	0	0	0	1	25	0	0	3	75	3	100	0	0	0	0
LEV	4	66,7	2	33,3	0	0	4	100	0	0	0	0	3	100	0	0	0	0
CIP	5	83,3	0	0	1	16,7	4	100	0	0	0	0	3	100	0	0	0	0
TOP	5	83,3	0	0	1	16,7	4	100	0	0	0	0	3	100	0	0	0	0
GN	6	100	0	0	0	0	3	75	1	25	0	0	3	100	0	0	0	0
AK	6	100	0	0	0	0	4	100	0	0	0	0	3	100	0	0	0	0
MEM	6	100	0	0	0	0	4	100	0	0	0	0	3	100	0	0	0	0
İPN	6	100	0	0	0	0	4	100	0	0	0	0	3	100	0	0	0	0
FEP	5	83,3	0	0	1	16,7	4	100	0	0	0	0	3	100	0	0	0	0
CPZ/SUL	6	100	0	0	0	0	4	100	0	0	0	0	3	100	0	0	0	0
CRO	5	83,3	0	0	1	16,7	1	25	0	0	3	75*	3	100	0	0	0	0
CAZ	5	83,3	0	0	1	16,7	4	100	0	0	0	0	3	100	0	0	0	0
PTZ	6	100	0	0	0	0	4	100	0	0	0	0	3	100	0	0	0	0
SAM	6	100	0	0	0	0	1	25	0	0	3	75*	1	33,3	0	0	2	66,7
TOTAL	n: 6/100						n: 4/100						n: 3/100					

*: Intrinsically Resistant. (n: Strain number, S: Susceptible, I: Intermediate, R: Resistant, TC: Ticarcillin, PIP: Piperacillin, SXT: Sulphamethox-Trimethoprim, CL: Colistin, TGC: Tigecycline, TE: Tetracycline, LEV: Levofloxacin, CIP : Ciprofloxacin, TOB: Tobramycin, CN: Gentamicin, AK: Amikacin, MEM: Meropenem, IPN: Imipenem, FEP: Cefepime, CTX: Cefotaxime, CPZ/SUL: Cefoperazone/Sulbactam, CRO: Ceftriaxone, CAZ: Ceftazidime, PTZ-Taz-Piperacillin : Ampicillin-Sulbactam, SAM : Ampicillin/Sulbactam).

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When we look at the susceptibility of *Sphingomonas paucimobilis* strains to the given antibiotics, resistance to CL was found at a rate of 66.7%. It is seen that there is no resistance against other antibiotics such as LEV, SAM, TK, CN, PIP, SXT, TGC, TE, AK, MEM, IPN, CPZ/SUL, PTZ, and PTZ, *Pseudomonas spp.* When we look at the susceptibility of the strains to antibiotics, it was found that 75% of them were resistant to TGC and TE. However, there is no resistance against other antibiotics such as TOB, CAZ, NEM, TK, PIP, LEV, CIP, CN, AK, IPN, FEP, CPZ/SUL, CAZ, and PTZ *Serratia spp.* When we look at the susceptibility of the strains to antibiotics, it is seen that 66.7% are resistant to SAM, except for colistin, which is naturally resistant (100%), and no resistance has developed against the remaining antibiotics. There was no significant difference in the resistance rates against all tested antibiotics for 3 bacteria ($p>0.05$) Table 6.

Only SXT and LEV were studied in the antibiotic susceptibility of *Stenotrophomonas maltophilia* strain and no resistance was detected against either antibiotic. In our study, 1 *Proteus mirabilis* and 1 *Pantoea agglomerans* were isolated. When we examine the sensitivity of Pantoea agglomerans to antibiotics, it is seen that it is resistant to TK and CL and sensitive to other antibiotics. Proteus mirabilis was resistant to TK, PIP, CL (naturally resistant to colistin), FEP, CAZ, SAM, TGC, TE, TOB, CN, and CRO. In the examination of ESBL distributions, 56.5% of Klebsiella spp and 57.1% of E. coli were found positive (Table 7).

Table 7. ESBL Distributions.

	ESBL (+)		**ESBL (-)**		**TOTAL**	
	n	**%**	**n**	**%**	**n**	**%**
Klebsiella spp.	13	56,5	10	43,5	23	100
E. coli	8	57,1	6	42,9	14	100
TOTAL	21	56,8	16	43,2	37	100

Discussion

Antibiotics, which seem to be our most important weapon in the fight against microorganisms, cause problems from time to time. Because the intensive (sometimes unnecessary) use of antibiotics, especially in the hospital environment, has led to an increase in resistant microorganisms. Most of the microorganisms resistant to antibiotics are bacteria resistant to various disinfectants, antiseptic agents, and external environmental conditions. For this reason, it settles in various parts of the hospital, especially in the intensive care units, causing outbreaks from time to time (Dhingra et al., 2020; van Dijk et al., 2022). While gram-positive microorganisms came to the fore as the causative agent of hospital infections, nosocomial infections caused by gram-negative bacteria started to draw attention after 1970. Today, depending on the centers, gram-positive bacteria come to the fore in some centers, and infection with gram-negative bacteria takes the first place in some centers. The situation of the centers, the patient population, and the antibiotics used are effective in this (Maugeri et al., 2019). Antibiotic resistance patterns may vary constantly between hospitals. It is essential to reveal resistance patterns, especially to guide the clinician (Rhomberg et al., 2004). Gram-negative nosocomial agents frequently encountered in the pediatric population are *Enterobacteriaceae* (*Escherichia coli, Klebsiella, Serratia, Proteus*, and *Enterobacter spp.*), *Pseudomonas aeruginosa*, *Acinetobacter spp., Stenotrophomonas maltophilia, Burkholderia cepacia,* and *Sphingomonas paucimobilis* (Boguniewicz et al., 2021). Most infections caused by these organisms occur in neonatal and pediatric intensive care unit patients. Underlying diseases

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such as malignancy, immunosuppressive diseases, burns, prematurity, intravascular and/or central nervous system catheter, mechanical ventilation and urinary catheterization are the main risk factors for developing these organism infections. Due to multidrug resistance among GNB, the number of antibiotics that can be used in the treatment is gradually decreasing, the development of resistance during treatment sometimes creates problems and almost incurable infections occur (Behzadnia et al., 2014; Oskouie et al., 2013). The first 4 of the most isolated bacteria in our study were *Klebsiella spp.* (22.7%), *Acinetobacter spp.* (20.8%), *Salmonella spp.* (14.8%) and *E. coli* (13.9%). When we look at the distribution of these bacteria by age, *Klebsiella spp., Acinetobacter spp.*, and *E. coli* are more common in children under 5 years of age, while *Salmonella spp.* It has been seen in children over 5 years old. Most of the isolates were obtained from the PIC unit, 26 (25.8%), 21 (20.8%) from the pediatric clinics, and 18 (17.9%) from the NN service. This is due to the dense patient population of these wards, the low average age, and the high number of invasive interventions. Invasive interventions in patients hospitalized in Intensive Care Units pave the way for Acinetobacter strains to colonize and cause infections (Garnacho-Montero et al., 2015; Iosifidis et al., 2017).

In our study, most of the *Acinetobacter* strains, 61.9%, were obtained from patients hospitalized in premature intensive care units. In a study, it was reported that the ward where *Acinetobacter* strains were most frequently isolated was the intensive care unit with 87.7% (Arslan Gülen et al. 2020). In our study, *Acinetobacter* spp. The most resistant antibiotic of the strains was ceftriaxone with 71.4%, followed by ceftazidime with 66.6%, cefepime, piperacillin, and ticarcillin with 61.9%. In a study, the rate of bacterial resistance against ceftriaxone was found to be 99.5% (Al-Tamimi et al. 2022). In another study, a total of 402 *A. baumannii* strains were 20.9% AK, 36.3% MEM, 40.5% IPN, 57.2% CIP, 66.4% PTZ, 69.4% CAZ, 69.7% SAM, 71.1%, CN, and 84.6 CRO, resistance was detected (Gazi H 2007). In our study, it was determined that the most effective antibiotics against Acinetobacter strains were 95.2%, colistin, and tigecycline. The high resistance of *A. baumannii* strains to many antibiotics makes the treatment of *A. baumannii* infections seriously difficult. The reason why the resistance rates are so high may be that although the notifications were made according to CLSI standards, clinics did not take these reports into account. It is thought that the controlled and rational use of broad-spectrum antibiotics currently used in hospitals may lead to the formation of more resistant strains. *Salmonella* is bacteria from the Enterobacteriaceae family that cause different clinical pictures. They can cause asymptomatic gastrointestinal carriage, gastroenteritis, typhoid or paratyphoid, and local organ infections (Nepal et al., 2022). In recent years, increased resistance to antimicrobials in Salmonella serotypes has been reported from many centers. The most important reason for this problem is the widespread use of antibiotics in the empirical treatment of febrile cases (la Tela et al., 2021). In one study, 41.66% salmonella spp. isolated from a total of 460 blood cultures. strains have been shown to be resistant to many antibiotics (Kashosi et al. 2018). In our study; *Salmonella spp.* strains were found to be 100% resistant to LEV and CIP, 2 (13.3%) strains were resistant to TK and PIP, and were susceptible to all the remaining antibiotics. When the literature is examined, the resistance of *Salmonella* strains to quinolones is low, but why the *Salmonella* strains in our study are so resistant should be further investigated. In addition, although it is a promising result that ESBL production was not detected in the tested isolates, it would be appropriate to direct the treatments according to the antibiogram results in order to protect this situation. The incidence of *E. coli*, which is the most common pathogen among urinary system infection agents, is 80-90% (Alanazi et al., 2018).

In our study, *E. coli* strains were mostly formed against PIP and TE with 71.4%, followed by CAZ with 64.3%, CRO, FEP, and SAM with 57.1%. Also, no resistance developed against AK, MEM, and IPN. These results show that multi-drug

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resistance has increased compared to previous studies. Especially the high resistance to cephalosporins draws attention. As in every hospital, our physicians must give conscious antibiotics according to the results of the antibiogram in our hospital. *Enterobacter* strains are among the leading causes of nosocomial infections and cause a wide variety of infections in humans, especially lung, surgical wounds, urinary tract infections, and bacteremia (Annavajhala et al., 2019). In our study, *Enterobacter cloacae* strains were found to be 100% resistant to SAM, to which they are naturally resistant, and no resistance was found against TGC, LEV, CIP, TOP, CN, AK, MEM, IPN, and FEP. The susceptibility rates to the other antibiotics studied were less resistant (12-25%) than the susceptibility rates in the studies. *S. paucimobilis* can cause community and hospital-acquired infections. *S. paucimobilis* can often be seen in people with additional diseases such as immunosuppression, malignancy, and diabetes, as well as in healthy people (Dsouza et al., 2021).

In our study, it was determined that S. paucimobilis strains were resistant to CL 66.7%, CIP, TOP, FEP, CRO, and CAZ 16.7% and were sensitive to other antibiotics studied. *P. aeruginosa* occupies a special place among the nosocomial infectious agents due to its resistance to many antibiotics. The rate of development of resistance to antibiotics varies according to the structure of that hospital, the characteristics of the patients, the spectrum and frequency of invasive interventions in the hospital, and most importantly, the antibiotic use policy (Pachori et al., 2019). Although the clinic of bacteremia due to *P. aeruginosa* is no different from bacteremia caused by other Gram-negative bacteria, mortality rates are higher in these cases (Horcajada et al., 2019).

In our study, *Pseudomonas spp*. strains were resistant to TE and TGC by 75% and CL by 25%, while no resistance was detected against the other antibiotics examined. *P. aeruginosa,* SXT, CRO, and SAM are inherently (100%) resistant. *P. luteola* was sensitive to all antibiotics except CL. Although resistance rates were found to be low in our hospital according to studies, the development of resistance should be followed up periodically. *Serratia spp.* They cause bacteremia, lower respiratory tract, surgical wounds, and skin and soft tissue infections and are responsible for 2% of nosocomial infections. The mortality rate in nosocomial infections originating from Serratia is reported to be 26% (Kim et al., 2015;Al-Tamimi et al., 2022). In our study, *Serratia spp*. SAM resistance was detected in 66.6% of the strains, except CL, which is naturally resistant (100%), and no resistance was observed to other antibiotics studied. *Klebsiella spp.* is gram-negative bacteria that mostly cause opportunistic infections. These microorganisms often show resistance to many antimicrobial agents (Siddiqui et al., 2016). In our study, 23 *Klebsiella spp*. The antibiotic susceptibility of the strain was investigated. Except for TK and PIP, which it is naturally resistant to (100%), resistance developed against FEP, CRO, and CAZ at the rate of 56.5%. Also, no resistance developed to CL, TGC, AK, MEM, and IPN. ESBL positivity was found to be 56.5% in *Klebsiella* strains, and ESBL negative strains were found to be sensitive to all antibiotics. The findings in our study were close to the findings of other studies. *S. maltophilia* is an increasingly important microorganism in hospital infections in recent years. *S. maltophilia* is intrinsically resistant to many antibiotics due to its genes encoding efflux pumps and enzymes that inactivate beta-lactamase, aminoglycoside acetyltransferase, and erythromycin. It is one of the bacteria whose treatment is problematic, since it can show resistance to many antibiotics used today, including carbapenems (Adegoke et al., 2017). In our study, 2 strains of *Stenotrophomonas maltophilia* were isolated. The antibiotic susceptibilities of these 2 strains were studied only for SXT and LEV, and no resistance was found to either antibiotic. In our study, 1 *Proteus mirabilis* and 1 *Pantoea agglomerans* were isolated. When we examine the sensitivity of *Pantoea agglomerans* to antibiotics, it is seen that it is resistant to TK and CL and sensitive to other antibiotics. *Proteus mirabilis* was resistant to TK, PIP, TGC, TE, TOB, CN, FEP, CRO, CAZ, and SAM, and sensitive to

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other antibiotics, except for colistin, to which it is naturally resistant.

ESBL-producing bacteria can be identified by showing resistance to CTX, CRO, CAZ, and aztreonam in routine susceptibility tests. The presence of ESBL in microorganisms causing infections is important in determining the treatment strategy (Castanheira et al., 2021). In our study, resistance patterns of ESBL positive and ESBL negative *Klebsiella* and *E. coli* strains were investigated. ESBL-negative *Klebsiella* strains were found to be sensitive to all antibiotics except TE and PIP, to which they were naturally resistant ESBL-positive *Klebsiella* strains were 61.5% SAM, 53.8% SXT, 38.5% PTZ, 30.8% TOB and GN, 15.4% TE, LEV, CIP and It was found to be resistant to CPZ/SUL. No resistance developed to MEM, IPN, CL, AK, and TGC. ESBL negative *E.coli* strains were 33.3% TK, PIP, and TE, 16.7% were resistant to CL, SAM, and CAZ, sensitive to other antibiotics, ESBL positive *E.coli* strains were 100% TK and PIP. , 87.5% SAM, 50% SXT and TE, 37.5% PTZ, 25% GN and CPZ/SUL, 12.5% LEV, CIP and TOB were found to be resistant. All ESBL-positive *Klebsiella and E. coli* strains were 100% resistant to CRO, FEP, and CAZ. Inadequate implementation of some basic rules, such as the high rate of ESBL in *E.coli* and *Klebsiella* strains isolated in our hospital, the high use of broad-spectrum antibiotics, the lack of attention to hand hygiene by healthcare professionals who are closely involved in the care and treatment of patients, and the isolation of patients infected with ESBL-producing strains may be associated with ESBL-producing microorganisms have often been found to be resistant to other antibiotics. Since treatment options are limited in infections caused by these resistant microorganisms, it is important to monitor the resistance profile and determine whether the isolated microorganisms produce ESBL. Especially *E. coli* and *Klebsiella spp*. ESBL positivity rates should be monitored regularly, and the use of broad-spectrum beta-lactam antibiotics should be decided by considering its advantages and disadvantages. Regarding colistin, since CLSI does not provide breakpoints for *Enterobacteriaceae* when testing colistin, European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC breakpoints for colistin could be used. The interpretationwas as follows: ≤2 mg/l susceptible and >2 mg//resistant (European Committee on Antimicrobial Susceptibility., 2015).

Conclusion

Our study showed that isolated Gram-negative bacteria showed high rates of antimicrobial resistance and multi-resistance in some strains. This high resistance in our hospital was mostly detected against cephalosporins, penicillins, cotrimoxazole, and quinolone group antimicrobials at rates ranging from 50% to 100%. In addition to these antimicrobials, up to 52%, carbapenem resistance was detected in Acinetobacter strains. These determined resistance rates are in dimensions that cannot be ignored. It is important to know these resistance mechanisms and to prevent their spread. When the findings in our study were evaluated, it showed that carbapenems and aminoglycosides are the most effective antimicrobials for resistant strains of GNB, except for Acinetobacter species. Colistin is considered the last-line drug for MDR Gram-negative bacteria and its susceptibility shoula be checked microbroth dilution method. Epidemiological studies to determine the characteristics of resistance are useful in guiding the clinician in empirical treatment. Considering the high resistance to antibiotics, it is necessary to reconsider antibiotic use habits in our hospital, determine rational antibiotic use policies and strictly follow these rules. Antibiotics should be used considering these data and in line with the recommendations of infection control committees. To prevent the spread of resistance, to strictly comply with hospital infection control measures, and comply with sterilization and disinfection rules, chronic patients should be followed especially in premature intensive care and pediatric intensive care units and in clinics where resistant strains are more common. To prevent the production of ESBL, first, great care should be

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taken to use antibiotics in the right indication for hospitalized patients; deciding on antibiotic therapy by making a good distinction between infection and colonization, especially in chronic patients with long-term follow-up; Inappropriate and unnecessary use of antibiotics should be avoided.

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