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Original Article

Monitoring antibiotic resistance with a cumulative antibiogram in a university hospital

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ABSTRACT

Aims: Treatment of infectious diseases is empirically regulated in many centers. It is very important to follow the antimicrobial resistance rates and resistance profile. For this, sharing the cumulative antimicrobial susceptibility results of each institution will contribute to clinicians in choosing antibiotics. This study aimed to contribute to clinicians' empirical treatment selection by determining the resistance rates of *Enterobacteriaceae* and nonfermentative gram-negative bacilli isolated from various clinical samples in hospitalized patients to some antibiotics.

Methods: A retrospective study of 23118 *Enterobacteriaceae* and 6864 non-fermentative gram-negative bacilli was performed over a 5-year period (2015-2019) at Ondokuz Mayıs University Faculty of Medicine Hospital. Isolates were identified and their antibiotic susceptibilities were determined using the Vitek MS (bioMérieux, France) system. Results were interpreted according to the EUCAST criteria of that year.

Results: The sensitivity rates of some of the investigated antibiotics have decreased over the years. Carbapenems are the most sensitive group for *Enterobacteriaceae* isolates, and aminoglycoside antibiotics remain important for non-fermentative bacteria.

Conclusion: To determine empirical treatment for microorganisms frequently isolated in the clinic and to reduce mortality and morbidity, many clinical microbiology laboratories should regularly publish cumulative antimicrobial susceptibility testing data. There is widespread agreement that cumulative antibiogram reports should be prepared and incorporated into hospital infection control policies.

Keywords: *Enterobacteriaceae*, non-fermentative bacteria, cumulative antibiogram, resistance

INTRODUCTION

Antibiotic resistance rates may vary over time and regionally. Clinical microbiology laboratories regularly share cumulative antimicrobial susceptibility testing data to determine empirical treatment for microorganisms frequently isolated in hospitals and to reduce mortality and morbidity.[1] Today, multidrug-resistant *Enterobacteriaceae* and non-fermentative gram-negative bacilli are prominent in hospital infections due to their limited treatment options and negative effects on patient survival rates.[2] Gram-negative bacilli of clinical importance in healthcare-associated infections are *Enterobacteriaceae* [especially *Klebsiella* species and *Escherichia coli (E. coli)*], *Pseudomonas aeruginosa (P. aeruginosa)* and *Acinetobacter baumannii (A. baumannii)*. Resistant strains of these bacteria are detected at high rates all over the world.[3] Antimicrobial susceptibility testing is used in hospitals to detect widespread antimicrobial resistance, monitor local trends, and guide targeted empirical treatment by determining antibiotic policy.[4] Cumulative antimicrobial susceptibility test reports are guiding in investigating resistance trends that develop over time in a region and in regulating antibiotic use. It is reported that each hospital's regular evaluation of its own data plays an important role in regulating treatment with culture and antibiogram results and preventing antibiotic resistance.[5] The aim of this study is to evaluate the cumulative antimicrobial susceptibility data of bacteria isolated from various clinical samples sent to the microbiology laboratory and to contribute to the antibiotic management policies of our hospital.

METHODS

The ethics committee approval for this study was obtained from the Ondokuz Mayıs University Faculty of Medicine Ethics Committee (Date: 27.11.2020, Decision No: 2020/657). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. A cumulative antibiogram is a cumulative report of the in vitro susceptibility percentage of clinically significant primary bacterial isolates to various antibiotics over a specific period (usually one year) in a healthcare facility. Bacterial species with >30 isolates are evaluated according to cumulative antibiogram guidelines.[6] Isolates were identified using an automated mass spectrometry microbial identification system (bioMérieux, France) employing VITEK MS, matrix-

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assisted laser desorption ionization time-of-flight (MALDI-TOF) technology, and antimicrobial susceptibility testing was performed using the VITEK® 2 COMPACT automated microbial identification system. The results were interpreted according to the criteria of the European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2020) for that year. Cumulative antibiogram reports of isolates were prepared according to the criteria in the CLSI M39-A4 2014 guideline for the analysis and presentation of antimicrobial susceptibility data and the 2019 guideline of the Association of Clinical Microbiologists (KLIMUD).[6] Bacterial species with 30 or more isolates during the study period were included in the study. Patients' first isolates were evaluated. Routinely tested antibiotics were included in the study, and susceptibility rates to these antibiotics were reported. Isolates were divided into two groups: *Enterobacteriaceae* and non-fermentative gram-negative bacilli. Descriptive statistics such as numbers and percentages were used for the samples included in the study. Routinely tested antibiotics were those tested for *Enterobacteriaceae* and non-fermentative gram-negative bacilli according to the EUCAST criteria for that year. These antibiotics are listed in the tables within the study. Antibiotics for which sensitivity rates could not be determined are left blank in the table.

RESULTS

The susceptibility rates of 23118 *Enterobacteriaceae* and 6864 non-fermentative gram-negative bacilli were retrospectively analyzed over a 5-year period (2015-2019) at Ondokuz Mayıs University Faculty of Medicine Hospital. Seven *Enterobacterales* and two non-fermentative gram-negative bacilli species were included in the study. The species distribution of the samples is shown in **Figure 1, 2**.

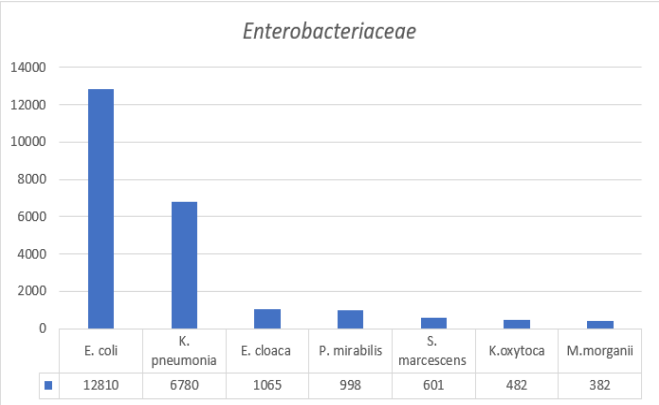

Figure 1. Types of *Enterobacteriaceae* isolates

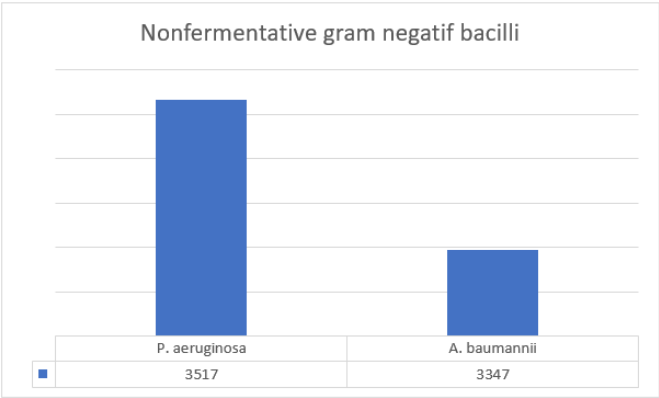

Figure 2. Types of nonfermentative gram-negative bacilli

Table 1. Antibiotic susceptibility rates of *E. coli* isolates

E. coli	2015	2016	2017	2018	2019
Ampicillin	28%	32%	32%	33%	32%
AMC	51%	47%	51%	35%	32%
Piperacillin	64.7%	63.2%	74.9%	75%	74%
Cefepim	73.6%	71.3%	49.6%	46%	40.8%
Cefixime	-	44.2%	%61.3	%52.6	%51.5
Ceftazidime	66.5%	60.6%	58.7%	52.1%	50.5%
Ceftriaxone	62.5%	60.6%	59.1%	52.2%	50.2%
Cefuroxime	54.3%	54.4%	53.7%	46.1%	43.3%
Imipenem	99.4%	99.1%	99%	94.7%	94.2%
Meropenem	99.4%	99.2%	98.8%	95.4%	93.8%
Ertapenem	97%	97%	98%	88%	92%
Ciprofloxacin	64.3%	60.2%	59.4%	51.1%	49.1%
Amikasin	86%	84%	89%	88%	90%
Gentamicin	82.8%	84.2%	83.5%	80.8%	84.3%
Tigecycline	98%	95%	94%	88%	92%

E. coli: Escherichia coli, AMC: Amoxicillin-clavulonic acid

Table 2. Antibiotic susceptibility rates of *K. pneumonia* isolates

K. pneumonia	2015	2016	2017	2018	2019
Ampicillin	NR	NR	NR	NR	NR
AMC	33%	36%	35%	26%	23%
Piperacillin	40%	40.2%	42.9%	37.5%	39.7%
Cefepim	41.4%	37.8%	34%	29.3%	23.4%
Cefixime	-	32.6%	42.7%	36.8%	34.8%
Ceftazidime	39%	36%	38.3%	32.5%	27.5%
Ceftriaxone	38%	36.1%	38.6%	33%	28%
Cefuroxime	34%	33.3%	35.2%	29.7%	26.4%
Imipenem	70.8%	74.5%	85.2%	73.6%	69.1%
Meropenem	72.8%	74.5%	81.4%	71.9%	67%
Ertapenem	59%	63%	65%	61%	59%
Ciprofloxacin	51.2%	52.6%	53.3%	43.3%	37.7%
Amikasin	73%	76%	83%	76%	70%
Gentamicin	74.2%	70.4%	68.2%	65.5%	62%
Tigecycline	80%	71%	75%	53%	53%

K. pneumonia: Klebsiella pneumonia, NR: Naturally resistant, AMC: Amoxicillin-clavulonic acid

The most frequently detected isolate among *Enterobacteriaceae* was *E. coli*, with *K. pneumoniae* coming in second. Among non-fermentative gram-negative bacilli, *P. aeruginosa* and *A. baumannii* isolates were also included in the study. When the antibiotic susceptibilities of *E. coli* isolates were compared over the years, it was observed that the susceptibilities of some antibiotics [amoxicillin-clavulonic acid (AMC), ceftazidime, ceftriaxone, imipenem, meropenem, ertapenem, ciprofloxacin] decreased. When *K. pneumoniae* isolates were examined over a five-year period, a decrease in the susceptibility rates of some antibiotics (AMC, piperacillin, cefepime, gentamicin) was observed. The highest susceptibility rates were seen with carbapenems in both groups. Antimicrobial susceptibility rates for *E. coli* and *K. pneumoniae* are given in **Table 1, 2**.

When *K. oxytoca* isolates were examined over a five-year period, AMC sensitivity decreased. No decrease in sensitivity

to other antibiotics was observed. The highest sensitivity rates were again observed in carbapenems. A decrease in cephalosporin susceptibility has been observed for *Enterobacter cloacae (E. cloacae)* isolates in the last two years. The highest susceptibility rates in both groups were observed for carbapenems and aminoglycosides. Susceptibility rates for *K. oxytoca* and *E. cloacae* are given in **Table 3, 4**.

Table 3. Antibiotic susceptibility rates *of K. oxytoca isolates*

K. oxytoca	2015	2016	2017	2018	2019
Ampicillin	NR	NR	NR	NR	NR
AMC	60.9%	74.8%	62.5%	54.9%	57%
Piperacillin	66%	79%	76%	80%	85%
Cefepim	71.6%	83.8%	72.4%	84.1%	94.3%
Cefixime	-	54.5%	80.4%	89%	75.7%
Ceftazidime	72.8%	84.8%	79%	87.6%	86.5%
Ceftriaxone	65.2%	68.5%	73.1%	83.1%	83.1%
Cefuroxime	63%	75%	72%	78%	83%
Imipenem	92.4%	96.7%	95.9%	95%	96.5%
Meropenem	96.7%	97.8%	96.6%	95.5%	96.6%
Ertapenem	77%	86%	92%	91%	97%
Ciprofloxacin	75%	93%	83%	87%	86%
Amikasin	95.6%	90%	95.8%	96.6%	96.6%
Gentamicin	76%	96%	88%	93%	97%
Tigecycline	93.75%	94.3%	92%	88.1%	96%

K. oxytoca: Klebsiella oxytoca, NR: Naturally resistant, AMC: Amoxicillin-clavulonic acid

Table 4. Antibiotic susceptibility rates of *E. cloacae* isolates

E. cloacae	2015	2016	2017	2018	2019
Ampicillin	NR	NR	NR	NR	NR
AMC	NR	NR	NR	NR	NR
Piperacillin	64%	57%	82%	58%	74%
Cefepim	80.5%	82.7%	80%	71%	72%
Cefixime	-	-	-	-	-
Ceftazidime	67%	84.8%	70.6%	59.7%	61.8%
Ceftriaxone	71.7%	68.5%	71.1%	59.7%	62%
Cefuroxime	24%	75%	6%	1%	2%
Imipenem	94%	97.6%	96.9%	93.5%	97.2%
Meropenem	95.4%	97.7%	98%	96%	97%
Ertapenem	87%	88%	92%	84%	89%
Ciprofloxacin	95%	96%	91%	80%	90%
Amikasin	97.4%	93%	96%	53.4%	98.5%
Gentamicin	95.4%	96.7%	90.5%	84%	95.8%
Tigecycline	71.7%	76.3%	89%	75.8%	84.7%

E. cloacae: Enterobacter cloacae, NR: Naturally resistant, AMC: Amoxicillin-clavulonic acid

Decreased susceptibility to ampicillin, AMC, ceftazidime, and ceftriaxone was observed in *Proteus mirabilis* isolates. Susceptibility rates for *Morganella morganii*, *Serratia marcescens* and *Proteus mirabilis* are shown in **Table 5-7**.

P. aeruginosa and *A. baumannii*, which are frequently isolated from non-fermentation bacteria, were analyzed, and their antimicrobial susceptibility rates are shown in **Table 8, 9**.

Table 5. Antibiotic susceptibility rates of *M. morganii* isolates

M. morgagni	2015	2016	2017	2018	2019
Ampicillin	NR	NR	NR	NR	NR
AMC	NR	NR	NR	NR	NR
Piperacillin	59%	76%	90%	92%	67%
Cefepim	66%	76%	92%	81%	60%
Cefixime	-	30	54.5%	46.5%	30.7%
Ceftazidime	45%	63%	73%	65%	49%
Ceftriaxone	48.5%	63.7%	75.3%	67%	52.3%
Cefuroxime	0%	3%	1%	0%	2%
Imipenem	95.2%	92.4%	93.7%	100%	88.5%
Meropenem	100%	99%	99%	100%	100%
Ertapenem	100%	97%	99%	100%	99%
Ciprofloxacin	45.4%	69%	75.3%	49.4%	52.3%
Amikasin	77%	90%	92%	99%	94%
Gentamicin	69.7%	81.3%	78%	73%	69.2%
Tigecycline	5.9%	12.8%	12%	7.9%	17.5%

M. morganii: Morganella morganii, NR: Naturally resistant, AMC: Amoxicillin-clavulonic acid

Table 6. Antibiotic susceptibility rates of *P. mirabilis* isolates

P. mirabilis	2015	2016	2017	2018	2019
Ampicillin	56.6%	52.2%	53.2%	42%	40%
AMC	86.6%	74.7%	75.3%	59.3%	69.4%
Piperacillin	94.2%	85.6%	90.2%	89.6%	96.7%
Cefepim	86.8%	79.6%	91.7%	68.6%	74.2%
Cefixime	-	69.6%	54.5%	71.7%	69.6%
Ceftazidime	84%	81%	81%	81%	79%
Ceftriaxone	89.7%	81.5%	82%	82.5%	77.5%
Cefuroxime	85.4%	80.5%	79.3%	78.1%	70.3%
Imipenem	96.7%	86%	90.8%	88.6%	93.8%
Meropenem	99.4%	92.6%	97.3%	95.7%	97.6%
Ertapenem	90.1%	86.6%	91.3%	80.7%	88.5%
Ciprofloxacin	77.7%	68.7%	77.4%	59%	60.5%
Amikasin	96%	89%	91%	88%	88%
Gentamicin	81%	73%	76%	74%	75%
Tigecycline	NR	NR	NR	NR	NR

P. mirabilis: Proteus mirabilis, AMC: Amoxicillin-clavulonic acid, NR: Naturally resistant

Table 7. Antibiotic susceptibility rates of *S. marcescens* isolates

S. marcescens	2015	2016	2017	2018	2019
Ampicillin	NR	NR	NR	NR	NR
AMC	NR	NR	NR	NR	NR
Piperacillin	73.4%	88.9%	75.2%	86.6%	90.3%
Cefepim	88.9%	95.2%	85.5%	88.1%	85%
Cefixime	-	18.2%	35.5%	-	23.8%
Ceftazidime	77.9%	90.7%	82.4%	85.9%	84.1%
Ceftriaxone	81.6%	88.1%	80.8%	82.8%	80.9%
Cefuroxime	NR	NR	NR	NR	NR
Imipenem	92.5%	99.1%	89.1%	98.2%	97.4%
Meropenem	100%	99%	93%	98%	99%
Ertapenem	88%	99%	83%	93%	95%
Ciprofloxacin	94%	94%	92%	90%	93%
Amikasin	87.7%	94.9%	85.6%	97.6%	98.4%
Gentamicin	86.7%	95.7%	84%	93.7%	97.6%
Tigecycline	22.6%	-	76%	68.4%	79.8%

S. marcescens: Serratia marcescens, NR: Naturally resistant, AMC: Amoxicillin-clavulonic acid

Table 8. Antibiotic susceptibility rates of *P. aeruginosa* isolates

P. aeruginosa	2015	2016	2017	2018	2019
Piperacillin	51.8%	56.3%	62.5%	57.3%	50.5%
Piperacillin-tazobactam	61%	56%	64.7%	61.4%	66.6%
Cefepim	72.8%	71.5%	79%	66.5%	68.8%
Ceftazidime	74.2%	76.1%	80.2%	76.9%	79.7%
Imipenem	75.5%	73%	70.8%	63.2%	64.3%
Meropenem	75.5%	73.5%	70.3%	62.5%	63.7%
Ciprofloxacin	82%	75.3%	72.6%	63.7%	63.4%
Levofloxacin	78.3%	69%	65.9%	58%	59.1%
Amikasin	90.8%	90.2%	88.2%	81.1%	79%
Gentamicin	88.8%	87.6%	87.8%	74.4%	81.9%

P. aeruginosa: Pseudomonas aeruginosa

Table 9. *Antibiotic susceptibility* rates of *A. baumannii* isolates

A. baumannii	2015	2016	2017	2018	2019
Imipenem	16.3%	13.7%	14.8%	15.4%	9.7%
Meropenem	16.5%	13.8%	14.8%	15.1%	9.6%
Ciprofloxacin	15%	92.1%	13.3%	14.1%	5.9%
Levofloxacin	15.4%	13.4%	13.4%	13.7%	9.2%
Amikasin	25%	47%	64%	73.6%	47.3%
Gentamicin	22.3%	28.2%	41.3%	38%	17.3%
Trimethoprim sulfamethoxazole	48.8%	29%	27%	25.9%	14.8%

A. baumannii: Acinetobacter baumannii

Imipenem and meropenem susceptibility were higher in *P. aeruginosa* than in *A. baumannii* isolates. Carbapenem susceptibility decreased over time in both species.

DISCUSSION

Preparation of cumulative antibiogram reports is crucial for antimicrobial stewardship.[7] Antibiotic resistance rates in *Enterobacteriaceae* and non-fermentative gram-negative bacilli vary over time. Therefore, regular reporting of antimicrobial susceptibility profiles and their characteristics is necessary for each site.[8] Because the incidence of antibiotic resistance varies geographically, clinicians need to understand regional resistance rates to best manage empiric treatment.[4] Monitoring the sensitivity rates of antibiotics used with cumulative antibiogram is an important part of antibiotic stewardship programs.[9] Choosing the right antimicrobial is possible by knowing the bacteria that are frequently identified as pathogens in the hospital and their antimicrobial susceptibility results.[6] Studies suggest that routine microbiology laboratories can contribute to the clinician's empirical treatment and to use antibiotics rationally by preparing annual cumulative antibiogram reports using data from antibiotic tests, thus achieving success in the treatment of resistant infections.[10] When we look at the studies on antimicrobial susceptibility of *Enterobacteriaceae* and non-fermentative gram-negative bacilli conducted in our country, it is observed that there has been an increase in multidrug-resistant *Acinetobacter* spp. and multidrug-resistant *P. aeruginosa* isolates, including carbapenems, and in extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* strains over the years.[11] In our study, a five-year retrospective analysis of data showed that carbapenems are still effective against *Enterobacteriaceae* but susceptibility to some antibiotics has decreased over time. Among non-fermentative bacteria, *P. aeruginosa* was found to have higher susceptibility rates to aminoglycosides, while *A. baumannii* isolates were found to have lower susceptibility rates to aminoglycosides and other antibiotics.[7] Evaluation of *E. coli* isolates revealed that the most effective antibiotics were amikacin, ertapenem, meropenem, cefotetan, fosfomycin, and piperacillin-tazobactam. Based on these results, carbapenems are the preferred antibiotic group for empirical treatment of *Enterobacteriaceae* until antibiogram results are available.[2] In a study conducted with *Enterobacteriaceae* and non-fermentative gram-negative bacilli from blood cultures, the antibiotics with the lowest resistance rates for *E. coli* and *K. pneumoniae* were found to be carbapenems, as in our study. For *P. aeruginosa* and *A. baumannii* the most effective group was found to be aminoglycosides, as in our study.[12] Various studies conducted on this subject in our country and other countries have revealed that resistance rates in *Enterobacteriaceae* and non-fermentative gram-negative bacilli have increased.[13] In a six-year study presenting antibiogram data of gram-negative bacteria, carbapenems were found to perform well for gram-negatives, but susceptibility to cephalosporins and fluoroquinolones was reduced.[14] In another study, similar to our study, it was found that susceptibility to cefepime, fluoroquinolones, aminoglycosides decreased in *Enterobacteriaceae* and non-fermentatives, and it was reported that limited prescription of carbapenems may be beneficial.[15] In a study conducted in our country on this subject, carbapenem resistance rates were found to be lower for *E. coli*, as in our study. However, carbapenem resistance rates for *Klebsiella, Pseudomonas*, and *Acinetobacter* were significantly increased.[16] A study examining data between 2014 and 2023 found a gradual increase in *E. coli* with the extended-spectrum beta-lactamase phenotype. Small but statistically significant decreases in *E. coli* susceptibility to ceftriaxone and meropenem were detected over the past decade. These data reveal a concerning trend.[17] In a study evaluating *E. coli* and *Klebsiella* spp. isolates, high susceptibility levels were observed for carbapenems, piperacillin/tazobactam, amikacin, and nitrofurantoin. It has been reported that they can be used in appropriate empirical treatment.[18] In our study, we examined the antimicrobial susceptibility profiles of the most frequently isolated bacteria by year. We sought to identify increasing resistance rates over a five-year period and the antibiotics to which the isolates were most susceptible. A disadvantage of our study is that the isolates were not discriminated against at the material level and their statistical analysis was not performed.

CONCLUSION

As a result, the resistance problem of *Enterobacteriaceae* and non-fermentative gram-negative bacilli is increasing in our region. More measures should be taken on infection control at hospital and sub-hospital level. It is thought that regular cumulative data collection may contribute to the prevention of antibiotic resistance. The cumulative antibiogram data presented in this study are expected to provide a scientific basis for updating our institution's empirical antibiotic treatment protocols and to contribute to the development of a more effective and targeted antimicrobial management strategy in the fight against antimicrobial resistance.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the the Ondokuz Mayıs University Faculty of Medicine Ethics Committee (Date: 27.11.2020, Decision No: 2020/657).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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