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RESEARCH ARTICLE

The Effect of Widespread Use of Tigecycline and Colistin on Gram-negative Bacteria with Intrinsic Resistance to Tigecycline and Colistin and Investigation of Bacterial Distribution

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ABSTRACT

Objective: Antibiotics resistance in bacteria is an important public health problem recently. Resistance rates vary from country to country, from region to region, and even from hospital to hospital. Recently, tigecycline and colistin have been widely used due to increasing multi-resistance in Gram-negative bacteria. The aim of the study was to investigate the changes in colistin and tigecycline intrinsic-resistant bacteria ratio and the effects of these drugs on the hospital flora throughout the hospital due to the widespread use of these drugs.

Materials and Methods: In our microbiology laboratory, clinical samples were processed according to the general microbiology procedure. Bacterial identification and antibiogram susceptibility tests were performed with VITEK®2 Compact, MALDI-TOF mass spectrometry (bioMérieux, France). Results were evaluated according to CLSI and EUCAST criteria. The data were scanned retrospectively between the years 2012 and 2019. Chi-square test was used in statistical analysis. Significance was evaluated at the $p<0.05$ level.

Results: While the number of *Escherichia coli* isolates decreased over the years, an increase was detected in *Klebsiella* spp. tigecycline intrinsic-resistant bacteria, *Proteus* spp., *Providencia* spp., and *Pseudomonas* spp. When evaluated with the general number of bacteria isolated over the years, *Pseudomonas* spp., a three-fold increase was found in 2018 and 2019 and in colistin intrinsic-resistant bacteria, *Morganella* spp., *Proteus* spp., *Providencia* spp., *Yersinia* spp., *Burkholderia* spp., and *Eliseabethkingea* spp. No statistically significant increase was detected. A significant increase was detected in *Serratia* spp.

Conclusion: Changes were detected in intrinsic-resistant bacteria and in antibiotic distribution. The antibiotic drugs used affect the entire flora, including the microbiota. The importance of patient care and antibiotic management should be emphasized, targeted therapies treatments should be made that the microbiota will not change, or fecal transplantation methods, which are new methods to replace microbiota, should be investigated.

Keywords: Bacterial distribution, colistin, flora, intrinsic resistance, tigecycline

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INTRODUCTION

Bacterial resistance rates vary according to patient population, hospital environment, and antibiotic used. As a result of the use of broad-spectrum antibiotics since hospitalization, the patient's flora undergoes changes.[1,2] This affects the hospital flora and bacterial distribution. In our country, according to 2015 data from the WHO's Central Asia and Eastern Europe antimicrobial surveillance network, third-generation cephalosporins and multi-drug-resistant (MDR) *Acinetobacter* spp. (carbapenem, fluoroquinolone, and aminoglycoside resistant) >50% resistance to third-generation cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems in *Klebsiella pneumoniae* isolates are between 20 and 50%.[3,4] Resistance to carbapenems is 1–86% and mortality is approximately 40–50% in the Middle East Between 2006 and 2018. [5] With increasing resistance rates over the years, an increase

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has been detected in the use of tigecycline and colistin, especially in intensive care units. Tigecycline, glycylcycline class of semisynthetic antimicrobial agents, reversibly inhibits protein synthesis by binding the 30 S ribosomal subunit of bacteria. It is similar in structure to tetracyclines. Tet (A-E) in *Acinetobacter* spp. and *Enterobacteriaceae* which is responsible for tetracycline resistance has a wider spectrum of action than tetracyclines because it is not affected by the efflux pump. Studies on tigecycline, which was approved by the FDA in 2005, show that the drug is effective in complicated skin and soft-tissue infections and complicated intra-abdominal infections. It is agreed that it is an antibiotic that can be preferred in polymicrobial infections caused by MRSA, *Enterobacteriaceae* species, ESBL-producing Gram-negatives, MDR *Acinetobacter* spp., and resistant Gram-positive cocci.[6] Resistance occurs by efflux pump and ribosomal protection mechanism. Bacteria that are intrinsically resistant to tigecycline and that we frequently encounter in the laboratory are *Proteus* spp., *Providencia* spp., and *Pseudomonas* spp.

Colistin (polymyxin E) is made up of oligopeptides synthesized outside the ribosome by *Bacillus polymyxa* subspecies colistinus. Colistin, a cationic peptide, binds to the anionic lipopolysaccharides of Gram-negative bacteria, causing the cations (Ca and Mg) to be displaced and degraded. Colistin is effective on the following bacteria: *Acinetobacter* spp., *Pseudomonas aeruginosa, Klebsiella* spp., *Citrobacter* spp., *Enterobacter* spp., *Escherichia coli*, *Salmonella* spp., *Shigella* spp., *Yersinia pseudotuberculosis*, *Haemophilus influenza*, and *Bordetella pertussis*. Common strains with intrinsic resistance are *Morganella* spp., *Proteus* spp., *Providencia* spp., *Yersinia* spp., *Burkholderia* spp., and *Serratia* spp. Resistance generally develops due to gene mutation.[7]

The aim of the study is to determine whether the intensive use of colistin and tigecycline in recent years has changed the distribution of Gram-negative bacteria in our hospital, whether there has been an increase in infections caused by microorganisms intrinsically resistant to colistin and tigecycline and how the hospital flora has changed.

MATERIALS and METHODS

In our microbiology laboratory, clinical samples were processed according to the general microbiology procedure. The principles of the Helsinki Declaration were followed. The study was approved by the local ethics committee (Number: 2019/3963). Bacterial identification and antibiogram susceptibility tests were performed with VITEK®2 Compact, MALDI-TOF mass spectrometry (BioMérieux, France). Results were evaluated according to CLSI and EUCAST criteria. The data were scanned retrospectively between the years 2012 and 2019 (as the data for 2014 was transferred to the central laboratory program, the data are irregular and excluded).

Statistical Research

Number Cruncher Statistical System Statistical Software (Utah, USA) program was used for statistical analysis. While evaluating the study data, the Chi-square test was used to compare the qualitative data. Significance was evaluated at the $p<0.05$ level.

RESULTS

The distribution of bacteria isolated according to years is given in Table 1. A statistically significant difference was found in *E. coli* isolate incidence rates ($p<0.01$). While there was an increase from 2012 to 2017, the decline in 2018 and 2019 was remarkable (Fig. 1). A statistically significant difference was found between the incidence of *Klebsiella* spp. according to years ($p<0.01$). Over the years, the incidence of *Klebsiella* has also increased (Fig. 2). No statistically significant difference was found between the incidence rates ($p>0.05$) of *Enterobacter* spp., *Morganella* spp., *Proteus* spp., and *Providencia* spp. over the years. A statistically significant difference was found between the incidence of *Acinetobacter* spp. ($p<0.01$) and *Citrobacter* spp. ($p<0.05$) according to years, *Pseudomonas* spp. a three-fold increase was found in 2018 and 2019. In colistin intrinsic-resistant bacteria, *Morganella* spp., *Proteus* spp., *Providencia* spp., *Yersinia* spp., *Burkholderia* spp., and *Eliseabethkingea* spp., no statistically significant increase was detected. A significant increase was detected in *Serratia* spp. (Figs. 3, 4).

DISCUSSION

Resistance has become an important public health problem in recent years.[8] Especially in large-scale hospitals, hospital infections with resistant strains in areas with critical patient groups such as intensive care units, transplantation units, and hematology-oncology clinics cause mortality, morbidity, and also cost increases. It affects the distribution of bacteria by causing changes in the hospital flora. In our study, changes in bacterial distribution according to years were determined. When Gram-negative bacterial infections in our hospital were evaluated (their distribution according to years is given in Table 1), *E. coli* was the most common Gram-negative bacteria. While *E. coli* tended to decrease in the past 2 years (2018–2019) compared to previous years, an increase was observed in *K. pneumoniae* isolates and carbapenem-resistant *Klebsiella* spp. strains have also increased over the

Table 1. Evaluations of microorganisms isolated according to years (2012–2019)

	n	2012–2013	2015	2016	2017	2018	2019	p
Escherichia coli	15624	3256 (57.8)	2800 (57.2)	2175 (61.7)	2812 (62.4)	2204 (48.2)	2377 (42.8)	<0.001**
Klebsiella spp.	5312	943 (16.7)	848 (17.3)	679 (19.3)	811 (18.0)	861 (18.8)	1170 (21.1)	<0.001
Enterobacter spp.	1133	201 (3.6)	198 (4)	134 (3.8)	185 (4.1)	196 (4.3)	219 (3.9)	0.524
Morganella spp.	286	61 (1.1)	58 (1.2)	36 (1)	45 (1)	38 (0.8)	48 (0.9)	0.486
Citrobacter spp.	319	61 (1.1)	61 (1.2)	30 (0.9)	52 (1.2)	37 (0.8)	78 (1.4)	0.047*
Proteus spp.	1062	223 (4)	202 (4.1)	121 (3.4)	164 (3.6)	149 (3.3)	203 (3.7)	0.234
Providencia spp.	32	5 (0.1)	6 (0.1)	4 (0.1)	6 (0.1)	5 (0.1)	6 (0.1)	0.992
Pseudomonas spp.	2811	504 (8.9)	372 (7.6)	200 (5.7)	245 (5.4)	669 (14.6)	821 (14.8)	<0.001**
Burkholderia spp.	34	10 (0.2)	0 (0)	3 (0.1)	1 (0)	9 (0.2)	11 (0.2)	0.005**
Acinetobacter spp.	1363	220 (3.9)	243 (5.0)	104 (2.9)	132 (2.9)	263 (5.8)	401 (7.2)	<0.001**
Serratia spp.	368	86 (1.5)	54 (1.1)	27 (0.8)	36 (0.8)	71 (1.6)	94 (1.7)	0.001**
Sphingomonas spp.	62	18 (0.3)	5 (0.1)	0 (0)	5 (0.1)	5 (0.1)	29 (0.5)	0.001**
Stenotrophomonas	278	47 (0.8)	47 (1.0)	13 (0.4)	10 (0.2)	64 (1.4)	97 (1.7)	0.001**
Total	28684	5635	4894	3526	4504	4571	5554	

Chi-square test; *: p<0.05; **: p<0.01

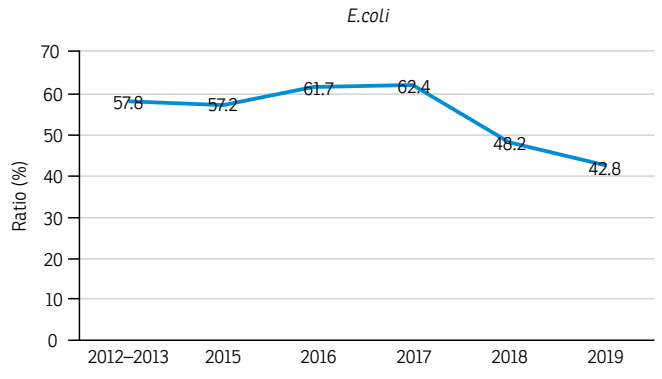

Figure 1. *Escherichia coli* distribution

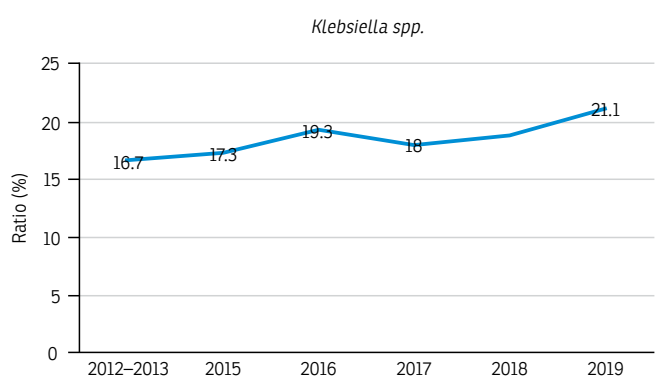

Figure 2. *Klebsiella* spp. distribution

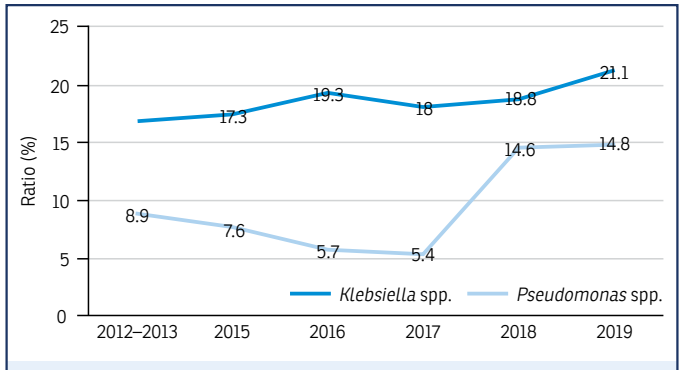

Figure 3. *Klebsiella* spp. and *Pseudomonas* spp. distribution

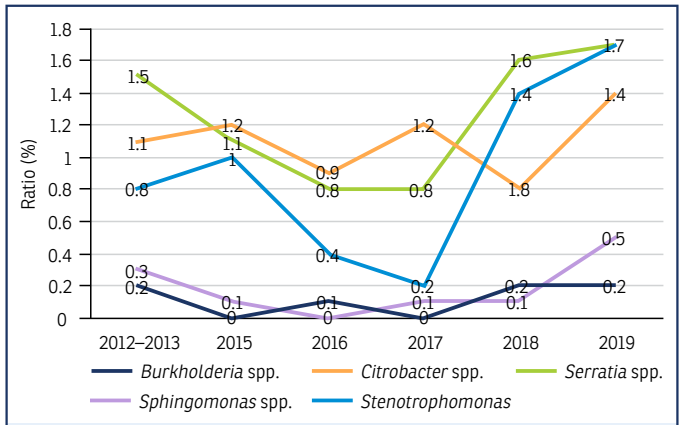

Figure 4. *Burkholderia* spp., *Citrobacter* spp., *Serratia* spp., *Sphingomonas* spp., *Stenotrophomonas* spp. distribution

years. While there was no significant increase in tigecycline intrinsic-resistant *Proteus* spp. and *Providencia* spp., a three-fold increase was observed in *Pseudomonas* spp. strains in recent years (2018–2019). No increase was detected in colistin intrinsic-resistant strains *Morganella* spp., *Proteus* spp., *Providencia* spp., and *Yersinia* spp. Although the increase in *Burkholderia* spp. was statistically significant, it was excluded because the number of bacteria was low. An increase was detected in colistin intrinsic-resistant *Serratia* spp. in 2018 and 2019. The most striking finding is a three-fold increase in *Psedomonas* spp. In different studies, the effects of antibiotics used on the flora and the environment were examined.[9] It has been emphasized that patient care-related infections and antibiotic management should be improved.[8] It is emphasized that the care conditions of hospital environments should be improved and colonization and contamination should be prevented in long-term hospitalizations.[10] Depending on the intensity of the antibiotic drugs used, changes occur in the flora and this cross-contamination may affect other patients.[11] In our study, there was an increase in some of the intrinsic-resistant bacteria and changes in bacterial distribution were observed. Changes in the composition of the gut microbiota, known as dysbiosis, can be induced by a variety of exogenous factors, probably the most important being antimicrobial use. The results of different studies showed that; Taking into account the antibiotic pharmacokinetic and pharmacodynamic properties, new strategies for selective digestive decontamination and fecal microbiota transplantation to regulate the gut microbiota have also been tested in different conditions with variable results. The modulation of the gut microbiota and its effects on infection control and antimicrobial management were investigated. At a further stage, gut microbiota profiling through metataxonomic analysis may provide further insight into modulating microbial communities in the context of infection prevention and control. New strategies for selective digestive decontamination and fecal microbiota transplantation to regulate the gut microbiota have also been tested in different conditions with variable results.[12,13] In our study, the distribution of Gram-negative bacteria by years was examined, but advanced methods and metataxonomic analyzes could not examine the gut microbiota profile. Due to the increasing associations between an impaired microbiota and susceptibility to infectious disease, research has been directed toward new approaches that protect the microbiota while eliminating pathogens, in particular[14] and new possibilities and treatment modalities have been produced in which wholesale replacement of the microbiota can be used as a highly effective treatment.

CONCLUSION

As a result, to prevent the change in the flora, controlling infection, improving health-care services, and preventing long-term and broad-spectrum use of unnecessary antibacterials, new methods such as developing targeted treatment strategies that protect the microbiota or fecal transplantation after antibiotic use can be tried.

Disclosures

Ethics Committee Approval: The study was approved by the Ümraniye Training and Research Hospital Clinical Research Ethics Committee (No: 2019/3963, Date: 20/02/2019).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer reviewed.

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

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