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EVALUATION OF PATHOGENS AND ANTIBIOTIC RESISTANCE PROFILES ISOLATED FROM LOWER RESPIRATORY TRACT SAMPLES

ALT SOLUNUM YOLU ÖRNEKLERİNDEN İZOLE EDİLEN PATOJENLER VE ANTİBİYOTİK DİRENÇ PROFİLLERİNİN DEĞERLENDİRİLMESİ

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Abstract

Objective: In this study, we aimed to guide clinicians in planning empirical treatment and contribute to regional data by presenting bacterial lower respiratory tract infection agents and antibiotic resistance profiles.
Methods: All lower respiratory tract samples from patients admitted to our laboratory between January 01 and December 31, 2021 were evaluated retrospectively. Bacterial identification and susceptibility tests were performed using the VITEK 2 automated system and evaluated in accordance with the recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).
Results: Significant growth was detected in 461 of 923 lower respiratory tract samples. Antibiotic susceptibility test results of 340 samples were evaluated after excluding the repeated samples of same patient. Gram negative bacteria was isolated in 309 (90.9%), *Staphylococcus aureus* in 17 (5%) and *Candida albicans* in 14 (4.1%) of 340 samples. The most frequently isolated Gram-negative bacteria were *Pseudomonas aeruginosa* (121, 39.2%), *Acinetobacter baumannii* (88, 28.5%), *Klebsiella pneumoniae* (64, 20.7%) and *Escherichia coli* (36, 11.6%), respectively. Resistance rates of *A. baumannii* isolates to carbapenems, piperacillin/tazobactam, ceftazidime and fluoroquinolones were found to be over 90%, and higher resistance was observed in intensive care units (ICU) than in wards.
Conclusion: The increased antibiotic resistance observed in lower respiratory tract infections from hospitalized patients in ICUs, is remarkable. As a result, knowing the causative agents and current resistance profiles is important, especially for hospitalized patients in ICUs, in order to initiate appropriate empirical treatment and to ensure treatment success. The data obtained from our study will guide clinicians in planning empirical treatment.

Keywords: *Lower respiratory tract infections, antibiotic resistance, Acinetobacter baumannii, Pseudomonas aeruginosa*.

Öz

Amaç: Bu çalışmada hastanemize başvuran hastalardan izole edilen bakteriyel alt solunum yolu enfeksiyonu etkenleri ve antibiyotik direnç profilleri ortaya konularak ampirik tedavinin planlanmasında klinisyenlere yol gösterici olmak ve bölgesel verilere katkı sağlamak amaçlanmaktadır.
Yöntem: Hastanemiz farklı birimlerine 01 Ocak – 31 Aralık 2021 tarihleri arasında başvuran hastalardan gönderilen alt solunum yoluna ait tüm örnekler retrospektif olarak değerlendirildi. Tespit edilen etkenlerin tanımlama ve duyarlılık testleri VITEK 2 otomatize sistemi kullanılarak yapıldı. Antibiyotik duyarlılıkları ise European Committee on Antimicrobial Susceptibility Testing (EUCAST) önerileri doğrultusunda değerlendirildi.
Bulgular: Toplam 923 alt solunum yolu örneğinden 461'inde anlamlı üreme saptandı. Aynı hastaya ait tekrarlayan örnekler ve az sayıda üreyen bakterilerin olduğu örnekler çıkarıldığında kalan 340 örneğe ait antibiyotik duyarlılık test sonuçları değerlendirildi. 340 örnekten 309'unda (%90,9) Gram negatif bakteriler izole edilirken 17'sinde (%5) *Staphylococcus aureus*, 14'ünde (%4,1) *Candida albicans* üredi. En sık izole edilen Gram negatif bakteriler sırasıyla *Pseudomonas aeruginosa* (121, %39,2), *Acinetobacter baumannii* (88, %28,5), *Klebsiella pneumoniae* (64, %20,7) ve *Escherichia coli* (36, %11,6) idi. *A. baumannii* izolatlarının karbapenem, piperasilin/tazobaktam, seftazidim ve florokinolon direnç oranları %90'ın üzerinde saptandı ve yoğun bakım ünitelerinde (YBÜ) servislere göre daha yüksek direnç izlendi.
Sonuç: Özellikle YBÜ'lerinde yatan hatan hastalardan izole edilen alt solunum yolu enfeksiyonu etkenlerinde gözlenen artmış antibiyotik direnci dikkat çekicidir. Sonuç olarak solunum yolu enfeksiyonu etkenlerinin ve güncel direnç profillerinin bilinmesi özellikle YBÜ'leri gibi riskli birimlerde yatan hastalarda, hızla uygun ampirik tedaviye başlanması ve tedavi başarısının sağlanması açısından önemlidir. Çalışmamızda elde ettiğimiz verilerin ampirik tedavinin planlanmasında klinisyenlere yol gösterici olacağı düşünülmektedir.

Anahtar kelimeler: *Alt solunum yolu enfeksiyonları, antibiyotik direnci, Acinetobacter baumannii, Pseudomonas aeruginosa.*

Introduction

Respiratory tract infections are among the disease groups where antibiotic use is most common. Significant changes can be observed in the causative bacteria and antibiotic resistance profiles depending on whether they are community-acquired or health-related infections. *Streptococcus pneumoniae* and *Haemophilus influenza*, members of the *Enterobacteriaceae* family, *Staphylococcus aureus, Enterococcus* spp are the most common community-acquired agents, while *Acinetobacter baumannii* is encountered with increased resistance rates especially in hospital-acquired infections.[1,2]

Lower respiratory tract infections are the most common bacterial infection in the intensive care unit (ICU) patient population, occuring in 10-25% of all ICU patients and resulting in mortality rates of 22-71%.[3,4] The presence of underlying comorbidities, invasive procedures, prolonged hospitalisation and the use of broad-spectrum antibiotics in ICU patients make them more susceptible to infections. In addition, the widespread long-term use of broad-spectrum antibiotics in treatment also predisposes to the development of resistance in microorganisms.[5,6] The widespread antimicrobial drug resistance and multidrug-resistant microorganisms also complicate the treatment of invasive infections.[7]

Knowledge of common infectious agents and their current resistance profiles is important in guiding the empirical treatment to be initiated in the period until the identification of the pathogen at the genus and species level and reporting including antibiotic susceptibility testing. Bacteria causing respiratory tract infections and antibiotic resistance rates may vary by country, region, hospital and even clinic.[6]

Considering this situation, it is important for hospitals to prevent their own up-to-date data, to shape empirical treatment, to monitor these changes, to start appropriate empirical treatment rapidly and to ensure a higher rate of treatment success.

In this study, it is aimed to provide guidance to clinicians in the planning of empirical treatment and to contribute to regional data by revealing the bacterial lower tract infection agents and their antibiotic resistance profiles isolated from patients admitted to our hospital during a one-year period.

Methods

In this study, all specimens of the lower respiratory tract (sputum, bronchoalveolaer lavage (BAL), tracheal aspirate, etc.) sent to the Medical Microbiology Laboratory of Afyonkarahisar Health Sciences University Medical Faculty Hospital between January 01- December 31 2021 from patients admitted to different units of our hospital were retrospectively evaluated. Sputum and tracheal aspirate specimens sent with a culture request and optained properly, with >25 neutrophils/field and <10 squamous epithelium/field in Gram stained preperation according to Bartlett scoring were included in the evaluation. The samples were cultured on 5% sheep blood agar, chocolate agar and EMB (Eozin Methylene Blue) agar media. Cultivation of BAL samples was performed using quantitative method. The cultured plates were incubated at 35±1°C for 18-24 hours and the incubation time was extended to 48-72 hours when necessary. Identification of the grown microorganisms was performed using conventional methods (Gram staining, catalase, coagulase, oxidase, germ tube etc.) and VITEK 2 (bioMérieux, Fransa) automated system. Antibiotic susceptibilities were evaluated by VITEK 2 in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations.[8] Broth microdilution, which is the reference method for determining colistin susceptibility, could not be applied and the resistance rates given are the results obtained from the automated system. Antifungal susceptibility tests were also performed using VITEK 2 (bioMérieux, Fransa) automated system. Data were obtained from the hospital automation system, pathogens isolated from the lower respiratory tract samples and antibiotic resistance profiles were evaluated. The first bacteria isolated from the patients and their antibiotic resistance rates were evaluated. Repeated isolates from the same patient were not included in the study.

Statistical Analysis

IBM SPSS 25 (IBM CORP NY, ABD) programme was used for statistical analysis. In addition to the descriptive statistics of the data, the percentage expression of the findings was analysed. Chi-square test was used to compare categorical variables. The results were considered statistically significant when $p<0.05$.

Results

Between January 01–December 31 2021, 923 lower respiratory tract specimens from a total of 709 different patients were sent to our laboratory. Significant growth was detected in 461 of these samples and antibiotic susceptibility test were performed. The distribution of all bacteria isolated from the samples is shown in Table 1.

Table 1. Distribution of infectious agents isolated from lower respiratory tract specimens [n (%)]

Agent	n (%)
Pseudomonas aeruginosa	170 (36,87)
Acinetobacter baumannii	113 (24,51)
Klebsiella pneumoniae	73 (15,83)
Escherichia coli	37 (8,02)
Staphylococcus aureus	21 (4,55)
Candida albicans	17 (3,68)
Proteus mirabilis	7 (1,51)
Serratia spp.	4 (0,86)
Enterococcus spp.	3 (0,65)
Streptococcus pneumoniae	3 (0,65)
Pseudomonas spp.	3 (0,65)
Achromobacter xylosoxidans	2 (0,43)
Citrobacter spp.	2 (0,43)
Enterobacter cloacae	2 (0,43)
Non-albicans Candida	2 (0,43)
Klebsiella oxytoca	1 (0,21)
Stenotrophomonas maltophilia	1 (0,21)
Total	**461 (100)**

After excluding repetitive speciemens from the same patient and specimens with a small number of growing bacteria from the 461 specimens, the remaining 340 were included in the study to evaluate antibiotic resistance. Of these samples, 71.2% were male, 28.8% were female. When analysed by age groups, 52.6% of the patients were over 65 years of age and 38.2% were between 40-65 years of age. Of the samples evaluated, 170 (50%) were isolated from tracheal aspirate, 91 (26.8%) from suputum and 79 (23.2%) from BAL samples. In 309 (90.9%) of 340 samples, Gram-negative bacteria were the predominant organism, while

Staphylococcus aureus was isolated in 17 (5%) and *Candida albicans* in 14 (4.1%). The most frequently isolated Gram-negative bacteria were *Pseudomonas aeruginosa* (121, 39.2%), *Acinetobacter baumannii* (88, 28.5%), *Klebsiella pneumoniae* (64, 20.7%) and *Escherichia coli* (36, 11.6%). The most frequently isolated bacteria and their distribution according to clinics are given in Table 2. It was observed that 73%, 53%, 42% and 39% of the patients with *A. baumannii, K. pneumoniae, P. aeruginosa* and *E. coli* isolated from lower respiratory tract samples were hospitalized in the intensive care unit, respectively.

The most frequently isolated bacteria and their antibiotic resistance rates are shown in Table 3. Methicillin resistance (MRSA) was found in 35.3% of *S. aureus* isolates. Penicillin resistance was found in 82.3% of *S. aureus* isolates, while no resistance to vancomycin, teicoplanin and linezolid was observed.

The incidence of extended spectrum beta lactamase (ESBL) was 40.6% and 25% in *K. pneumoniae* and *E. coli* isolates, respectively. Resistance rates of *A. baumannii*, *K. pneumoniae* and *P. aeruginosa* strains isolated from patients in ICU and wards to frequently used antibiotics are given in Table 4. A statistically significant difference was found between ward and ICU strains in ciprofloxacin and piperacillin/tazobactam susceptibility for *P. aeruginosa* ($p<0.05$). As a result of the analysis of variance, amikacin and carbapenem resistance rates of *P. aeruginosa* isolates from ICU and ward inpatients were statistically significant (p<0.001). Although the resistance rates for *K. pneumoniae* were relatively lower, a significant difference was observed between ICU and ward samples (Table 4).

While no resistance to amphotericin B, caspofungin, flucytosine and micafungin was detected in *C. albicans* strains, 14,3% resistance to fluconazole and voriconazole was observed.

Table 2. Number and distribution of the most frequently isolated bacteria according to clinics [n (%)]

	Internal Intensive Care	Surgical Intensive Care	Internal Clinics	Surgical Clinics	Total
Pseudomonas aeruginosa	31	21	60	9	**121 (35,5)**
Acinetobacter baumannii	38	26	11	13	**88 (25,9)**
Klebsiella pneumoniae	18	16	27	3	**64 (18,8)**
Escherichia coli	12	2	18	4	**36 (10,6)**
Staphylococcus aureus	2	4	10	1	**17 (5,0)**
Candida albicans	6	-	6	2	**14 (4,1)**
Total	**107 (31,47)**	**69 (20,29)**	**132 (38,82)**	**32 (9,41)**	**340 (100)**

Table 3. Antibiotic resistance rates of most frequently isolated bacteria (%)

Antibiotic	***P. aeruginosa* (n=121)**	***A.baumannii* (n=88)**	***K.pneumoniae* (n=64)**	***E.coli* (n=36)**	***S. aureus* (n=17)**
Benzyl Penisillin	-	-	-	-	82,3
Ampicillin	-*	-	65,6	36,1	-
Piperacillin/Tazobactam	50,4	87,5	60,9	30,6	-
Cefoksitin	-	-	32,8	8,3	35,3
Ceftriaxone	-	-	42,2	25	-
Ceftazidime	43,6	-	59,4	36,1	-
Cefepime	44,6	-	48,4	25	-
Imipenem	27,3	90,9	10,9	0	-
Meropenem	21,5	87,5	29,7	0	-
Ertapenem	-	-	32,8	0	-
Erythromycin	-	-	-	-	29,4
Clindamycin	-	-	-	-	52,9
Tetracycline	-	-	-	-	11,7
Tigecycline	0	1,1	-	5,6	0
Gentamicin	22,3	55,7	14,1	19,4	0
Tobramycin	12,4	30,7	-	-	-
Amikacin	17,4	71,6	10,9	0	-
Trimethoprim/Sulfamethoxazole	-	-	42,2	30,6	5,8
Ciprofloxacin	33,1	90,9	62,5	52,8	11,8
Levofloxacin	28,1	88,6	-	-	5,9
Vankomycin	-	-	-	-	0
Teicoplanin	-	-	-	-	0
Linezolid	-	-	-	-	0
Colistin**	5,8	2,3	1,6	0	-

* Antibiotic not tested.
**Based on automated system data.

Table 4. Antibiotic resistance rates of the most frequently isolated bacteria in intensive care units (ICU) and services (%)

	Antibiotic Resistance %								
	P.aeruginosa			***A. baumannii***			***K.pneumoniae***		
	ICU (n=52)	**Service (n=69)**	***p***	**ICU (n=63)**	**Service (n=25)**	***p***	**ICU (n=34)**	**Service (n=30)**	***p***
Piperacillin/Tazobactam	69,2	36,2	**0,002**	92,1	76,0	**0,001**	76,5	43,3	**0,02**
Ceftazidime	57,7	33,3	**0,044**	92,1	80,0	**0,012**	76,5	40,0	**0,009**
Imipenem	46,2	13,0	**0,00**	98,4	72,0	**0,00**	14,7	6,7	**0,005**
Meropenem	36,5	10,1	**0,00**	92,1	76,0	**0,014**	41,2	16,7	0,090
Amikacin	32,7	5,8	**0,00**	76,2	60,0	0,29	11,8	10,0	0,17
Ciprofloxacin	50,0	20,3	**0,008**	96,8	76,0	**0,002**	79,4	43,3	**0,003**
Levofloxacin	34,6	23,2	0,300	95,2	72,0	**0,006**	11,8	6,7	**0,015**

Discussion

In respiratory tract infections where antibiotic use is very common, the etiologic agents are influenced by many factors such as the patient's age, comorbidities and the presence of risk factors, and treatment is often initiated empirically. Accurate estimation of the etiological agent is important in order to apply appropriate empirical treatment. Incorrect antbiotic selection is among the important factors that play a role in the development of resistance. Pneumonias are among the leading healthcare-associated infections seen in ICU and are among the important causes of morbidity and mortality.[9] Nonfermantative Gram-negative bacteria such as *P. aeruginosa* and *A. baumannii* are the most common agents.[5,10,11]

Multidrug resistance (MDR) observed in Gram-negative bacteria has reached alarming levels worldwide over the years. According to a study in the USA, 78% of Gram negative bacteria were resistant to all antibiotics except colistin (62% of *Acinetobacter* spp., 59% of *Pseudomonas* spp. and 52% of *Enterobacter* spp.).[12] It was observed that 37% of the nosocomial *A. baumannii* infections reported in France between 2001-2011 were respiratory tract infections.[13] According to the European Antimicrobial Resistance Surveillance Network (EARS Net) 2016 report, the MDR rate in invasive *Acinetobacter spp.* isolates in European Union (EU) countries varies between 0-84%, with EU average of 31.7%.[14] According to the National Antimicrobial Resistance Surveillance System (UAMDSS) 2016 data in our country, MDR in invasive *Acinetobacter* spp. isolates was reported as 83,5% and colistin resistance was reported as 6,7%.[15]

In different studies conducted in our country, antibiotic resistance rates in *Acinetobacter* isolates have been found to increase gradually over the years. In our study, carbapenem, piperacillin/tazobactam, ceftazidime and fluoroquinolone resistance rates were high in *A. baumannii* isolates and resistance rates were statistically significantly higher in ICUs than in wards. In our study, carbapenem resistance was found to be 90.9% for *Acinetobacter* isolates, whereas Özünel et al. found carbapenem resistance to be 86.7% for *Acinetobacter* strains from tracheal aspirate cultures between 2012-2013, Aydemir et al. found imipenem resistance of 93.3% in *Acinetobacter* strains grown in endotracheal aspirate cultures in 2015-2016.[3,5] In the study conducted by Sağmak Tartar et al. carbapenem resistance was found 97.7% for *Acinetobacter* isolates.[16] Similar to our data, Altay Koçak et al. found that carbapenem, fluoroquinolone, ceftazidime and piperacillin/tazobactam resistance rates of *A. baumannii* isolates were above 90% and resistance rates were higher in ICUs than in wards.[17] They determined that colistin resistance, which is becoming a worldwide problem, was lower than the national average (2%). In our study, it would not be correct to comment on colistin resistance in *A. baumanni* isolates since it was not confirmed by the reference method.

High resistance rates observed in *Pseudomonas aeruginosa* strains are encountered especially in ICUs. Different resistance rates have been reported in our country, ranging between 8-59% for imipenem and 18-47% for meropenem.[4-6,17,18] In our study, resistance rates of 27.3% for imipenem and 21.5% for meropenem are compatible with the data of our coutry and suggest that ther may be difficulties in treatment in the future. In addition, increasing resistance rates lead to the use of colistin in *P. aeruginosa* infections and colistin resistance was found to be 5.8% in our study. According to the surveillance data of our country, the rate of MDR isolates in invasive *P.aeruginosa* isolates is 32.6% and colistin resistance in these isolates is 5.2%.[15] Küme and Demirci determined the most susceptible antibiotics of *Pseudomonas* strains from lower respiratory tract samples of patients in ICUs as amikacin, piperacillin/tazobactam, imipenem, gentamicin, ciprofloxacin, cefaperazone-sulbactam and tobramycin, respectively.[19] In our study, 41.4% of *P. aeruginosa* isolates from ICU patients and the most resistant antibiotics were piperacillin/tazobactam (50.4%), cefepime (44.6%) and ceftazidime (43.8%).

In UAMDSS data, carbapenem resistance in invasive *K. pneumoniae* isolates was found to be around 40% and MDR was 46,1%.[15] Altay Koçak et al. found carbapenem resistance 42.4% in *K. pneumoniae* isolates, 79,5% of which were isolated from patients in ICU.[17] In our study, capbapenem resistance rates were lower and were 10.9, 29.7 and 32.8% for imipenem, meropenem and ertapenem, respectively. According to the 2020 data in the Antimicrobial Resistance Surveillance in Europe 2022 report, carbapenem resistance in *E. coli* strains was 3.7% and ciprofloxacin resistance was 69%.[20] Carbapenem resistance was not detected in *E. coli* strains and ciprofloxacin was the most resistant antibiotic with a resistance rate of 52.8%.

According to UAMDSS 2016 data, the rate of MRSA in invasive *S. aureus* isolates was 23.6%. [15] According to the 2020 data in the Antimicrobial Resistance Surveillance in Europe 2022 report, the EU average of MRSA in invasive *S. aureus* isolates was 16.7% and the average of our country was 33.4%.[14] In our study, the MRSA rate was similar to the national average (35.3%) and penicillin resistance rates were similar to 82.3%.

Conclusion

In conclusion, intensive and uncontrolled use of antibiotics increases the selection and spread of resistant strains. Antibiotic susseptibilities of microorganisms vary from hospital to hospital, between clinics in the same hospital and even from year to year. In our study, we found that the growth of resistant bacteria was higher in ICUs than in wards, and especially the high carbapenem resistance found in *A. baumannii* isolates leads to treatment difficulties. Although it is not yet a serious problem for our hospital, there is a need for us to determine our own microorganism distribution and resistance status. So that we can regulate empirical treatment protocols like every other centre in order to be prepared for possible drug resistances that may develop in frequently isolated *P. aeruginosa* and *K. pneumoniae* isolates. Continuous and close follow-up of resistant infections in all healthcare institutions, rapid infection control measures and rational use of antibiotics will make a great contribution to prevent the development of resistance.

Limitations

The most important limitation of our study is that no reference method for the detection of colistin resistance was used in our laboratory during the period when the data were retrospectively analysed. The resistance data obtained from the automated system. Therefore, it would be wrong to comment on colistin resistance in *A. baumannii* isolates.

Conflict of Interest

The author declares no conflict of interest related to this article.

Compliance with Ethical Statement

Approval for this study was obtained from Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (03.12.2021-2021/13/556-2011-KAEK-2).

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Author Contribution

Study idea/Hypothesis: MG; Study design: MG, PÇ; Data preparation: MG, PÇ, HA, GŞ, FUA; Literature search: MG, PÇ, HA, GŞ, FUA; Manuscript writing: MG, PÇ

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