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Risk factors for antibiotic-resistant respiratory infections among patients requiring ward admission

Kerem Ensarioğlu, Berna Akıncı Özyürek, Tuğçe Şahin Özdemirel, Esma Sevil Akkurt, Özlem Özdağ, Hasan İbiş, Almıla Sena Akın Şencan

Department of Chest Diseases, Ankara Atatürk Sanatorium Training and Research Hospital, University of Health Sciences, Ankara, Turkiye

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ABSTRACT

Aims: The airway flora has been recognized as non-sterile, and sputum sampling is recommended for hospitalized patients with respiratory infections. Empiric antibiotic treatment is often initiated without culture confirmation, potentially contributing to antimicrobial resistance. This study aims to assess the influence of demographic factors, prior antibiotic use, and other risk factors on resistant respiratory cultures in ward-admitted patients.

Methods: A single-center cohort study was conducted in a pulmonary medicine ward of a tertiary hospital between the dates of March 2024 and September 2024. Patients over 18 years old with sputum, bronchoalveolar lavage (BAL), or endotracheal aspiration culture results were included. Demographic characteristics, comorbidities, vaccination status, prior infections, respiratory support needs, antibiotic history, and hospital admission records were collected. Nonparametric statistical analyses were used to evaluate associations, including the Mann-Whitney U and Kruskal-Wallis tests.

Results: Among 70 patients (mean age 68 ±9 years, 87% male), chronic obstructive pulmonary disease (COPD) (71.4%) was the most prevalent comorbidity. A total of 75.7% of cultures were from sputum samples, with *Pseudomonas* spp. (27.1%), *Klebsiella pneumoniae* (20%) and *Escherichia coli* (14.3%) being the most frequently isolated organisms. Resistant cultures were more common in patients with intensive care unit (ICU) admission history (p=0.007), intubation history (p=0.003), and non-invasive mechanical ventilation (NIMV) use (p=0.038). No correlation was found between prior antibiotic use and resistance.

Conclusion: ICU admission and respiratory support requirements were key risk factors for resistance. Contrary to previous studies, prior antibiotic use and comorbidities did not significantly impact resistance rates. These findings highlight the need for targeted antimicrobial stewardship and careful risk assessment among patients requiring pulmonary ward admission.

Keywords: Antimicrobial resistance, hospitalization, respiratory tract infections, risk factors

INTRODUCTION

The airway and its associated anatomical structures have been known to possess their own flora and are thus no longer assumed to be aseptic in nature. Guidelines suggest that while not mandatory for outpatient evaluations, sputum sampling should be performed for patients requiring inpatient care due to respiratory diseases.[1] While this suggestion remains especially important for patients with additional comorbidities and repeated admission history due to inadequate sampling, issues with sample care and transportation, patients being not suitable for sputum sampling or further invasive methods for airway sampling, in many cases, empiric treatment of respiratory infections is often initiated without a supporting culture result. Studies regarding possible causes of resistant culture originating from the respiratory tract remain an important topic, as respiratory infections remain the most common cause of infectious-related hospital admissions.[2]

Recent studies have shown that, over time, respiratory tract sampling results have been growing more resistant to standard treatment, with a higher sample count being reported.[3,4] In addition to being innate depending on the species, drug resistance is affected by environmental factors, including former antibiotherapy history and patient-related factors.[3] *Streptococcus pneumoniae, Haemophilus influenzae, Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Staphylococcus* spp. could be counted among commonly isolated samples with varying degrees of resistance. While originating from different families, the presence of resistant gram-positive coccus, pseudomonal, or actinobacteria spp. requires aggressive and specific treatment, with recommendations in place even for cases where a definitive culture with resistance could not be observed for patients with known risk factors.[5]

Corresponding Author: Kerem Ensarioğlu, kerem.ensarioglu@gmail.com

Current guidelines and studies consider recent intensive care unit (ICU) admission, antibiotherapy history within three months, immunosuppressive states, and structural lung diseases as leading risk factors of resistant respiratory infection presence. Initially performed for pneumonia evaluation, similar studies have been performed for other underlying respiratory diseases, including chronic obstructive pulmonary disease (COPD). Pailhories et al.[3] stated that antibiotherapy regimens over time had changed the underlying microbiome in patients, with Zhao et al.[6] reporting similar findings in patients with cystic fibrosis.

In this study, we aimed to investigate the potential role of demographic parameters, former antibiotherapy regimens, and other risk factors on the resistant respiratory sampling results from patients requiring ward admission.

METHODS

The study was prepared as a single-center cohort study in the pulmonary medicine ward of a tertiary hospital. The study was conducted with the permission of the Scientific Studies Ethics Committee of Ankara Atatürk Sanatorium Training and Research Hospital (Date: 28.02.2024, Decision No: 2024-BÇEK/7). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study evaluated patients who were admitted to the pulmonary medicine ward between the dates of March 1, 2024 and September 1, 2024.

Patients who were over 18 years old and had at least one sputum, bronchial lavage, bronchoalveolar lavage (BAL), or endotracheal aspiration culture result were included in the study. Per the pulmonary medicine ward's routine testing, at least one sampling for sputum was performed for all patients unless other contraindicated, such as those with active hemoptysis. Exclusion criteria could be summarized as refusal to participate, inadequate patient information available due to the patient's wishes, and inadequate treatment duration in the ward, defined as a requirement for admission to another ward or ICU during the initial admission. Patients admitted for interventional procedures or additional pulmonary treatments which required admission such as chemotherapy were also removed from the study.

Patients' demographic characteristics, comorbidities, vaccination status, and history of smoking and alcohol were retrieved from the hospital records. Patients' infectious disease history, including former tuberculosis history, coronavirus disease 2019 (COVID-19) history, and any respiratory infection presence among caregivers, were also noted. Respiratory support requirements, including long-term oxygen support (LTOT) and non-invasive mechanical ventilation (NIMV), former antibiotic history within three months, and hospital admission status within a year prior to the study, were recorded from the national healthcare database. The definition of immunosuppressive treatment history included any treatment that was stated to be a treatment regimen equal to 20 mg methylprednisolone daily for at least 21 days. These statements and results were altogether present in a questionnare given to the patients, and was filled under the supervision of at least one pulmonary medicine specialist. The data present in the system and answers given to the questionnare were double-checked and any discrepancies were further validated with patients.

A culture result from respiratory tract sampling, which included sputum, bronchial lavage, BAL or endotracheal aspiration, was deemed positive if a specific bacteria or species were reported. A sample result was considered resistant if the culture was evaluated as resistant to high-use antibiotics for respiratory infections. A sample was deemed inadequate if inappropriate sampling was observed, such as above 10 epithelial cells per low power field for sputum sampling or contamination for BAL samples. If a sample was observed to be inadequate, that sample was removed from the study, and the patient was excluded from the study if the mentioned sample was the sole result of culture evaluation.

Total positive culture counts, including resistant culture counts, as a definition, included the count of culture that was observed during the patient's ward admission. The total positive culture count consists of any positive result, which includes the resistant samples. All analyses were performed separately for each group.

Statistical Analysis

The patients' results were put into a Microsoft Excel file for overall evaluation. After investigating any mis-input and values, the data were moved to a statistics module (IBM Version 25th for Windows). The initial assessment was performed by descriptive analysis, for which values were given with mean and standard deviation or with median and 25th to 75th percentiles as required. Parametric distribution was evaluated using a Q-Q plot analysis. Spearman's rho was utilized to analyze correlations between nonparametric scale variables. Mann-Whitney U test was used for nonparametric group comparison. Kruskal Wallis test was utilized for nonparametric comparison for groups with more than two nominal groups. P values at or below 0.05 were accepted as statistically significant. The study's sample size was calculated by G.Power 3.1.9.7. To evaluate a difference from the constant, due to the lack of a control group in the study by design; at least 53 patients were required to investigate an effect size of 0.5, with a type 1 error of 0.05% and power of 95%.

RESULTS

A total of 348 patients' admissions were investigated between the dates of March 1, 2024 and September 1, 2024. After the exclusion of repeated admissions (n=44), patients admitted due to chemotherapy regimens (n=120), patients admitted to ICU (n=19), and patients admitted to other wards (n=14), the remaining 151 patients were included in the study. Fourteen patients were excluded due to inadequate data, while 67 patients refused to participate in the study. The remaining 70 patients were accepted as the study population. Most of the patients were male (n=61), and the mean age was 68 (±9). Fifty-seven (81.4%) of the patients had a smoking history, with a mean smoking package/year of 51 (±29), and less than half of the patients had consumed alcohol regularly (n=31, 44.3%). COPD was the most prominent respiratory comorbidity (n=50, 71.4%), followed by lung carcinoma (n=17, 24.3%) and bronchiectasis (n=8, 11.4%). Other prevalent comorbidities

were hypertension (n=23, 32.9%) and diabetes mellitus (n=14, 20%). Twenty-five (35.7%) patients had a former COVID-19 history, 12 patients (17.1%) had a history of tuberculosis (including those treated for latent tuberculosis), and 16 patients (22.9%) had a former immunosuppressive treatment history. Six patients had a respiratory infection among caregivers or companions at home (Table 1).

Table 1. Demographic parameters and comorbidities

Parameters		**n (%)**
Gender	Male	61 (87.1)
	Female	9 (12.9)
Age (years, SD)		68 (9)
Smoking history	No	13 (18.6)
	Present	57 (81.4)
Smoking (package/year, SD)		51 (29)
Chronic obstructive pulmonary disease	No	20 (28.6)
	Present	50 (71.4)
Asthma	No	66 (94.3)
	Present	4 (5.7)
Bronchiectasis	No	62 (88.6)
	Present	8 (11.4)
Lung carcinoma	No	53 (75.7)
	Present	17 (24.3)
Interstitial lung disease	No	66 (94.3)
	Present	4 (5.7)
Hypertension	No	47 (67.1)
	Present	23 (32.9)
Coronary arterial disease	No	60 (85.7)
	Present	10 (14.3)
Congestive heart failure	No	64 (91.4)
	Present	6 (8.6)
Diabetes mellitus	No	56 (80)
	Present	14 (20)
Extrapulmonary malignancies	No	68 (97.1)
	Present	2 (2.9)
Alcohol	No	39 (55.7)
	Present	31 (44.3)
Tuberculosis history	No	58 (82.9)
	Present	12 (17.1)
COVID-19 history	No	45 (64.3)
	Present	25 (35.7)
Immunosuppressive treatment history	No	54 (77.1)
	Present	16 (22.9)
Respiratory infection among caregivers	No	64 (91.4)
	Present	6 (8.6)

SD: Standard deviation

Most patients were vaccinated for COVID-19 (n=67, 95.7%). Pneumococcal (n=28, 40%) and seasonal flu (n=38, 54.3%) vaccinations were also prevalent among patients. The majority of the patients (n=45, 64.3%) had been on LTOT, while 15 patients (21.4%) also required NIMV. Fifty-seven (81.4%) patients had at least one emergency ward admission history, with a median admission count of 3 (1-5) within a year. The median admission to a pulmonary medicine ward was reported to be 1 (0-2), with nearly half (n=37, 52.9%) of the patients requiring at least one admission. ICU history was present in 27 (38.6%) patients, with seven (10%) requiring intubation. Antibiotic usage within 3 months before admission was observed in 37 (52.9%) patients, with oral penicillin or cephalosporin regimens being the most reported antibiotic regimens (59.5%) (Table 2).

Table 2. Vaccination, respiratory support requirement, admission history and antibiotic usage of patients

Parameters		**n (%)**
Seasonal flu vaccination	No	32 (45.7)
	Performed	38 (54.3)
Pneumococcal vaccination	No	42 (60)
	Performed	28 (40)
COVID-19 vaccination	No	3 (4.3)
	Performed	67 (95.7)
Long term oxygen support	No	25 (35.7)
	Present	45 (64.3)
Non-invasive mechanical ventilation	No	55 (78.6)
	Present	15 (21.4)
Emergency ward admission history	No	13 (18.6)
	Yes	57 (81.4)
Emergency ward admission count (median, 25^{th}-75^{th})		3 (1-5)
Ward admission history	No	33 (47.1)
	Yes	37 (52.9)
Ward admission count (median, 25^{th}-75^{th})		1 (0-2)
Intensive care admission history	No	43 (61.4)
	Yes	27 (38.6)
Intubation history	No	63 (90)
	Yes	7 (10)
Antibiotic usage before admission	No	33 (47.1)
	Yes	37 (52.9)
Antibiotic regimen before admission	Oral penicillin or *Cephalosporin regimens*	22 (59.5)
	Macrolides	4 (10.8)
	Macrolides and oral penicillin/ Cephalosporin combination	7 (18.9)
	Respiratory fluoroquinolones	4 (10.8)

A median of 2 (1-3) positive culture counts with a median of one (1-2) count of resistant culture results were observed. Most cultures were from sputum samples (n=53, 75.7%). The most observed specimen in culture sampling was pseudomonas species (n=19, 27.1%), followed by Klebsiella pneumonia (n=14, 20%) and Escherichia coli (n=10, 14.3%). In correlation analysis, emergency ward admission count did not correlate with positive or resistant culture counts (p-value 0.243 and 0.120, respectively). Ward admission was observed to be weakly associated with resistant culture count (p-value 0.005 and correlation coefficient 0.329). However, no correlation

Table 3. Correlation between positive culture results and admission

Parameters		Positive culture count	Resistant culture count
Positive culture count (median, 25th-75th)			2 (1-3)
Resistant culture count (median, 25th-75th)			1 (1-2)
Sample origin	Sputum		53 (75.7)
	Lavage		14 (20)
	Endotracheal aspiration		3 (4.3)
Culture result	*Pseudomonas spp*		19 (27.1)
	Klebsiella pneumoniae		14 (20)
	Escherichia coli		10 (14.3)
	Enterobacteria spp		8 (11.4)
	Acinetobacter spp		4 (5.7)
	Moraxella catarrhalis		4 (5.7)
	Stenotrophomonas maltophilia		5 (7.1)
	Serratia spp		3 (4.3)
	Streptococcus pneumonia		1 (1.4)
	MRSA		1 (1.4)
	Haemophilus influenzae		1 (1.4)
Positive culture count	Correlation coefficient		0.804
	p value		0.001
Resistant culture count	Correlation coefficient	0.804	
	p value	0.001	
Emergency ward admission count	Correlation coefficient	0.141	0.188
	p value	0.243	0.120
Ward admission count	Correlation coefficient	0.221	0.329
	p value	0.066	0.005

spp: Species, MRSA: Methicillin resistant Staphylococcus aureus Spearman's Rho was used for correlation analysis

was observed with positive culture count (p-value 0.066) (Table 3).

Regarding culture count results, vaccination status, and former infectious disease history (tuberculosis and COVID-19) did not differ. Similarly, culture results did not vary according to comorbidities (Table 4).

Patients requiring NIMV support were observed to have a higher resistant culture count compared to those without (p-value 0.038); this observation was not present regarding the LTOT requirement. Intubation history affected both positive and resistant culture counts, as patients requiring intubation had a higher count in both groups (p-values 0.026 and 0.003, respectively). Patients with a history of ICU admission had a higher count of resistant culture sampling. However, a difference was not observed regarding the total positive culture count (p-values 0.007 and 0.149, respectively). Antibiotic usage before admission did not vary between groups (Table 4).

Resistant culture presence was found to be correlated with sample origin, with endotracheal sample results being more positive for resistance; however, the patient distribution within groups was not considered sufficient for analysis. Culture results and antibiotic regimen types did not affect the positive and resistant culture counts.

DISCUSSION

The study showed that ward admission was correlated, albeit weakly, with resistant culture counts, similar to ICU admission history, while other admission histories, including emergency ward admission, did not affect positive or resistant culture counts. Despite having a role in resistant culture results, ward admission and ICU admission history did not affect overall positive sampling. Comorbidities, a history of the former infectious disease, and antibiotic usage before admission also did not affect overall and resistant culture presence. Respiratory support requirement also had affected culture results, with patients requiring NIMV having a higher resistant culture count, while those with intubation history have a higher positive and resistant culture count. LTOT requirement was an exception, as patients did not vary in terms of culture results depending on oxygen support. These observations overall state that, for patients requiring pulmonary ward admission, different factors may contribute as risk factors to microbial resistance.

ICU admissions have been evaluated as a risk factor for resistance in bacterial isolates, with studies suggesting an increase in resistant sampling among patients in ICU units.[7] Former hospital admission was also shown as an additional risk factor for resistant sampling among ICU patients.[8] While

Table 4. Correlation between culture results and risk factors

Parameters		Positive culture count				Resistant culture count		
		n	Mean rank	Z	p	Mean rank	Z	p
Seasonal flu vaccination	No	32	35.59	-0.037	0.97	36.17	-0.3	0.764
	Performed	38	35.42			34.93		
Pneumococcal vaccination	No	42	34.13	0.729	0.466	32.87	1.568	0.117
	Performed	28	37.55			39.45		
Smoking history	No	13	36.5	-0.209	0.835	39.35	-0.894	0.371
	Present	57	35.27			34.62		
Alcohol	No	39	35.78	-0.138	0.891	37.47	-1.078	0.281
	Present	31	35.15			33.02		
Tuberculosis history	No	58	33.48	1.929	0.054	34.7	0.858	0.391
	Present	12	45.25			39.38		
COVID-19 history	No	45	33.56	1.135	0.257	34.1	0.914	0.361
	Present	25	39			38.02		
Immunsuppresive treatment history	No	54	35.48	0.015	0.988	35.09	0.364	0.716
	Present	16	35.56			36.88		
Long term oxygen support	No	25	30.92	1.485	0.138	30.28	1.893	0.058
	Present	45	38.04			38.4		
Non-invasive mechanical ventilation	No	55	33.57	1.605	0.108	33.27	2.075	0.038
	Present	15	42.57			43.67		
Chronic obstructive pulmonary disease	No	20	32.98	0.695	0.487	32.35	0.969	0.332
	Present	50	36.51			36.76		
Bronchiectasis	No	62	34.42	1.308	0.191	35.23	0.361	0.718
	Present	8	43.88			37.56		
Lung carcinoma	No	53	35.46	0.029	0.977	35.71	-0.178	0.858
	Present	17	35.62			34.85		
Hypertension	No	47	36.4	-0.562	0.574	36.1	-0.414	0.679
	Present	23	33.65			34.28		
Coronary arterial disease	No	60	35.69	-0.204	0.838	34.93	0.675	0.499
	Present	10	34.35			38.9		
Diabetes mellitus	No	56	35.82	-0.109	0.913	35.15	0.339	0.735
	Present	14	35			36.89		
Intensive care admission history	No	43	32.87	1.442	0.149	31.07	2.721	0.007
	Yes	27	39.69			42.56		
Entubation history	No	63	33.79	2.226	0.026	33.48	2.954	0.003
	Yes	7	50.86			53.71		
Antibiotic usage before admission	No	33	32.92	1.058	0.29	32.38	1.434	0.151
	Yes	37	37.8			38.28		

Z: Standardized Test Statistic. Independent Samples Mann-Whitney U test was utilized for the analysis.

ICU admission does not necessarily require a wide-spectrum regimen empirically, such as in pneumonia management, a history of ICU admission appears to be a risk factor for more resistant samples.[9] For *Pseudomonas aeruginosa*, this observation was stated in the study of Restrepo et al.[10], in which independent risk factors were reported for resistant *Pseudomonas aeruginosa* samples. All hospitalization history was stated to be a risk factor, in addition to COPD, indwelling catheter, and former respiratory infection history. Our study presents similar results and states that while ICU admission is a risk factor for resistant sampling, it does not increase the number of positive culture samples for patients admitted to the ward overall. Regarding ward admission, unlike ICU admission, studies remain limited, as most definitions were created with hospital admission in mind or included long-term facility care in addition to ward admission. Under these definitions, a review by Tacconelli[11] supports hospital admission within a year as a separate risk factor for resistant culture presence. Our results differ in these observations, as while ICU admissions remain a risk factor, other admissions were not considered a risk factor. This might be attributed to the respiratory nature of the study, as patients with other

comorbidities or those admitted due to non-respiratory causes may differ in resistance evaluation.

Microbial resistance is routinely attributed to former antibiotic usage, with even treatment regimens narrowed to a positive culture result, causing possible resistance later during the clinical course.[12] Former resistance culture presence has been reported as an area of interest, with one study recommending the exclusion of a drug that was reported to be resistant in a positive culture result within a year.[13] In our study, former treatment history or infectious disease history did not affect the positive or resistant sampling count. This could be attributed to the select patients of the pulmonary ward having different susceptibility or that, while the presence of a positive culture might be related, the culture count did not correlate well with the patients, especially those with respiratory comorbidities.

Vaccination history also did not correlate with microbial resistance in our study. Current literature supports vaccination's protective role in combatting possible resistance, especially in low-resource settings.[14] While our study did have patients with different vaccination histories and combinations of vaccines, a correlation could not be observed. This could be explained by patient selection, as those in the respiratory ward might be admitted due to pathogens that could not be targeted with vaccines, such as resistant species of Pseudomonas or Acinetobacter, as stated by the formerly referenced study and a review by Mishra et al.[14,15] Another factor could be that, while vaccination may protect against most commonly encountered pathogens, patients requiring admission to the pulmonary ward could have already been treated for these pathogens empirically before admission. Thus, an extensive treatment approach could have masked the protective role of vaccination.

An unexpected observation in our study was the lack of correlation between former treatment history and microbial resistance despite patients having a variety of former treatment histories. A possible contributing factor to this lack of correlation could be the exact duration of the former treatment and the general approach of abstaining from the same regimens upon admission. As stated by Kuster et al.[16], repeated treatment with the same regimen is often not chosen for the sake of possible underlying resistance, and the main component of failure, if such regimens were indeed chosen, would be the exact time of the former treatment. This exact time of former treatment, rather than the given range of three months, could have affected the presence of resistance; however, our study's design and difficulty of estimation of former treatment made the given range a more viable evaluation method.

Limitations

The study's main limitation was the patient population, in which more than 70% of the possible patients had to be excluded due to the study's design. While this was performed to evaluate the remaining patients better, excluding patients admitted for daily interventions, such as chemotherapy, might have caused a selection bias. However, including these patients could have caused unintentional issues, as patients admitted for treatment had already been screened for possible infectious processes and were also susceptible to infection as per the nature of underlying malignancy and immunosuppression from treatment regimens. Altogether, these factors would have affected the results. The detailed questionnaires also contributed to the limited patient pool, as patients and their caregivers had refused to participate in roughly half of the cases, with the majority of them stating that they would not be able to give adequate answers, were not sure if they could give correct answers, or refused to answer due to personal reasons. This also could be counted as a selection bias, as more cooperative patients had partaken in the study, naturally contributing to a larger study pool, while those with issues that limited this could not participate. As such, while we believe a reasonable estimation of possible risk factors was present in the study, patients with a lower socioeconomic and/or educational status may not be adequately represented. With a larger group of patients, we believe the results, at least regarding the pulmonary ward, would not have changed; however, a subgroup analysis, especially in the case of confirmed bacterial samples, such as Pseudomonas spp, could have been made.

CONCLUSION

Antibiotic resistance remains a topic of interest among patients admitted to the pulmonary ward. Risk factors contributing to resistant culture presence may not affect overall culture positivity. While the role of comorbidities and former treatment appears to be limited, sufficient demographic information, especially with the inclusion of former admission history and additional respiratory support requirements, appears to provide information regarding microbial resistance. As such, patients with these characteristics should be considered for possible resistance.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Scientific Studies Ethics Committee of Ankara Atatürk Sanatorium Training and Research Hospital (Date: 28.02.2024, Decision No: 2024-BÇEK/7).

Informed Consent

All patients signed and free and informed consent form.

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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