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Necessity of Alternative Strategies to Combat Antibiotic Resistant Strains Detected in Northern Cyprus

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Abstract

BACKGROUND/AIMS: Antibiotic resistance is becoming an important global health crisis. This study aims to investigate the alteration in the distribution and antibiotic resistance patterns of pathogens isolated from aspirate and sputum samples of patients admitted to a microbiology laboratory in Northern Cyprus over a period of 5 years.

MATERIALS AND METHODS: A total of 3669 samples between 2018 and 2022 were involved in the study retrospectively. The VITEK 2 (bioMérieux) compact automated system was used for microorganism identification and antibiotic susceptibility tests. Antibiotic susceptibility tests were evaluated according to the European Committee on Antimicrobial Susceptibility Testing criteria, and antibiotics detected as intermediate were considered resistant.

RESULTS: While the five-year growth rate was 52.7%, these rates were 52.0%, 51.6%, 45.5%, 52.2% and 61.1% in 2018, 2019, 2020, 2021 and 2022, respectively. Of the bacterial growth, 82.7% (n=1597) were gram-negative, 8.9% (n=171) were gram-positive, and 8.5% (n=164) were Candida species. Accordingly, the most frequently isolated gram-negative bacteria were *Pseudomonas aeruginosa* (20.3%) and *Acinetobacter baumannii*-calcoaceticus complex (18.3%), which were most resistant to aztreonam (78%), levofloxacin (70.5%), and imipenem (69.1%). *Klebsiella pneumoniae* (18.0%) showed resistance to ampicillin (91.1%) and cefuroxime (63.1%). The most frequently isolated gram-positive bacteria were *Staphylococcus aureus* (62%) and *Enterococcus* spp. (29.2%) The rate of methicillin-resistant *S. aureus*, extended-spectrum beta-lactamase, and vancomycin-resistant enterococci was 55.7%, 43.3%, and 6%, respectively, with high resistance to erythromycin (45.5%) and tetracycline (40.7%).

CONCLUSION: Identifying highly resistant pathogens indicates the need for close monitoring of patients and the development of alternative treatment approaches to reduce antibiotic resistance against commonly used antibiotics.

Keywords: Drug resistance, anti-bacterial agents, infectious diseases

INTRODUCTION

Antibiotics have been among the most important medical achievements in treating infectious diseases over the last few decades.[1] The use of antimicrobials, while critical to improving our health and quality of life, has led to the development of antimicrobial resistance (AMR) in recent years, which poses a major threat. The most important consequences of AMR are treatment failure, the risk of global spread of resistant infections, the triggering of serious diseases, prolonged hospital

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stay and treatment, and consequently increased healthcare costs and significant mortality rates. More and more organisms are becoming multidrug-resistant (MDR), and the infections they cause are more difficult to treat. However, extensively drug-resistant and pandrug-resistant organisms, which are the serious and dangerous forms, are of critical concern.[2] The World Health Organization (WHO) estimated that AMR directly caused 1.27 million deaths and contributed to 4.95 million deaths worldwide in 2019.[3] In addition to its negative impact on mortality and morbidity, AMR has a significant economic impact. The Centers for Disease Control and Prevention estimates that healthcare costs of AMR infections are 4 to 5 billion United States Dollars (USD), annually. Additionally, the World Bank projects estimate an increase of 1 trillion USD in healthcare expenditures by 2050 and alongside annual gross domestic product losses ranging from 1 trillion to 3.4 trillion USD by 2030.[3-5]

The increase in AMR infections, especially following the coronavirus disease-2019 (COVID-19) pandemic, is considered a global public health crisis at the human, veterinary and environmental levels.[6] There will be an impact on the ecosystem, agricultural output, impoverished conditions, health security, and the United Nations Sustainable Development Goals, highlighting the necessity of a multisectoral One Health plan to reduce AMR.[4] The continuous prevalence of this silent pandemic particularly affects clinically significant *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter species*, and *Escherichia coli* (ESKAPEE) pathogens. This is putting increased pressure on the healthcare, veterinary, and agricultural sectors.[7] Although official statistics on antibiotic use and AMR in the Turkish Republic of Northern Cyprus (TRNC) are not available on the official websites of the Ministry of Health, studies on AMR in the TRNC have revealed that AMR poses an increasing threat to both the health sector and society in Northern Cyprus.[8,9] Therefore, the study aimed to demonstrate the distribution and antibiotic resistance patterns of pathogens isolated from aspirate and sputum samples, and to raise awareness about the necessity of alternative treatments in the fight against AMR.

MATERIALS AND METHODS

The study involved 3669 sputum and aspirate samples taken from both inpatients and outpatients admitted to the University Hospital between 2018 and 2022. The results of the patients were evaluated as a single study group and not as community and hospital environment groups. The patient's demographic data, such as age and gender, were included. Microbial detection and antibiotic susceptibility testing were performed using the VITEK 2 (bioMérieux) automated system and were evaluated according to the European Committee on Antimicrobial Susceptibility Testing criteria.[10] The ethical approval of the study was obtained from the Near East University Ethical Committee (approval number: 2023/112, date: 30.03.2023). Informed consent forms were not obtained from the patients as the study was conducted retrospectively.

Statistical Analysis

The SPSS Demo Ver 22 (SPSS Inc., Chicago, IL, USA) software package was used for statistical analysis. Pearson chi-square, Fisher's exact test, and one-way ANOVA tests were used to analyze variables, and p-values <0.05 were considered significant.

RESULTS

Of the samples, n=1121 (57.6%) were aspirates and n=424 (42.4%) were sputum. Microbial growth was reported in 52.7% (n=1932/3669) of the samples. Of those with growth, 58% were aspirates and 42% were sputa. No growth was detected in 47.3% (n=1737) of the specimens in the study. Sixty-five percent (n=1254) of the patients with bacterial growth were male, while 35.1% (n=678) were female. The mean age of these female patients was 69.63 ± 17.17 years (range 0-100 years). In the study, the growth rate in males was higher than that of females (p=0.012). By years, the growth rates were 52.0% (270/519), 51.6% (313/607), 45.5% (363/798), 52.2% (n=467/895%) and 61.1% (519/850), in 2018-2022 respectively. The highest growth rate was detected in 2022, with an increase of 61.1% compared to the previous years, indicating statistical significance (p=0.0001). Of the bacterial growth, the rates of gram-negative bacteria, gram-positive bacteria, and Candida species were found to be 82.7% (n=1597), 8.9% (n=171), and 8.5% (n=164), respectively. The most commonly identified gram-positive bacteria were *S. aureus* (62%, 106/171) and *Enterococcus* spp. (29.2%, 50/171). Methicillin-resistant *S. aureus* (MRSA) was detected at a rate of 55.7% (59/106). The rate of vancomycin-resistant enterococci (VRE) was 6% (3/50). Amongst gram-negative bacteria, enteric and non-enteric bacteria were reported at 46.6% (n=744) and 53.4% (n=853), respectively. *K. pneumoniae (*46.6%, 347/744) and *E. coli* (19.5%, 145/744) were the most commonly isolated enteric bacteria, while *P. aeruginosa* (46.0%, 392/853) and *A. baumannii* (42.1%, 359/853) were the most common non-enteric bacteria (Figure 1). The extended-spectrum beta-lactamase (ESBL) positivity rate in gram-negative enteric bacteria was 43.3%. This rate was 41.3% (202/489) in males and 47.1% (120/255) in females; no statistically significant relationship was found between sex and ESBL positivity (p=0.133). When we compared gender and MRSA rates, it was found that females (62.7%, 32/51) had more MRSA strains in cultures compared to males (41.7%, 20/48), which was statistically significant (p=0.036)

Antibiotic resistance patterns in enteric bacteria (Table 1) between 2018 and 2022 show that the highest resistance was detected in ampicillin (91.1%), cefuroxime (63.1%), and ceftriaxone (49.5%) while the highest sensitivity was reported for amikacin (87.5%), gentamicin (85.1%), and meropenem (83.7%). Amongst non-enteric bacteria (Table 1), the highest resistance was reported to aztreonam (78%), levofloxacin (70.5%), and imipenem (69.1%), while the highest sensitivity was observed for colistin with a rate of 93.4%. For gram-positive bacteria, the highest resistance was reported against erythromycin (45.5%), clindamycin (35.4%), and tetracycline (40.7%), while the highest sensitivity was reported for tigecycline, linezolid, and daptomycin with rates of 99.2%, 98.1%, and 92.1%, respectively (Table 2). Table 2 shows antibiotic profiles in gram-positive bacteria between 2018 and 2022. The highest resistance was reported against tetracycline (40.7%), erythromycin (45.5%), and clindamycin (35.4%).

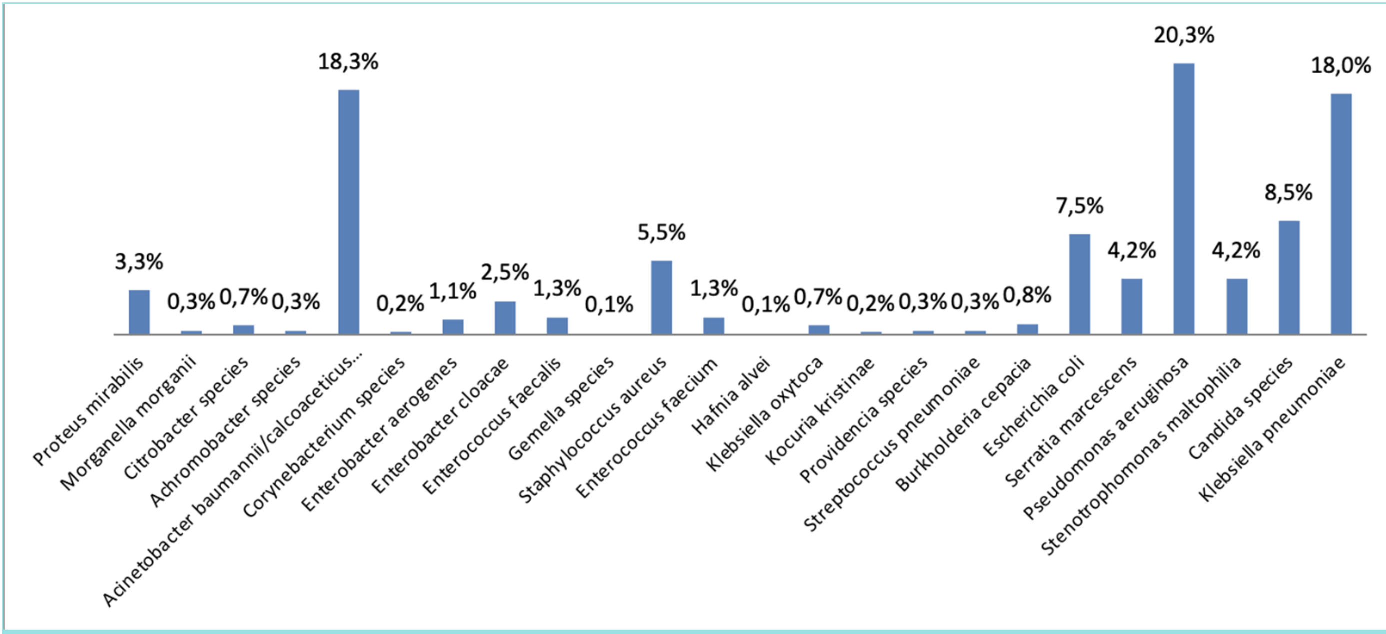

Figure 1. Distribution of bacteria isolated from sputum and aspirate samples between 2018-2022 (%).

Table 1. The antibiotic resistance patterns in gram-negative bacteria

Antibiotic	Enteric bacteria (%) sensitive	resistant	Antibiotic	Non-enteric bacteria (%) sensitive	resistant
Amikacin	87.5	12.5	Amikacin	58.1	41.9
Ampicillin	8.9	**91.1**	Aztreonam	22.0	**78.0**
Aztreonam	60.6	39.4	Cefepime	45.2	54.8
Cefepime	55.8	44.2	Ceftazidime	49.6	50.4
Ceftazidime	56.3	43.7	Ciprofloxacin	32.3	67.7
Ceftriaxone	50.5	**49.5**	Colistin	93.4	6.6
Cefuroxime	36.9	**63.1**	Gentamicin	46.3	53.7
Ciprofloxacin	56.2	43.8	Imipenem	30.9	**69.1**
Ertapenem	72.1	27.9	Levofloxacin	29.5	**70.5**
Gentamicin	85.1	14.9	Meropenem	31.4	68.6
Imipenem	82.5	17.5	Netilmicin	38.7	61.3
Meropenem	83.7	16.3	TZP	42.8	57.2
TZP	66.4	33.6	Tigecycline	83.4	16.6
Tigecycline	72.2	27.8	Tobramycin	57.3	42.7
SXT	64.4	35.6	SXT	34.9	65.1

TZP: Tazobaktam, SXT:Sulfamethoxazole + Trimethoprim (Bactrim, Septra).

Table 2. The antibiotic resistance patterns in Gram-positive bacteria

Antibiotic	Sensitive (%)	Resistant (%)
Ciprofloxacin	73.6	26.4
Clindamycin	64.6	**35.4**
Daptomycin	92.1	7.9
Erythromycin	54.5	**45.5**
Gentamicin	84.2	15.8
Levofloxacin	76.0	24.0
Linezolid	98.1	1.9
Teicoplanin	91.5	8.5
Tetracycline	59.3	**40.7**
Tigecycline	99.2	0.8
SXT	65.4	34.6
Vancomycin	95.8	4.2

SXT: Sulfamethoxazole.

DISCUSSION

AMR continues to pose an increasing threat globally. This study investigated the distribution of pathogens and drug resistance profiles against various antibiotics over 5 years. Bacterial growth was detected in aspirate/sputum samples over 50%, the peak growth rate was detected in 2022 (61.1%), and the lowest growth rate was detected in 2020 (45.5%). The restrictions implemented during the last pandemic may have caused a decrease in access to healthcare systems in 2020, which may have led to a false report of a reduction in bacterial growth rates. However, by 2022, many countries had lifted COVID-19 restrictions (such as masks and distancing), which increased person-to-person contact and bacterial transmission. Additionally, people who avoided hospitals in previous years may have contracted more severe bacterial infections in 2022. These factors may have also contributed to the increased growth rate. Additionally, the significant difference in microbial growth between males and females may be due to various factors such as underlying diseases, smoking, and exposure to infection.

Our findings revealed that high levels of resistance to some important pathogens including *P. aeruginosa*, *A. baumannii*/calcoaceticus complex, *K. pneumoniae,* MRSA, VRE, and ESBL were in circulation in Northern Cyprus between 2018 and 2022. Additionally, due to ESBL detection at notable rates and the presence of significant MRSA resistance especially in women, it is important to investigate the underlying causes such as access to health care, predisposing factors, or healthcare-related exposure. The isolated pathogens in the study were highly resistant to major antibiotics such as ampicillin (91.1%), aztreonam (78%), levofloxacin (70.5%), imipenem (69.1%), cefuroxime (63.1%), erythromycin (45.5%) and tetracycline (40.7%). The high rate of resistance to these antibiotics appears to pose a serious risk to public health and hospital infection management. The WHO reported that overuse of antibiotics in COVID-19-infected hospitalized patients during the pandemic triggered AMR. Globally, although only 8% of these patients had bacterial co-infections requiring antibiotics, approximately 75% of them received prophylactic antibiotic treatment, which may have triggered the trend of antibiotic overuse.[11] During the COVID-19 outbreak in Northern Cyprus, the application of prophylaxis regimens to hospitalized patients and unnecessary antibiotic use by the community may have led to an increase in resistant pathogens. This situation demonstrated the importance of antimicrobial stewardship policies. A similar study conducted in Nepal revealed that *P. aeruginosa* (30.7%), *A. baumannii* (29.8%), *Burkholderia* spp. (1%) and *Stenotrophomonas* spp. (2.8%) had high growth rates, and these pathogens were highly resistant to cefepime (95%), imipenem (92%), and levofloxacin (86%), highlighting the need to monitor resistant pathogens to reduce mortality.[12] In China, *P. aeruginosa*, *A. baumannii*, and *K. pneumoniae* were the most commonly isolated pathogens in sputum samples with the highest resistance to all antibiotics tested except colistin, indicating AMR that AMR is widespread worldwide.[13] On the other hand, colistin, used as one of the last resort antibiotics against MDR infections, has excellent efficacy against *A. baumannii* and *K. pneumoniae*, indicating the appropriate use of colistin in our hospital.

Study Limitations

Firstly, since the study only included sputum/aspirate samples, it may not reflect the resistance patterns of all microorganisms circulating in the population. Secondly, we did not separately evaluate the community and hospitalized patients or their antibiotic resistance profiles. Therefore, the study does not provide the main origin of the resistant strains. Also, molecular analysis was not performed to identify resistant strains and virulence genes in the study.

CONCLUSION

The detection of antibiotic-resistant pathogens suggests that infection control measures should be implemented alongside antibiotic resistance surveillance. Due to increasing resistance rates, more research is needed on developing alternative treatment options such as phage therapy, CRISPR-Cas 9, and new antibiotics, to combat resistant bacterial strains effectively. In addition, unnecessary and excessive use of antimicrobials should be monitored, and the community should be educated on limiting such use in the country.

MAIN POINTS

- Highly resistant pathogens were in circulation between 2018 and 2022 in Northern Cyprus.
- Close monitoring of patients and the development of alternative treatment approaches are needed to reduce antibiotic resistance to commonly used antibiotics.
- Unnecessary and excessive use of antimicrobials should be monitored in the country.

ETHICS

Ethics Committee Approval: The ethical approval of the study was obtained from the Near East University Ethical Committee (approval number: 2023/112, date: 30.03.2023).

Informed Consent: Informed consent forms were not obtained from the patients as the study was conducted retrospectively.

Footnotes

Authorship Contributions

Concept: E.G., K.S., A.A., Design: E.G., K.S., A.A., Data Collection and/or Processing: E.M.O., E.G., Analysis and/or Interpretation: E.M.O., E.G., K.S., A.A., Literature Search: E.M.O., Writing: E.M.O., E.G., K.S.

DISCLOSURES

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

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