CASE REPORT

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Non-Prescription Drug Use: Development of Antimicrobial Resistance

Ayşe Arıkan[1,2,3], Kaya Süer[4]

[1]Department of Medical Microbiology and Clinical Microbiology, Near East University Faculty of Medicine, Nicosia, North Cyprus
[2]DESAM Research Institute, Near East University, Nicosia, North Cyprus
[3]Department of Medical Microbiology and Clinical Microbiology, Kyrenia University Faculty of Medicine, Kyrenia, North Cyprus
[4]Department of Infectious Diseases and Clinical Microbiology, Near East University Faculty of Medicine, Nicosia, North Cyprus

Abstract

Antimicrobial resistance (AMR) is becoming a major health problem worldwide. Different factors contribute to the emergence of resistance, including excessive and inappropriate use of antibiotics. Non-prescribered antibiotic use is still widespread and contributes to antibiotic resistance. This study presents the development of drug resistance in a woman with recurrent urinary tract infection, highlighting the role of antibiotics taken without a prescription and emphasizing the importance of culture and antibiotic susceptibility tests in the success of treatment. In this case, inappropriate use of antibiotics triggered AMR, and consequently, the treatment has failed. An effective medication management system is necessary to monitor non-prescription antibiotic use in North Cyprus. Raising public awareness through education programs can reduce inappropriate and excessive antibiotic use. The development of resistance to commonly used antibiotics also reveals the need to develop new treatment strategies in the country.

Keywords: Antibiotic resistance, antibiotic susceptibility testing, infectious disease, non-prescription drugs

INTRODUCTION

Antimicrobial resistance (AMR) is becoming a major global threat in all countries due to the excessive and unregulated use of antibiotics.[1] In 2019, there were 4.95 million deaths worldwide due to AMR, of which 1.27 million were associated with AMR.[2] Additionally, uncontrolled and unscientific use of antimicrobials in livestock contributes to the emegence of resistant pathogens.[3] AMR means that microorganisms causing bacterial, viral, fungal, and parasitic infections have developed resistance and cannot be killed by the drugs meant to treat these infections.[3] Due to the emergence of drug-resistant pathogens and difficulties in treating widespread bacterial infections, vital procedures such as surgery, organ transplantation, and cancer treatments, etc. are also becoming increasingly risky.[2] Additionally, the coronavirus disease-2019 (COVID-19) pandemic has contributed to the silent spread of AMR recently due to the widespread overuse of antibiotics for severe and hospitalized patients.[4] The World Health Organisation (WHO) reported that only 8% of hospitalized COVID-19 patients required antibiotic treatment due to bacterial co-infection while, 75% of the remaining were treated to prevent possible bacterial co-infections, leading to unnecessary antibiotic use. Between 2020 and 2022, the rate of antibiotic consumption rose from 33% to 83%, especially in the Eastern Mediterranean and the African regions, while decreasing in Europe and the Americas over time.[4,5]

The WHO's Global Antimicrobial Resistance Surveillance Report revealed AMR mainly in *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella* spp., *Acinetobacter* spp., *Staphylococcus aureus*, *Neisseria gonorrhea*, and *Streptococcus pneumoniae*, in regions of Africa, the Americas, South East Asian, European, Eastern Mediterranean,

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ORCID IDs of the authors: A.A. 0000-0003-1942-1203; K.S. 0000-0002-2565-3425.

Corresponding author: Ayşe Arıkan
E-mail: aysearikancy@yahoo.com
ORCID ID: orcid.org/0000-0003-1942-1203

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and Western Pacific.[6] The rise in resistance of third-generation cephalosporin-resistant *E. coli*, methicillin-resistant *S. aureus*, and the reduced susceptibility of *E. coli* to commonly prescribed antibiotics, including ampicillin, co-trimoxazole, and fluoroquinolones, in urinary tract infections (UTIs), poses a significant concern.[2] Moreover, decreased susceptibility of *K. pneumoniae* to critically important drugs complicates treatment management. Increasing levels of resistance potentially lead to increased use of last-choice drugs such as carbapenems, and when the efficacy of these last-choice drugs is compromised, the risk of untreatable infections increases.[2] Additionally, there is a growing concern about resistance to antiviral drugs used in the treatment of human immunodeficiency virus, multidrug resistance to isoniazid and rifampin in tuberculosis, partial resistance to artemisinin in *Plasmodium falciparum* infections, resistance to rifampin and clofazimine in leprosy infections, resistance to melarsoprol for trypanosomiasis, and resistance to pentavalent antimonials and miltefosine for leishmaniasis.

This study examines the development of drug resistance in women with UTI due to non-prescription antibiotic use and highlights the importance of performing urine culture and antibiotic susceptibility tests for treatment success.

CASE REPORT

A 41-year-old female patient was admitted to the microbiology laboratory with recurrent urinary tract symptoms, including pain and burning during frequent urination; foul-smelling cloudy urine; pain in her back; and hematuria. The initial symptoms started at the beginning of July 2024, while traveling to Bali, Indonesia, from North Cyprus. During a 13-hour plane trip, the patient experienced difficulty due to excessive water intake and was unable to urinate properly. Due to the sudden onset of the similar symptoms mentioned above, the patient used fosfomycin for two doses 3 days apart, without admitting to a hospital and performing a urine culture test. As she felt recovered, a microscopic urinalysis test and urine culture were not performed after she came back to her country. In mid-August 2024, the same symptoms recurred. During another summer vacation when the symptoms started, the patient could not access a clinic to have a urine culture performed again. Therefore, she used a cefuroxime film tablet every 12 hours for 5 days without a doctor's prescription. On the second day, she felt better, and the symptoms regressed. However, she did not feel fully recovered on the fifth day of the treatment. Consequently, she was admitted to a hospital and performed urine microscopy and culture tests two days after the antibiotic treatment. In her cloudy light yellow urine, nitrite positivity, strong leukocyte positivity, and trace blood positivity were reported in the urine strip test. In microscopic urinalysis, plenty of leukocytes, 4-6 erythrocytes, sparse squamous epithelium cells, and plenty of bacteria were detected. After 24 hours of incubation, growth was detected on the blood agar and eosin methylene blue (EMB) agar (>100.000 CFU/mL). Microbial identification and antibiotic susceptibility testing were performed using the VITEK2 (Biomerieux) automated system and evaluated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria.[7] According to the analysis, extended-spectrum beta-lactamase (ESBL) producing *E. coli* was reported in the urine culture. The detected pathogen was resistant to amoxicillin/clavulanate, ampicillin, cefepime, ceftazidime, ceftriaxone, cefuroxime-axetil, ciprofloxacin, piperacillin/tazobactam and trimethoprim/sulfamethoxazole. Susceptibility was detected for amikacin, cefoxitin, cefixime, ertapenem, gentamicin, meropenem, and nitrofurantoin. A cefixime tablet every 24 hours for 5 days was prescribed for the case. After 5 days of treatment, microscopic urinalysis and urine culture with the same techniques were repeated and the results were reported as negative.

Although there was no vaginal odor, itching, burning, or pain, a vaginal culture was also taken because of the slight vaginal discharge and the possibility of contamination due to UTI. A vaginal fresh smear, gram staining, culture, and A.F. genital system (Liofilchem, Italy) were performed to identify vaginal pathogens. The vaginal swab sample was inoculated on blood and EMB agars and incubated for 24-48 hours at 36 °C. Bacterial identification and antibiotic resistance patterns were determined with the VITEK2 (Biomerieux) automated system according to EUCAST guidelines.[7] In the vaginal fresh smear, 9-10 vaginal epithelial cells, increased leukocytosis, and bacteria were reported. In Gram staining, gram-negative bacilli were detected, while Döderlein's vaginal bacilli disappeared in the flora. Clue cells, gram (+)/(-) cocci, gram (+)/(-) bacilli, gram (-) diplococci, *Candida* spp, and *Trichomonas vaginalis*, were not detected in gram staining. Additionally, *Ureaplasma* spp. and *Mycoplasma hominis* were not detected in the A.F. genital system. In the vaginal culture, *E. coli* ESBL was identified. The isolate was found to be resistant to cefixime, amoxicillin, amoxicillin/clavulanate, gentamicin, amikacin, ceftriaxone, and cefuroxime, while susceptible to ciprofloxacin and norfloxacin, and susceptible to ampicillin/sulbactam, trimethoprim/sulfamethazole, and ofloxacin. The patient was prescribed ampicillin + sulbactam every 12 hours for 5 days. As prophylaxis, tioconazole (200 mg), tinidazole (300 mg), and lidocaine (100 mg) vaginal ovule were used for 3 days (1x1) to prevent fungal infections. Moreover, *Lactobacillus acidophilus* (100 million) and estriol (0.03 mg) vaginal tablets were used for 6 days for renewal of flora. The patient recovered after treatment without developing any complications.

DISCUSSION

AMR is a growing health problem worldwide, affecting the sectors of human health, food production, animal, and environment. In 2015, WHO released the Global Action Plan on AMR, which includes developing and implementing multisectoral action plans, raising awareness, increasing surveillance and data, reducing infection rates, ensuring safe and effective use of antimicrobials, and developing new treatment strategies and alternatives,[8] in North Cyprus, dispensing non-prescription antibiotics has been prohibited since April 1, 2016. Although the law is now in force in North Cyprus, there is no effective monitoring system for users and healthcare systems.[9] Drug tracking and e-prescription systems, modern technologies required for health services, were planned in North Cyprus but could not be implemented. These systems should be implemented urgently to cover all public and private physicians, pharmacies, and pharmaceutical warehouses.[10] In this case, the patient was able to purchase medication without a prescription during travel abroad, and, when she felt unwell, she preferred self-medication. Since her complaints recurred within a month and coincided with her next vacation, she repeated the use of non-prescription antibiotics, which contributed to the development of resistance. Various factors such as lack of time to perform antibiotic susceptibility testing, as in this case, lack of awareness or education, and inadequate access to healthcare systems during disasters may contribute to the development of antibiotic resistance globally. Unal Evren et al.[11] reported increased ESBL positivity among

uropathogens during COVID-19 in North Cyprus. The decrease in the rate of pandemic period admissions was reported as a possible contributing factor to this result.[11] The detection of ESBL positivity in untreated cases due to inappropriate antibiotic use and the detection of ESBL in approximately 30% of travelers, highlights the need for antibiotic susceptibility testing and the importance of appropriate antibiotic use for treatment success.[12]

Countries where self-medication is widespread and uncontrolled, are triggering AMR and also leading to high costs and side effects resulting from long-term treatment failure. Using antibiotics without a prescription is more generally reported in low-income countries than in high-income countries.[13] Many factors contribute to this approach, including traveling abroad, lack of education among the population and even among pharmacy staff, expensive or difficult access to healthcare services, and lack of healthcare insurance.[12-15] According to the survey-based studies on non-prescription drug use and sales in North Cyprus in 2014, Süer et al.[9] revealed that 97.5% of pharmacies in different cities in North Cyprus answered "yes" to whether they sell medicines without a prescription. In another study conducted on the population, it was determined that 87% of people have used non-prescription drugs at least once in their lives.[16] In those years, The high rates of drug sales and purchases without complying with the rules in North Cyprus showed that a regulatory intervention was necessary. In recent studies, antibiotic consumption and use without a medical prescription were reported at 43.8%, 45%, and 47% in different regions in the United States and some low and middle-income countries.[17,18] In a systematic review, the prevalence of non-prescription antibiotic dispensing from community pharmacies reached 63.4%, with the highest rates in sub-Saharan Africa, East Asia, and the Pacific, Latin America, and the Caribbean.[19] In a similar study conducted by Gravningen et al.[15] between 2015-2016, Thailand, Türkiye, and Spain had the highest rates of purchasing antibiotics without a prescription (10.7%, 5.5%, and 3.6%, respectively). The prevalence of antibiotic dispensing without a medical order remains high in other countries (63.1%). The study revealed that the most common antibiotics sold without a valid prescription in China were cephalosporins (44.1%) and amoxicillin (39.0%).[20]

To combat the emergence of AMR, it is important to raise awareness among the public and health workers and to carry out effective inspections to prevent the purchase of medications without a prescription. Our case highlights that using antibiotics without a prescription contributes to antibiotic resistance and reduces treatment success. Antibiotic susceptibility testing is critical for determining the most appropriate treatment option and improving success.

CONCLUSION

In conclusion, insufficient monitoring of non-prescription antibiotic use and selling in North Cyprus triggers antibiotic resistance. Raising public awareness through educational programs can reduce inappropriate and excessive antibiotic use. The development of resistance to basic antibiotics also reveals the necessity of developing alternative therapeutic approaches.

MAIN POINTS

- Inappropriate antibiotic use may have contributed to antimicrobial resistance in North Cyprus.
- Culture and antibiotic susceptibility testing should be performed before prescribing antibiotics, to reduce antibiotic resistance.
- An effective monitoring system for users and health systems should be implemented to reduce inappropriate antimicrobial use in North Cyprus.

ETHICS

Informed Consent: The consent form was obtained for the case.

Footnotes

Authorship Contributions

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

DISCLOSURES

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