

Antibiotic Consumption and Bacterial Resistance Pattern During Three Years at a Tertiary Hospital in Mashhad, Eastern Iran

Sepideh Hasanzadeh^{1,2,†}, Ali Mehri^{3,†}, Mahin Sadat Shahabifar⁴, Kiarash Ghazvini^{1,5,*}

¹Antimicrobial Resistance Research Centre, Mashhad University of Medical Sciences, Mashhad, Iran

²Department of Medical Laboratory Sciences, Varastegan Institute for Medical Sciences, Mashhad, Iran

³Endoscopic and Minimally Invasive Surgery Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

⁴Pharmacy of Ghaem Educational Hospital, Mashhad University of Medical Sciences, Mashhad, Iran

⁵Department of Microbiology and Virology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Email address:

ghazvinik@mums.ac.ir (Kiarash Ghazvini)

*Corresponding author

† Sepideh Hasanzadeh and Ali Mehri are co-first authors.

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Abstract: One of the most significant global public health challenges is antimicrobial resistance (AMR). Improper use of antibiotics is among the leading causes of drug resistance to various substances. In Eastern Iran's Mashhad, a tertiary hospital has undertaken research on antibiotic usage and bacterial resistance patterns for three years, as part of a regional action plan to combat healthcare-associated illnesses. The Ghaem hospital's pharmacy and microbiology lab have diligently collected information on antibiotic use and bacterial resistance over this period. The data revealed that Meropenem, Ceftriaxone, and Ciprofloxacin were the most frequently used antibiotics in 2017, 2018, and 2019, respectively. Between 2017 and 2019, *E. coli*, *A. baumannii*, and *K. pneumonia* exhibited significant changes in their resistance rates (RR) to various antibiotic classes, with the exception of Imipenem. Notably, *S. aureus* displayed declining trends in Ciprofloxacin RRs. Our findings indicate a reduction in the use of several antibiotics at Ghaem hospital during this period, while Metronidazole, Imipenem, and Cefepime remained preferred choices. The overuse of broad-spectrum antimicrobials has resulted in serious public health issues. Hence, continued efforts are essential to optimize antibiotic administration, mitigate antibiotic resistance, and gather additional data for policy-making.

Keywords: Antibiotics, Antimicrobial Resistance, Multidrug-Resistant, Resistance Rates

1. Introduction

Antimicrobial resistance (AMR) is a new, worldwide issue that has an impact on morbidity, mortality, and costs [1]. Annually, AMR kills around to 10 million people worldwide. It is well recognized that AMR affects low- and middle-income countries (LMICs) more severely [2]. The Eastern Mediterranean region has recently been labeled as weak in the fight against AMR by the WHO due to the absence of national-level action plans, a lack of awareness, disjointed information

systems, poor monitoring, insufficient laboratory capacity, improper prescription, and use of fake and illegal drugs and medications [3]. The WHO is aware of the problem and a program was launched in April 2011, named "Against drug resistance: no action today, no drugs available tomorrow."

The rate of drug usage in Iran is three times higher than the global rate [4]. Over-use and over-prescription of antibiotics is an old problem in the Iranian healthcare system. Fifty years ago, researchers warned against the inappropriate use of antibiotics and the resulting AMR as an upcoming

challenge for the Iranian healthcare system [5]. Increasing antibiotic resistance has helped to better recognition of inappropriate antimicrobial treatment of acquired hospital-acquired infections [6]. Based on findings in the past 20 years in Iran, antibiotics were the best-seller of all drugs [7].

At least one in three hospitalized patients receives antibiotic therapy, while half do not need it. Based on previous studies, antibiotics comprise 30 to 50 percent of the prescribed drugs, while 30-60% are unnecessary [7]. Antibiotic-resistant strains of *Staphylococcus aureus*, *Pneumococcus*, *Enterococcus*, and Gram-negative gut bacteria have been on the rise in recent years as a result of improper antibiotic usage [8]. Studies have revealed that cultural, dietary, educational, and health care system variations among nations affect the prescribing of antibiotics [9]. According to previous studies, few studies have been conducted to date on improper prescribing and self-medication performance of Iranian specialists [10].

Hospital and community-acquired infections (HAIs) and the development of multidrug-resistant (MDR) bacteria are inextricably linked [11]. Additionally, a number of MDR microbes, notably MDR gram-negative bacteria, have been found in common ailments (including gonorrhea, pneumonia, TB, and urinary tract infections) over the past several decades [12]. The most prevalent organisms responsible for hospital-acquired infections, particularly in the critical care unit, are those that generate broad-spectrum beta-lactamases (ESBLs), such as *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and other Enterobacteriaceae [13]. Additionally connected to diseases acquired in the community are gram-positive bacteria. The most representative microbe in this context is methicillin-resistant *Staphylococcus aureus* (MRSA), which was once solely associated with HAIs and has expanded broadly throughout the neighborhood [14]. In this study, our objective was to investigate antibiotic consumption and the pattern of antibiotic resistance in the Intensive Care Units (ICUs) of Ghaem Hospital in Mashhad, Iran. The significance of this research stems from the fact that the excessive and irrational use of antibiotics is a primary factor contributing to the development of pathogen resistance, and there is limited data available on this matter in Iran.

2. Methods and Materials

2.1. Hospital Settings and Data Collection

In Ghaem Hospital, a tertiary referral teaching hospital connected to Mashhad University of Medical Sciences in Mashhad, Iran, with an annual admission rate of around 43000 and a bed capacity of 900, we carried out a prospective observational research over a period of three years.

Through the hospital's health information system (HIS), information on antibiotic usage in ICUs was gathered retrospectively at the monthly level from March 2017 to March 2020. All medications that the ward requested and that the hospital pharmacy supplied were included in the data gathered. Therefore, we distinguished antibiotics from the

information we collected.

2.2. Determining the Indicator

In this "Drug Assessment" study, we introduce the Anatomical Chemotherapy Classification (ATC) System. The Defined Daily Dose (DDD) is the daily maintenance dosage for an adult patient receiving the drug's primary indication, as a gold standard unit of measurement for international, national, and local research on used Drugs by the WHO Collaborative Center for Drug Statistics [15]. The data was then reported as DDD/100 Bed Days (Defined Daily Dose per 100 Bed Days). The WHO Anatomical Therapeutic Chemical (ATC) categorization system was used to construct indicators for each type of antibiotic [15, 16]. Utilizing linear regression, the three-year consumption pattern from 2017 to 2020 was evaluated.

2.3. Antibiotic Resistance Pattern

Data on bacterial pathogens that are usually responsible for human illnesses were acquired using standard clinical antibiotic susceptibility data from the microbiological laboratory at Ghaem hospital. This data was gathered utilizing a retrospective collection method. The procedures of disk diffusion and minimum inhibitory concentration were used in each individual clinical laboratory in order to carry out microbiological identification as well as regular antibiotic susceptibility testing. When the isolates exhibited non-susceptibility to at least one of the antibiotics that belonged to a certain class, it was determined that they had acquired resistance to the antibiotic class in question. The resistance rates (RRs) for each antibiotic were determined by performing the following calculation: the number of non-susceptible isolates (i.e., resistant or intermediate isolates) was multiplied by the total number of isolates, and that number was then multiplied by 100, which was the number of species that were tested against the respective antibiotic. The Chi-Square test was used to do a statistical analysis on trends from 2017 to 2020 for each indicator that was associated to antibiotic resistance.

3. Result

3.1. Antibiotic Consumption

Antibiotic consumption for the Anatomical Therapeutic Chemical (ATC) class J01 (i.e., antibacterial use) was 221.72 Defined Daily Dose (DDD) per 100 patient-days in 2017 310.24 DDD per 100 patient-days in 2018, and 303.46 DDD per 100 patient-days in 2019. The most commonly used classes were Meropenem (43.79 DDD per 100 patient-days), Ciprofloxacin (43.06 DDD per 100 patient-days) and Ceftriaxone (37.17 DDD per 100 patient-days) in 2017, Ceftriaxone (45.68 DDD per 100 patient-days), Ciprofloxacin (37.92 DDD per 100 patient-days) and Meropenem (36.14 DDD per 100 patient-days) in 2018, Ciprofloxacin (53.62 DDD per 100 patient-days), Vancomycin (42.88 DDD per 100 patient-days) and

Meropenem (37.33 DDD per 100 patient-days) in 2019. Figure 1 shows the annual consumption of antimicrobials by ATC groups, expressed as DDD per 100 patient-days, in Ghaem tertiary hospital. In comparing consumption data within the entire surveillance period (2017–2019), no significant differences were observed, except for the

Ceftriaxone, Imipenem, and Meropenem consumption, which decreased significantly from 37.17 to 27.83, 12.05 to 93.46 and 43.79 to 37.33 DDD per 100 patient-days ($p = 0.027$), respectively. Vancomycin and Ciprofloxacin consumption increased considerably from 3.32 to 42.87 and 43.05 to 53.62 DDD per 100 patient-days ($p = 0.015$), respectively.

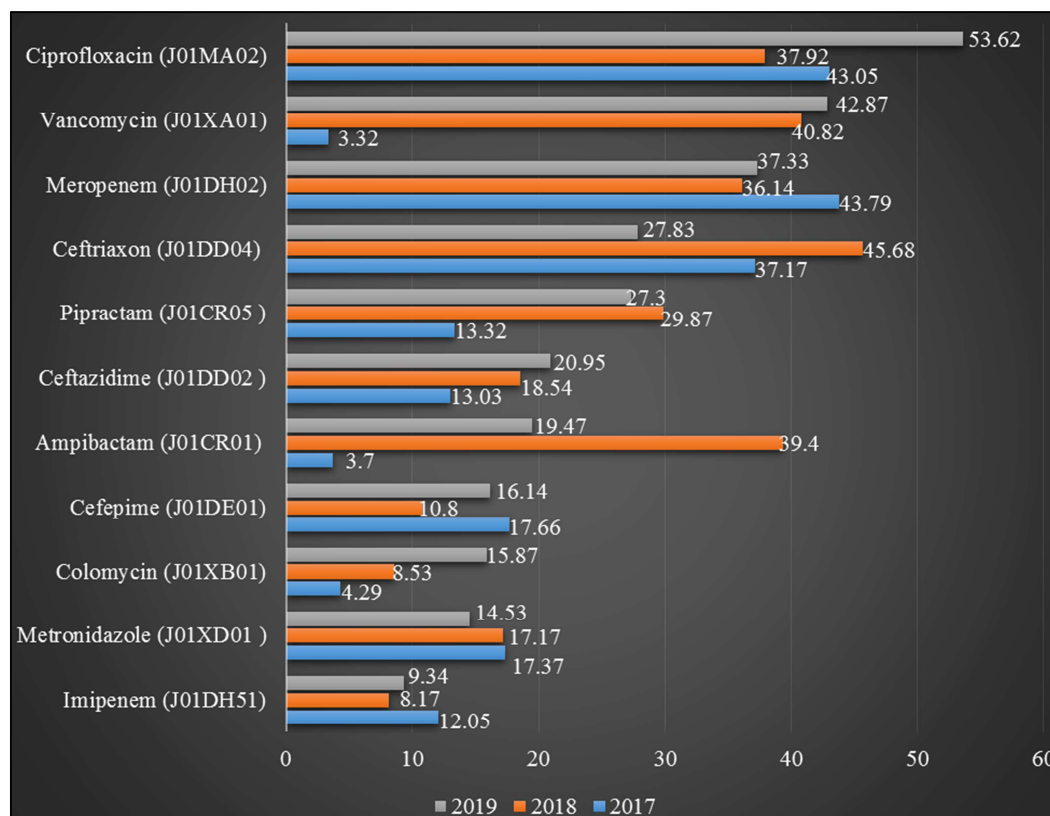


Figure 1. Consumption of antibiotics in Ghaem Hospital (expressed as Defined Daily Dose per 100 patient-days) by Anatomical Therapeutic Classification groups in 2017 (A), 2018 (B), and 2019 (C), in Mashhad (Southern Iran).

3.2. Resistance Rates

E. coli, *A. baumannii*, and *K. pneumonia* exhibited notable alterations in resistance rates (RRs) across all antibiotic classes, with the exception of Imipenem. Furthermore, RRs of *S. aureus* to Ciprofloxacin displayed a significant

declining trend. However, RRs of other microorganisms remained relatively unchanged throughout the study duration. Please refer to Table 1 for the RRs calculated based on the data provided by public and private healthcare facilities, which covered the entire study period.

Table 1. Antibiotic consumption in the community during the three years (2017–2019).

Microorganism	Antibiotic	Resistance Rates			p-Trend *
		2017	2018	2019	
<i>E. coli</i>	Amikacin	7.9	7.7	9.7	<0.001
	Cephalosporins	45.6	55.8	64.2	<0.001
	Ampicillin	85.5	85.1	33.3	<0.001
	Imipenem	12.1	30	16.6	0.065
	Ciprofloxacin	51.4	56.7	70	0.004
<i>A. baumannii</i>	Amikacin	83.3	77.3	83	<0.001
	Cephalosporins	94.7	93.8	90.2	0.004
	Ampicillin	95	95.5	99.7	<0.001
	Imipenem	84.8	63.9	75	0.099
	Ciprofloxacin	84.8	82.5	80	<0.001
<i>K. pneumonia</i>	Amikacin	47.6	35.4	42.3	0.022
	Cephalosporins	71.5	76.3	81.1	0.004
	Imipenem	39.3	55.1	44.7	0.038
	Ciprofloxacin	64.2	55.1	77.8	<0.001

Microorganism	Antibiotic	Resistance Rates			p-Trend *
		2017	2018	2019	
<i>S. aureus</i>	Vancomycin	7.6	3.3	6.7	<0.001
	Erythromycin	59.4	69.3	67.9	0.004
	Cefoxitin	47	58.4	57.8	<0.001
	Gentamicin	23	25.7	25.5	0.004
	Ciprofloxacin	63	48	46.3	<0.001

4. Discussion

Our study determined the antibiotic consumption rate in Ghaem hospital of Mashhad over three years. The results can inform decision-makers, health care providers, and the public. The tendency of AMR to cause potentially fatal infections makes its fast expansion a worldwide health issue [17]. AMR had risen to a hazardous level, which may transport us back in time to the era before antibiotics, when there was still a chance that ordinary diseases might cause death [18]. The misuse of antibiotics is the main factor contributing to the development of AMR. Antibiotic misuse promotes the establishment and selection of AMRs and undermines infection control, allowing these bacteria to spread even further [19].

Critical locations like intensive care and surgical units need specific consideration in order to create efficient infection control methods [20]. The misuse of antibiotics in the healthcare context and the veterinary and agricultural fields leads to increased global pollution, contributing to a more significant presence of antibiotics in the environment. Horizontal transmission of genes through microorganisms also reinforces the AMR [21].

AMR is widespread, according to the WHO (World Health Organization), however there is no reliable assessment of its financial impact in Iran. According to the WHO, Iran has a significant frequency of AMR in a few specific harmful bacteria and has antibiotic resistance to more than five drugs for each bacterium that is requested [23]. However, there is not enough information about AMR in major isolates in the country. In Iran, prevalent are methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-insensitive *Streptococcus pneumoniae*, vancomycin-resistant enterococcus (VRE), and extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae. As of 2014, the World Health Organization (WHO) reported widespread antibiotic resistance in *S. aureus*, *S. pneumoniae*, *E. coli*, *K. pneumoniae*, *Shigella* species, *Salmonella*, *Neisseria gonorrhoeae*, and others. Notably, *E. coli* exhibited the highest resistance, at 54%, against fluoroquinolones, while *K. pneumoniae* demonstrated the highest resistance among all microorganisms tested in Iran, particularly to carbapenems [24, 25].

We found that over the course of three years, the number of *K. pneumoniae* strains that were resistant to fluoroquinolones and third-generation cephalosporins rose. In contrast, there were fewer *E. coli* strains that were ampicillin resistant. Concerning *A. baumannii*, the death trend was evident over three years: strains resistant to most antibiotics

showed a steady, unchanged trend. A significant proportion of antimicrobial resistance (AMR) was detected in *A. baumannii*, *K. pneumoniae*, and *E. coli*, underscoring the dearth of efficacious antimicrobial therapy against these microorganisms and accentuating the necessity for multimodal strategies to ensure judicious utilization of antibiotics. Data from the WHO, information on antibiotic use in Iran was 38.8 DDD per 1000 people per day. The utilization patterns of notable antibiotic subgroups indicate that in 2017 and 2019, Ciprofloxacin was the most frequently used antibacterial agent (43.05 and 53.68 DDD per 100 inhabitants per day, respectively), whereas in 2018, the highest consumption was attributed to Ceftriaxone (45.68 DDD per 100 inhabitants per day).

In Iran, as well as in Afghanistan, Pakistan, China, and other Asian countries with higher antibiotic consumption, ciprofloxacin consumption was 53.62 DDD per 100 inhabitants per day. Throughout 2017-2019, Meropenem, vancomycin, and Ceftriaxone emerged as the second most prevalent classes of antibiotics in Iran, frequently employed to combat infections with remarkable efficacy. [26].

Considering data regarding consumption of Ceftriaxone, the DDD per 1000 inhabitants per day in 2017 and 2019 was 37.17 and 27.83, respectively, which was compatible with China, where the consumption was 25.0 DDD per 1000 inhabitants per day. Nevertheless, Iran stands amongst the nations with elevated antibiotics consumption. Notably, countries such as China, India, Malaysia, Azerbaijan, and several others presented significant data concerning total consumption in the year 2019. Our findings are congruent with those from other Asian nations, such as Malaysia and India, and are not comparable to those of a research done in 48 primary health care institutions in six provinces of China [27]. The following were the study's limitations: First, information on the usage of antibiotics was gathered from only one public health facility. The total amount of antibiotics used in Khorasan Province may be somewhat inflated. Antibiotic usage trends and patterns, however, may be clearly seen. The research also examined data on antibiotic usage, which is a direct reflection of real medication use and the sorts of diseases that call for antibiotics [28]. In a related research conducted at the same location, the appropriateness of antibiotic delivery techniques was assessed. Despite the fact that the approach is widely recognized, the DDD and DID data it produces cannot be provided to specific patient requests. In the future, prescription analysis and AMR monitoring should be combined to evaluate population-based antibiotic use, enhancing decisions and improving clinical relevance [29].

5. Conclusion

In conclusion, this study shows a significant fluctuation in antibiotics usage within Iran from 2017 to 2020, with consistent preference observed for Metronidazole, Imipenem, and Cefepime. These findings provide information on patterns of antibiotic use and the consequences for national healthcare policies.

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