THE ANTIMICROBIAL RESISTANCE SITUATION IN IRAN: THE NATIONAL INITIATIVE AND R&D TO FACE AMR

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Antimicrobial resistance (AMR) in Iran, as it is elsewhere, is one of the foremost important health issues today. Public and private sectors are exploring different ways to address the problem. Knowledge of accurate prescription and optimal use of antibiotics for different groups of patients is poor. Actually, AMR has been a topic for discussion in Iran for several years. On the other hand, antibiotic susceptibility testing is rarely asked for by clinicians. Therefore, the widespread use of antimicrobial agents in primary care clinics and animal husbandry has allowed for the rapid emergence of resistant bacteria. The increasing antimicrobial resistance rate in Iran, requires a rational drug administration effort in collaboration with infection control committees, as well as the establishment of a national surveillance system.

In Iran, methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-non-susceptible *Streptococcus pneumoniae*, vancomycin-resistant enterococci (VRE), and extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae have emerged and spread into communities and hospitals. During the last two decades, many antimicrobial agents – such as extended-spectrum cephalosporins, carbapenems, fluoroquinolones, and aminoglycosides – have been introduced and empirically used as first-line drugs to treat these resistant bacteria. This has further accelerated the development and dissemination of drug-resistant bacteria. In 2014, the World Health Organization (WHO) reported extensive antibiotic resistance in *S. aureus*, *S. pneumoniae*, *E. coli*, *K. pneumoniae*, *Salmonella*, *Shigella species*, *Neisseria gonorrhoeae* and others *(1)*. It was reported that *E. coli* resistance to fluoroquinolones and *K. pneumoniae* resistance to carbapenems were most frequent with 54% among all microorganisms tested in Iran (Table 1). A systematic review and meta-analysis about epidemiology of multidrug-resistant (MDR) *A. baumannii* strains in Iran showed that the pooled prevalence of MDR- *A. baumannii* was 72% annually *(2)*. In addition, relative frequency of MDR-*A. baumannii* in several studies varied from 22.8 to 100%. Therefore, since the prevalence of MDR- *A. baumannii* is higher than several different countries, measures should be taken to keep the emergence and transmission of these strains to a minimum.

Iran, like many other parts of the world, has experienced a significant increase in the number of ESBLs in the hospitals and communities. In the community setting, ESBL-producing Gram-negative bacteria (GNB) mostly have a lower prevalence than in the hospital. However, it should be considered that the prevalence of ESBL genes varies in several geographical areas. The present rates in some parts of the country are very high, particularly in the central part of Iran, like Tehran Province. Therefore, the highest rate of ESBL-producing *A. baumannii*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae* has been reported in the hospitals of Tehran in the recent years. Other parts of the country even have high prevalence of ESBL-producing GNB in both hospitals and communities. It is clear that ESBL-producing organisms are widely distributed globally; however, this rate is lower in different parts of the world than Iran. Most frequent types

Table 1: **Major antibiotic resistance in Iran between 2013–2014 (WHO, 2014)**

Microorganisms	Resistance (%)	No. tested isolates	Type of surveillance, population or samples	Period for national data collection	Year of publication or report
Escherichia coli: Resistance to third-generation cephalosporins	41	885	Invasive isolates	2012	2013
Escherichia coli: Resistance to fluoroquinolones	54	885	Invasive isolates	2012	2013
Klebsiella pneumoniae: Resistance to third-generation cephalosporins	48	110	Invasive isolates	2012	2013
Klebsiella pneumoniae: Resistance to carbapenems	54	35	Invasive isolates	2013	2013
Staphylococcus aureus: Resistance to methicillin (MRSA)	53	2,690	Invasive isolates	2012	2013
Streptococcus pneumoniae: Resistance, or non-susceptibility, to penicillin	33.9	115	Invasive	2007	2013
Nontyphoidal Salmonella (NTS): Resistance to fluoroquinolones	6.3	125	Invasive isolates	-	2013
Shigella species: Resistance to fluoroquinolones	2.7	260	Targeted	2012	2013
Neisseria gonorrhoeae: Decreased susceptibility to third-generation cephalosporins	-	-	-	-	2013

of ESBL enzymes in Iran include TEM, CTX-M, SHV, and OXA; however, there are other ESBL enzymes with different frequencies among GNB such as PER, GES and VEB. In most reports, TEM, CTX-M, and SHV are the predominant and OXA-type ESBLs have been found mainly in *P. aeruginosa* and *A. baumannii* isolates in this region. Therefore, the presence of ESBLs genes is a risk factor for the future use of antimicrobial treatment in Iran. ESBLs distribution and the facilitation of their spread in different regions may be caused by factors such as "mobility" of ESBL genes, strong selective pressure of antibiotic use, purchase antibiotics without prescriptions, lack of observing hand hygiene, use of antibiotics in animals, travel, and different weather conditions. Also, the areas with less prevalence of ESBL-producing GNBs and ESBL genes must be considered in order to take specific measures and increase supervision in the hospitals and the community in case any changes or increase occur in terms of prevalence *(3)*.

Increasing resistance to carbapenems by carbapenemase-producing organisms, significantly *Acinetobacter spp.* and *Pseudomonas spp.*, is another concern in this country *(4)*. Carbapenem resistance has been increasingly common issue among *A. baumannii* isolates in Iranian hospitals in recent years with the majority of isolates showing multidrug resistance. Considerably high prevalence (99%) of the isolates were MBL-producing which can be a main cause of high carbapenem resistance among *A. baumanni* isolates. Recent studies have shown the existence of multiple MBLs producing clones of *A. baumannii* in Iran.

The use of colistin and polymyxin B as a therapeutic agent has been prompted by increasing resistance to antimicrobials including the carbapenems, which it had been used with increasing frequency to treat patients infected with MDR-GNB such as *A. baumannii* in the last several years. Iranian data showed that the rate of colistin-resistant *A. baumannii* was 11.6%. So, as the frequency of resistance to colistin is low, it can be used as an easily available drug for treatment of MDR *A. baumannii* strains, which are susceptible to colistin *(5)*.

In April 2015, WHO reported 3–5.9% of all new tuberculosis (TB) cases being MDR *(6)*. Even more serious, the percentage of previously treated TB cases that developed MDR-TB in Iran was 30–49.9%. A meta-analyses regarding the prevalence of drug-resistant tuberculosis in Iran revealed that 23% of new cases and 65.6% of previously treated cases were resistant to at least one drug *(7)*. The highest rate of resistance in new and previously treated cases was seen against streptomycin (19%) and isoniazid (47%), respectively *(7)*.

According to the data, clindamycin and rifampin are good choices for empiric treatment of patients who acquire *S. aureus* or MRSA infections until the results of culture and antibiotic susceptibility pattern become available. However, because of high prevalence of TB infection in this country and rifampin being one of the most important drugs in anti-TB therapy, care

should be exercised in using this drug for non-tuberculous infections, and to prevent occurrence of rifampin-resistant *M. tuberculosis*, physicians should list rifampin as the last choice in treatment of hospital-associated MRSA infections. As a study found linezolid resistance among MRSA and methicillin-susceptible *S. aureus* strains, it was suggested that an antibiotic sensitivity test for all isolates was carried out before using this new and expensive antibiotic *(8)*.

In Iran, several studies targeted various populations, including healthy populations and patients of different ages, and showed lower antimicrobial resistance rates of *Streptococcus pneumoniae* in comparison with other Middle East countries. Since 2007, among healthy Iranian children, penicillin, erythromycin, cotrimoxazole and tetracycline resistance fluctuated between different surveys *(9-11)*. However, Iran was the only Middle Eastern country that reported tolerance or resistance to vancomycin among healthy and sick populations *(10, 11)*. Within clinical isolates from sterile body sites, a variable percentage of resistance to penicillin, erythromycin, FQ and cotrimoxazole was also reported *(12-14)*.

New Iranian data on other microorganisms showed multi-resistant strains in *Campylobacter jejuni*, *Arcobacter* species, *Helicobacter pylori*, *Bordetella pertussis*, *Enterococcus spp.*, *Acinetobacter spp.*, *Candida spp.*, and others. Also, for viral infections including human influenza virus, Hepatitis B virus and HIV, the numbers of isolates resistant towards key antiviral agents are also on the rise. Most notable is the increase in so-called MDR nosocomial pathogens, including VRE. Further research is ongoing to reduce the risk for increasing resistance in human pathogens caused by antibiotic use in animal husbandry. The two main tasks are to restrict use of antibiotics for trivial upper respiratory tract infections and to avoid inappropriate use of antibiotics for surgical prophylaxis.

Iran veterinary organization (IVO) has seriously investigated AMR over the past years. AMR data has been gathered by IVO from various public and private laboratories across the country. The following findings were obtained:

- AMR in *E. coli* from poultry to "old" antimicrobial drugs such as Oxytetracycline and Flumequine was high, up to 80%.
- AMR to "old" antimicrobials was high (up to 70%) in regions with low density of breeding (vs "finishing") farms.
- There is direct relation between use of antibiotics and appearance of resistance.
- For "new" antimicrobial drugs, such as Florfenicol and Fosfomycin Calcium, susceptibility is high and resistance low compared to "old" antimicrobial drugs.
- AMR in *E. coli* was most common against Enrofloxacin (up to 60%), Oxytetracycline (up to 80%) and Flumequine (up to 70%).
- In young chicken, AMR was mainly found against "old" antimicrobial drugs while with increasing age, AMR was also found against "new" antimicrobials like Doxy-tetracycline- Danofloxacin -Florfenicol.
- Highest resistance levels were observed in animals in which antibiotics were used in the feed for disease prevention.

Policies

In order to control hospital-acquired infections and AMR, effective programmes are needed; however, without information about the prevalence of nosocomial infections the burden of estimation and effective programming for such infections is almost impossible. There were limited studies about nosocomial infections in Iran, which supposed 8%–10% prevalence rate, however, additional information is needed to determine the countrywide presence of nosocomial infections. According to regulations proposed by the Ministry of Health and Medical Education, each hospital must have an active hospital infection control committee. In this regard the Nosocomial Infection Surveillance System (NISS) was initiated in March 2007, which based itself on a guideline prepared by the Iranian Center for Disease Control (ICDC).

Every year since its inception, the Food and Drug Administration's National Committee on Rational Use of Medicine in Iran has used public education activities and projects to improve the rational use of antibiotics. As access to effective antibiotics is necessary for all aspects of modern healthcare, an informational campaign was developed targeted at the general public. In 1999, the National Committee on Rational Use of Medicine started a campaign focusing mainly on women and children with only 20% of the educational programmes targeted specifically at men. This was decided as women and children were seen to be more accessible and also in Iran, women are responsible for the family. By educating the women, they could continue spreading the messages within the family. The work in Iran is still ongoing and furthermore, an evaluation for women to measure knowledge after this type of intervention is currently under development. Continued educational programmes for the public are needed to change behaviour, increase knowledge, and enable the public to make good decisions regarding the use of antibiotics.

Summary

In summary, it is very obvious that the prevalence of such isolates is currently high and on the rise in Iran, particularly for the antibiotics of choice. AMR highlights the critical need for a comprehensive Iranian national antimicrobial drug resistance survey to monitor MDR isolates from all parts of country. Considering the increasing antimicrobial resistance

rate in Iran, a committee for rational drug administration is needed to collaborate with infection control committees. The establishment of a surveillance system is also required for registering and reporting antimicrobial resistance of laboratory isolates in hospitals for the purpose of effective and well-timed antimicrobial therapy. Such a surveillance system should continuously report the prevalence of microorganisms and their resistance pattern to hospital wards and the committee for infection control; such information will be used in making decisions at management levels. ■

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In Iran, the Ministry of Health and Education has been developing national surveillance according to WHONET guideline and all universities were instructed to improve public knowledge and apply antibiotic stewardship in hospitals. We thank all university hospitals for their collaborations and improvements.

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