

Review Article

Chances and prevention of antibiotic resistance in primary health care: literature review

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ABSTRACT

Many concerns have been expressed in the field of clinical practice regarding antimicrobial resistance since many infections with severe complications and bad prognosis have been described since the end of the last century. In primary healthcare facilities, the risks for developing high rates of antibiotic resistance is high, probably due to the high prevalence of bacterial infections in these places, and due to the overuse of antibiotics without any relevance of evidence of bacterial infections. For instance, people usually administer high doses of broad-spectrum antibiotics for non-severe, self-limiting respiratory tract infections. Moreover, for fighting bacterial infections, patients usually discontinue the treatment course once the symptoms of the disease were relieved. These factors among many others had led to the high prevalence of antibiotic resistance which may lead to serious complications. Many approaches are being made to reduce the resistance that has been reviewed in this review. These include optimizing the dosage and timing of antibiotics administration which can be achieved by more understanding of the pharmacology of the antibiotics. Moreover, training and education programs that target the prescribers and patients have been proven to be efficient in reducing the rates. These efforts are encouraged to last and target more people for more favorable outcomes.

Keywords: Antibiotic, Resistance, Primary care, Education, Prevalence, Prevention

INTRODUCTION

Many concerns have been expressed in the field of clinical practice regarding antimicrobial resistance since many infections with severe complications and bad prognosis have been described since the end of the last century. Moreover, the prevalence of the resistance has been shockingly increasing in the last few decades which may also contribute to a bad prognosis of the bacterial infection paving the way for more severe reactions that can subsequently lead to severe complications and may even end up in death.¹ Many organisms have been associated

with the high prevalence rates of antimicrobial resistance. Vancomycin-resistant *Enterococcus* (VRE) species, methicillin-resistant *Staphylococcus aureus* (MRSA) species, imipenem-resistant *Acinetobacter baumannii* bacteria, multidrug-resistant (MDR) *Pseudomonas aeruginosa*, cephalosporin-resistant *Escherichia coli*, and *Klebsiella pneumonia* have been regularly reported for this purpose and are said to have a great impact on the prognosis of infected patients.²⁻⁴

Extended-spectrum β -lactamase (ESBL)-producing organisms such as *Klebsiella pneumonia* and *Escherichia*

coli and MRSA have been reported as endemic organisms in many hospitals all over the globe.⁵ These types of infections have been also recently reported to occur in local community healthcare facilities.⁶ Among the major resistance problems, fluoroquinolones carbapenem are still sensitive and are considered the last defensive modalities against the different types of *Enterobacteriaceae*, especially *A. baumannii*, and *P. aeruginosa*. Therefore, further resistance against such antibiotics may complicate things and induce catastrophes.^{5,7-9} Additionally, the problem of bacterial resistance is not only found with humans, unfortunately, but previous investigations also showed that resistant bacterial isolates of *E. coli* and *Salmonella enterica* were found in food animals.^{10,11} Resistance to *Mycobacterium tuberculosis* has been also reported as a concerning problem that threatens public health and especially patients affected by the pathogen.¹² Besides, *Helicobacter pylori* infection has been also identified as a major health problem in recent decades due to the rising prevalence rates of several antibiotics which compelled the use of triple and quadruple antibiotic regimens.¹³⁻¹⁵

Primary healthcare facilities are used to describe the small local clinical establishments that usually offer healthcare services for a local, defined population with the quality of service less than that provided by secondary and tertiary hospitals which are considered high-level facilities. Patients at such facilities are more prone to caught infections due to the low levels of sanitation and personal protective measures in addition to the overuse of antibiotics which is attributable to the low level of education and the absence of strict measures by the healthcare officials. Therefore, such places are more prone to high prevalence rates of antibiotic resistance, which we aim to review in this literature and overview of the possible preventive measures.

METHODS

We performed an extensive literature search of the Medline, Cochrane, and EMBASE databases on 08 November 2020 using the medical subject headings (MeSH) or a combination of all possible related terms. Papers discussing the chances and prevention of antibiotic resistance in primary health care were screened for relevant information. We did not pose any limits on date, language, and age of participants or publication type.

DISCUSSION

Chances of antibiotic resistance (prevalence and associated factors)

The prevalence of antimicrobial resistance is hugely variable among the different types of antibiotics, the targeted bacteria, and the pattern of antibiotic consumption in the reported populations. Wojkowska-Mach *et al* conducted a ten-year analysis study to study the association between anti-microbial consumption and the

prevalence of antibiotic resistance in Poland.¹⁶ The authors reported that antibiotic consumption in Poland accounted for the highest rate among other European countries included in the analysis. This subsequently leads to an increase in the prevalence of antibiotic resistance in the country from 2007 to 2016. In 2018, Naylor *et al* conducted a meta-analysis of 214 studies that investigated the global burden of antimicrobial resistance among the included patients and countries.¹⁷ The authors reported that among the included studies, 48% of them estimated that antimicrobial resistance was significantly associated with increased mortality rates and healthcare burdens. A systematic review conducted by Shiadeh *et al* aimed to estimate the global prevalence of antibacterial resistance in certain bacterial isolates including the blood-isolated *Enterococcus faecalis* and *Enterococcus faecium* where the authors managed to include 291 studies in the meta-analysis.¹⁸ The authors estimated that the prevalence rate was variable by country and according to the culture. *Enterococcus faecalis* was found to be highly resistant to quinupristin/dalfopristin (97%) while the lowest resistance rate was found to be associated with linezolid antibiotics (0.8%). Moreover, the authors reported that America, Europe, and countries of the western pacific accounted for the lowest prevalence rate among other countries for linezolid and vancomycin antibiotics. Resistance to vancomycin was also found to be highest in South-East Asia and Eastern Mediterranean regions while analysis by country showed that Sweden possessed the lowest prevalence rate while Japan and Nepal recorded the highest. *Enterococcus faecium* showed the highest resistance of penicillin (85%) while resistance to tetracycline (1%) and linezolid (1.7%) was the lowest. The reported antibiotic resistance by country showed that the Netherlands had the lowest prevalence rates (0.1) while Brazil had the highest (67%) for this organism. Based on these results, the prevalence of antimicrobial resistance seems to increase by time as authors reported that, for instance, resistance to vancomycin in the aforementioned organisms increased by time from 2000 to 2016. Vancomycin-resistant enterococci (VRE) prevalence rate was also variable among studies in the literature. In Ethiopia, Melese *et al.* estimated the prevalence rate to be 14.8% (95% CI: 8.7-24.3) while in Nigeria, Wada *et al* estimated the prevalence of VRE from 19 original investigations to be 25.3% (95% CI: 19.8-30.8%) *Acinetobacter baumannii* resistance to antibiotics was also reported by many previous investigations which showed that the prevalence rate of this resistance was hugely variable according to the applied antibiotic per country.^{19,20} Pormohammad *et al* analyzed the results of 150 original investigations in a single meta-analysis to estimate the prevalence rate of cefotaxime and colistin by country.²¹ Africa had a 99% prevalence resistance rate to cefotaxime which was the highest while countries in the Western Pacific had the lowest prevalence rate of 1.1%. Moreover, the analysis showed that Germany (0.2%) had the lowest prevalence rate for colistin while Lebanon (17.5%), and China (12%) possessed the highest rate for the same antibiotic. Another meta-analysis by Pormohammad *et al*

showed that *E. Coli* was highly resistant to amoxicillin (70.5%; 9% CI: 57.5%-81%) while resistance to colistin was found to be the lowest for this organism (0.8%; 95% CI 0.2%-3.8%) in human isolates.²² Other associated factors are related to the patient's demographics, health status, and the presence of other comorbidities that may lower the patient's immunity.²³ Moreover, factors related to the type and efficacy of the healthcare facilities and experts have been also reported.²⁴ These results indicate the fact that antibiotic resistance is highly variable per each organism and for each antibiotic which is hard to cover in a single report. However, we hope that we shed more light on the seriousness of the issue and that serious preventive measures should be considered to reduce these rates and enhance the prognosis of eliminating such organisms and reducing their mobidities.

Preventive measures for reducing the resistance

Although antibiotic resistance has been a major problem in the past years with many mortalities and complications and no effective management modalities, previously published studies proposed various approaches to reduce the prevalence of the resistance. These measures are discussed as follows from the findings of previous investigations.

Optimizing the antibiotic

The antimicrobial stewardship programs (ASPs) have been now widely accepted by many institutions worldwide in this field.²⁵ It has been first proposed by the infection diseases society of America (IDSA) and the society of healthcare epidemiology of America (SHEA) in 2007.²⁶ These programs are built on previous investigations on different types of antibiotic resistance materials and their organisms. These include vancomycin and VRE, fluoroquinolones, and MRSA, cephalosporine, and cephalosporine-resistant *Enterobacteriaceae*, in addition to carbapenem in *pseudomonas*, carbapenem-resistant *Acinetobacter*, and *Enterobacteriaceae*.²⁷⁻³³ The program targets education about antibacterial resistance in addition to the front and back-end strategies that are targeted to limit the availability of certain antibiotics to the public and reconsidering the use of broad-spectrum antibiotics in addition to applying the most relevant antibiotics based on the susceptibility test results.^{34,35} Many aspects have been also reported in such programs. These include: adapting the proper antibiotic in a situation-specific pattern; providing better education about the strategy for healthcare providers; results of antimicrobial testing; identification and culturing of the right organisms; dose optimization and proper treatment courses based on the more comprehension of the antibiotic pharmacodynamics and kinetics, in addition to; and preauthorization of absolute antibiotic intake. The latter aspect has been named as the main strategy according to the developing organizations and according to previous reports which showed that it is the main effective modality that can lead to a great reduction in the resistance rate by reducing the frequency of their intake.³⁵⁻³⁸ The relationship between antibiotic

underdosing and discontinuation of the course with the development of the resistance was first proposed by Stamey *et al*.³⁹ Drew *et al* indicated that the application of this program's criteria will lead to a much reduction in the resistance rates.²⁸ Cook *et al* showed that *P. aeruginosa* susceptibility to carbapenem improves by 10-25% by restricting the use of ciprofloxacin by 90% between 2009 and 2010.²⁷

Dose optimization is also an important factor as many healthcare providers usually prescribe unnecessary antibiotics for their patients. For instance, antibiotics are widely prescribed in idiopathic respiratory tract infections although they are self-limiting are usually treated by symptomatic approaches as previous studies showed that the benefit from prescribing antibiotics for respiratory tract infections is usually minimal and can be only used in severe complications contributing to secondary infection on top of the lesion.⁴⁰⁻⁴² In the same context, Hay *et al* showed concerns about why 88% of patients with self-limiting respiratory tract infections are treated with antibiotics.⁴³ This phenomenon differs greatly by country and region as previous investigations showed that it is associated with culture, socio-economic level, clinical autonomy, country background, and the cultural beliefs of the patients and prescribers.⁴⁴⁻⁴⁶ Hulscher *et al* expressed that in such countries, people are directed in this path by non-scientific misleading ideas.⁴⁶ Besides, antibiotics prescription is mainly based on personal suggestions of the prescribers not on scientific-based manners that require the identification of the infective organisms.⁴⁴⁻⁴⁶ In a review by Harbart *et al* the authors showed indicated this fact where antibiotics are being prescribed in association with diagnostic uncertainty.⁴⁷ The authors also showed that Southern European countries are more prone to antibiotic resistance than egalitarian societies due to the high intake and prescription of antibiotics in these countries. The socio-economic level of some countries has been also proven to take part in the over usage of antibiotics which results from the pressure of many pharmaceutical companies. Kirby *et al* showed that antimicrobial resistance differed from patients according to their economic incomes.⁴⁸ Another important factor that may influence antibiotic prescription is the attitude of the prescribing agents. Cole *et al* conducted a survey on 1000 general practitioners and found that 55% of them were influenced by patients' pressure to prescribe antibiotics while 44% prescribed antibiotics for patients to motivate them for leaving the surgical platform.⁴⁹ These factors indicate that optimization of antibiotic use is essential in decreasing the resistance, and therefore, effective measures should be approached targeting the patients, clinicians and on a local and global level.

Education about antibiotic resistance

In general, educational events can reduce the inappropriate behavior about drug prescription as indicated by Kunstler *et al* which summarized the results of 14 reviews on this topic.⁵⁰ Education about antibiotic resistance and about the

complications that may result from the phenomenon might be effective in reducing unnecessary consumption of antibiotics, and consequently, reduce the resistance. Education is directed to many audiences including prescribers, pharmacists, healthcare officials, and patients. The success of the ASPs has been also mostly due to successful training and education of GPs towards the daily prescriptions and reducing antibiotic consumption unless needed.⁵¹ Rodrigues *et al* conducted a clinical trial to investigate the efficacy of applying education as an interventional approach for patients, physicians, and pharmacists and its efficacy on improving antibiotic resistance to many organisms in primary care.⁵² The authors concluded that significant improvements were noticed regarding the prescription of penicillin combinations including β -lactamase inhibitors, third- and fourth-generation cephalosporins, and fluoroquinolones β -lactamase-sensitive penicillins, and the ratio of broad- to narrow-spectrum antibiotics. The frequency of educational outreach (EO) might also influence the results of antibiotic prescription. Chhina *et al* reported that after a single EO to their GPs by a therapeutic advisor, a significant increase in the non-recommended prescription of antibiotics was reduced by 74% in the EO group.⁵³ Clyne *et al* also showed that applying educational interventions significantly reduced the un-needed antibiotic prescription by the included participants.⁵⁴ Additionally, a meta-analysis of randomized controlled trials conducted by Fleming *et al* to assess the effect of educational interventions for physicians and nurses on antibiotic prescription in long-term healthcare facilities.⁵⁴ The authors estimated that, although the evidence was low in this study due to heterogeneity, educational approaches might influence the inappropriate prescription patterns of antibiotics in these facilities. In addition to educating physicians and pharmacists, previous studies also showed that other educational programs targeted patients and children to spread awareness about the benefits and dangers of antibiotics resistance.⁵⁵ Such programs may have an important role in influencing the public's understanding about the unnecessary and overuse of antibiotics, and therefore, may reduce the resistance rates.⁵⁶

Other interventional procedures

Hygiene and conducting disinfection in primary healthcare facilities have been also reported by previous investigations as preventive approaches against antibiotic resistance. It has been estimated that around 1.7 million cases of hospital-acquired infections occur each year which results in the development of severe complications and deaths in thousands of them.⁵⁷ Therefore, sticking to personal protective measures whenever in the hospital is highly recommended to avoid getting infected.⁵⁸ Personal protective measures might include continuous use of hand sanitizers, frequently washing hands, and wearing masks.⁵⁹ This can effectively reduce the incidence of infection and consequently reduce the need to administrate large amounts of antibiotics which can intervene against bacterial resistance. Lee *et al* also reviewed some other

procedures to decrease the burden of antibiotic resistance.⁵⁹ They reported that using antibiotics in veterinary medicine might have also contributed to the overall emergence of resistance in humans as many of these approaches were not for therapeutic purposes in the first place, and therefore, restricting the use of these antibiotics should be done. Moreover, the study reviewed the previous literature which indicates the emerging novel ideas of probiotics and novel antibiotics which may replace the existing non-bacterial sensitive ones.

CONCLUSION

Antibiotic resistance will remain an issue of concern in the years to follow due to the uprising prevalence rates of this phenomenon. Public health policies are urged to take action to reduce consumptions and spread awareness about the hazards of this situation which may affect many lives. Many approaches are being made to reduce the resistance that has been reviewed in this review. These include optimizing the dosage and timing of antibiotics administration which can be achieved by more understanding of the pharmacology of the antibiotics. Moreover, training and education programs that target the prescribers and patients have been proven to be efficient in reducing the rates. These efforts are encouraged to last and target more people for more favourable outcomes.

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