World Health Organization Report: Current Crisis of Antibiotic Resistance

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Abstract

Antibiotic resistance is the most challenging clinical and public health problem. Despite of living in the era of novel technologies in biomedical research, many of untreatable infectious diseases are ranked as the main causes of human death worldwide. Increased antibiotic use in human and use in animal production are the two major causes of emergence of resistant bacteria in hospitals, human communities, and also animal farms. Current body of evidences is indicating that major factors that led to existing crisis on antibiotics worldwide are poor educational programs on hygiene and health, inappropriate prescription in addition to the overprescription in clinical settings (mainly in developing countries with easier access to the antibiotics) and lack of accurate diagnostic tools in laboratories in order to control the emergence of antibiotics against widely used drugs in community. It sounds using the antibodies against problematic bacteria in farms has more benefits than treating them with susceptible antibiotics. As best strategy, we pointed that the crisis of antibiotic resistance may be solved when all contributors be acknowledged to their responsibilities and duties to minimize this global problem threatening the human health. China and the USA as the two main antibiotics user in industrial scale should have taken new policy in meat industry. Currently, antibiotic resistance presents a growing health threat worldwide being the cause of many nosocomial and often deadly infections.

Keywords Antibiotic resistance · Crisis · Bacterial infection · *P. aeruginosa* · *A. baumannii* · *E. coli* · Carbapenemase

1 Background

Sir Alexander Fleming's discovery saved millions of human lives. His life-saving finding increased life expectancy of

populations of developed countries by three decades [1, 2]. Life expectancy increase of Third World countries was also significant but more modest. During his Nobel prize speech, Fleming warned about the possibility of emergence of drug-resistant bacteria, especially if exposed to low doses of antibiotics with marginal efficacy [3]. Neglect of his warnings resulted in present crisis in fight with infectious diseases since many previously curable infectious diseases became untreatable and are ranked again as main causes of human mortality and morbidity [4]. New antibiotics were quickly discovered after Fleming's discovery. Cephalosporins, penicillins, aminoglycosides, tetracycline, and glycopeptides were added to prescriptions. In the end, over ten thousands of bacterial secondary metabolites were found to successfully eradicate persistent infectious diseases [5–10]. These antibiotics and bacterial metabolites were also overused as prophylactic protective measures against any potential bacterial infections [11–15]. Shortly after the discovery of antibiotics, this resulted in a considerable proportion of these drugs becoming inefficient due to what has been later termed “antibiotic resistance” [16–18]. Antibiotic resistance (AR) played a major role in the reduction of efficacy of fight against the infectious agents [19–22]. From a microbiological point of view when exposed

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to antibiotics, propagation of bacterial resistant phenotypes follows mechanisms of evolutionary selection [23, 24]. It is known that cardiovascular diseases are the first cause of death in many of countries. However, untreatable infectious diseases are still the second in the ranking of deadly diseases in developing countries [25]. Excessive use of antibiotics and poor systems of control of infections and prevention (often caused by substandard or even sloppy hygienic practices) are the two major contributors to the emergence and spread of resistant bacteria in hospitals and communities. Around 4.5% of patients treated in German hospitals suffered from NI (nosocomial infections) in 2017 [26]. Antibiotic resistance is rapidly increasing at national and international levels, while only few available solutions exist [27, 28]. In conclusion, the “golden age” (1940–1980s) of efficient use of antibiotics did not last long and the arising resistances resulted in several, often fatal, complications during the hospitalisations. Hence, it is important to reconsider antibiotic usages. Thus, in the following sections:

- First, the relevancy of the term “crisis” of antibiotic resistance worldwide will be explained.
- Second, practical approaches tackling with the speedy globalization of antibiotics resistance will be discussed in the light of the recent World Health Organization (WHO) report.

2 Crisis of the Resistance and WHO Report

Antibiotic resistance has reached global dimensions as a public health major threat. The obvious question is “Why is there still no practical solution to this crisis?”. In order to answer this question, we should first note that proceedings of many workshops, national/international congresses, and thousands of papers, which warn about the threats of spread of antibiotic resistance, keep being published. However, in the last decade, there has been little if none systematic coordination of prevention campaigns. For example, (i) European Society for Clinical Microbiology and Infectious Diseases (ESCMID), (ii) the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America (IDSASHEA), (iii) Validation of European Centre for Disease Prevention and Control (ECDC), and (iv) Committee on Infectious Diseases (CID), Committee on Fetus and Newborn, Revised guidelines for prevention of early-onset group B streptococcal [GBS] infection are the short list of scientific Committees that addressed this issue, but the main problem was the lack of coherence in the questions raised [29–35]. The WHO published its first and the only available surveillance data couple of years

ago [36]. It was the most comprehensive report on antibiotic resistance on a global scale. It addressed correctly the importance of using surveillance data since they show the drift of antibiotic resistances and allows to design alternative and effective therapies, particularly for multidrug-resistant strains [36]. What the world of microbiology forgot is that having a comprehensive and global surveillance system can slow down the speed of the antibiotic failure. The main obstacle in creating a global surveillance survey is the lack of universal agreement on its methodology. So far, there are only two studies examining the cost of antibiotic resistance for humanity. First, a European report in 2007, recording 25,000 death cases due to the drug-resistant infections with *Escherichia coli*, *Klebsiella pneumoniae*, and *Streptococcus pneumoniae* [37]. Second analysis came from the USA, reporting death rates of infected people with multidrug-resistant isolates of Gram-negative bacteria and fungi [38]. Another publication predicts more than ten million deaths of people infected with the antibiotic-resistant bacteria worldwide within the next 30 years, if urgent measures are not taken now [39]. In the light of what we know, it is very disturbing that Kelly et al. predict a decrease in funding for development of new antibiotics in the next few years [40]. The current grim situation should stimulate to adopt efficient strategies and policies to protect existing antibiotics against their obsolescence due to emergence of bacterial resistances. The first step is to accept the existence of an ongoing crisis of antibiotics use worldwide. In this regard, the WHO report is a good starting point for microbiologists and clinicians to design better strategies to overcome the crisis.

3 WHO Report on Resistant Bacteria

On February 27, 2017, using a multicriteria decision analysis technique, WHO experts together with researchers from the Division of Infectious Diseases at the University of Tübingen, Germany, published a list of microorganisms with relatively high rate of antibiotic resistances that need to be better managed. They classified these microorganisms into three groups (critical, high, and medium) according to the urgency of a need to develop new antibiotic treatment and the levels of reported antibiotic resistances. Only microorganisms with critical priority (*Acinetobacter baumannii*, carbapenem-resistant, *Pseudomonas aeruginosa*, carbapenem-resistant and *Enterobacteriaceae*, carbapenem-resistant) are described on the basis of recent update of their antibiotic resistance profiles. Furthermore, this text aims to propose novel approaches to resolve the current crisis caused by the drug-resistant pathogenic bacteria.

3.1 Carbapenem-Resistant *Acinetobacter baumannii*

Acinetobacter baumannii (*A. baumannii*) is a nonmotile, coccobacillus and opportunist bacterium that is now recognized as a pathogen responsible for many of human diseases including bloodstream, wound and soft tissue, urinary tract infections (UTI), and ventilator-associated pneumonia [41, 42]. This Gram-negative microorganism got onto a top of community-acquired infections list over the last decade [43]. Usually, the bacteria with high virulence are labeled as emerging pathogens, but in the case of *A. baumannii*, the term was used because of its antibiotic resistant properties. Generally speaking, *A. baumannii* infection is clonal and naturally resistant to a wide range of antibiotics. However, large amount of data failed to find the lineage origin for the clonal infections. The *A. baumannii* genome was first sequenced and analyzed about 10 years ago [44]. Thereafter, genetic comparison of a couple of sequenced strains revealed a high similarity in the content of plasticity regions, which contains resistance genes. This finding fits well with a microbiological concept that *A. baumannii* is naturally resistant in any type of colonization sites. In clinical settings, *A. baumannii* is an emerging pathogen associated with hospital and community outbreaks [45–47]. It is clear that *A. baumannii* contains two main features of a successful nosocomial pathogen: sufficient antibiotic resistance elements as well as immense capacity for environmental colonization [48, 49]. Unlike other pathogens, *A. baumannii* cannot be characterized by a single prominent feature, like virulence of *Salmonella typhimurium* or ability to colonize harsh environments as *Pseudomonas aeruginosa* [50, 51]. Indeed, this resilient bacterium is able to acquire and maintain genetic elements responsible for phenotypic and genotypic antibiotic resistances. Thus, we propose to apply the term “pan-drug” resistance for *A. baumannii*. Moreover, there is no exact definition of multidrug resistance (MDR) or extensive drug resistance (XDR) for any microorganisms (*Mycobacterium tuberculosis* excluded), especially for highly resistant ones [52, 53]. Pan-drug definition appears to be suitable for *A. baumannii*, since according to reports from different countries, it is highly resistant to all currently available antimicrobial agents. However, the lack of a uniform definition leads to some arbitrary interpretations of resistance, which is one of the main reasons for inconsistency of the results of parallel studies [54, 55]. Many of the clinical and environmental isolates of *A. baumannii* were reported to be resistant to various prescribed antibiotics in the past, but since 1991, there has been a growing evidence of emergence of carbapenem-resistant *A. baumannii*. From that time, carbapenem-resistant *A. baumannii* was classified as a global threat deserving strict control. Due to the alarming frequency of MDR, the infections caused by bacteria with acquired and intrinsic mechanisms, including *A. baumannii*, are extremely difficult to cure regardless of colonization site. Recent reports

showed *A. baumannii* to be one of the six most successful multidrug-resistant bacterial colonizers in hospitals [47, 56]. From a clinical perspective, the fact that *A. baumannii* is resistant to at least three different classes of antibiotics classifies it as a MDR strain [45, 57, 58]. Undoubtedly, MDR strains are causing many lethal outbreaks in hospitals worldwide [59–63]. Occurrence of antibiotic resistance of *A. baumannii* is the main trend in reported outbreaks of MDR bacterial infections in hospitals (Table 1) [76]. Recent reports indicate that the antibiotic resistances of *A. baumannii* become more frequent and require urgent interventions [77, 78]. A common list of proposed antibiotics against *A. baumannii* includes tetracycline, aminoglycosides, and β -lactams. However, MDR *A. baumannii* isolates are resistant to those antibiotics. In some reports, colistin was suggested as an alternative medication [79, 80]. For a while, colistin was the only available efficient antibiotic used against *A. baumannii*; however, recent studies have shown also growing *A. baumannii* resistance against it. The emergence of colistin resistance eliminated all options of therapy against MDR-*A. baumannii* in clinical setting [81–83]. This is the main reason why WHO labeled *A. baumannii* as critical pathogen, which heteroresistance and resistance to colistin should be closely observed and taken into account [84, 85]. Clinically, carbapenems have shown the best therapeutic results in treating an MDR-*A. baumannii*. A routine therapy of *A. baumannii* includes a combination of (i) beta-lactamase and (ii) aminoglycoside such as amikacin. In the case of carbapenem-resistant *A. baumannii* strains, colistin and tigecycline are the main recommended drugs [86]. Currently, carbapenem-resistant *A. baumannii* is considered as an XDR strain, which is recognizing its menace and is underlining pressing need for the discovery/conception of alternative treatments against this pathogen [87, 88].

It is likely that the current problems with carbapenem-resistant *A. baumannii* will continue for the next decade (see Table 1); thus, the latest WHO report should encourage clinicians to reconsider the use novel antibiotics against wide range of resistant Gram-negative bacteria. Based on the 2017 WHO report, we must classify infections with carbapenem-resistant *A. baumannii* as very difficult to cure until new antibiotics are discovered. According to the local susceptibility tests, the some hopes are raised by a combination therapy with colistin and the remaining effective antibiotics.

3.2 Colistin and MDR-*A. baumannii* Infection: Hope for Reality?

Primarily, colistin was used to treat an MDR-*A. baumannii* infections as an ultimate measure when other antibiotics were inefficient. It should be highlighted that the use of colistin was prohibited in 1980s, because of its secondary effects—nephrotoxicity [89, 90]. Interestingly, the first report of

Table 1 Major outbreaks caused by carbapenem-resistant *A. baumannii* in the last decade (2008–2018)

Study	Sample size	Methods of detection	Carbapenemases used	Year	Country	Reference
Nowak et al.	104	Multiplex-PCR	<i>OxA-51</i> <i>OXA-23</i>	2012	Poland	[64]
Agodi et al.	26	PFGE	<i>OxA-51</i> <i>OxA-82</i>	2014	Italy	[65]
Kohlenberg et al.	32	PFGE, Multiplex-PCR	<i>OXA-23</i>	2009	Germany	[66]
Kulah et al.	145	PCR AFLP	<i>OXA-23</i> <i>OXA-24</i> <i>OXA-58</i>	2010	Turkey	[67]
Barisic et al.	32	PFGE	<i>OXA-72</i>	2011	Croatia	[68]
Suk Choi et al.	57	PFGE	N/D	2010	South Korea	[69]
Zong et al.	22	PCR	<i>OXA-23</i> <i>OXA-66</i>	2008	China	[70]
Bedenić et al.	185	PCR	<i>OXA-24</i> <i>OXA-40</i> <i>OXA-58</i> <i>bla TEM-1</i>	2014	Croatia	[71]
Yang et al.	49	PFGE	<i>OXA-23</i>	2009	South Korea	[72]
Takagi et al.	19	PFGE	<i>OXA-51</i>	2009	Brazil	[73]
Enoch et al.	163	Agar dilution	N/D	2008	UK	[74]
Giannouli et al.	71	PFGE	<i>OXA-58</i>	2010	Italy	[75]

N/D not determined, AFLP amplified fragment length polymorphism

emergence of a resistant *A. baumannii* phenotype against this drug was published in 1999 in Tchek Republic [91]. Since all other antibiotics were inefficient against an MDR-*A. baumannii*, clinicians were forced to use colistin [92, 93]. An increased number of reported MDR-*A. baumannii* outbreaks, as well as a rising carbapenem resistance worldwide, left the use of a potentially dangerous colistin as the only therapeutic option [94]. Additionally, a combination of drugs (colistin and tigecycline) might be an alternative way of treating patients carrying MDR and XDR-*A. baumannii*. A worrying number of reported cases of colistin resistance worldwide require case-controlled and randomized clinical trials (RCT) before its new combination with sulbactam or other drugs can be introduced as therapeutic treatments. Noteworthy, colistin is also used in therapies against the two major Gram-negative microorganisms *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* after failure of traditional therapies [95, 96]. In other words, an increasing number of multidrug-resistant infections caused by MDR and XDR bacteria boosted the prescriptions and the uses of colistin in clinical settings. However, in order to avoid the emergence of resistances, there is need for a strict management of a colistin administration in private clinics and hospitals.

3.3 *Pseudomonas aeruginosa*, Carbapenem-Resistance

The Gram-negative and nonfermenting bacterium *Pseudomonas aeruginosa* (*P. aeruginosa*) is a

metabolically versatile pathogen, which is able to adapt and survive in various clinical and artificial settings for colonization [97]. *P. aeruginosa* modulates and alters human immune responses causing severe damages and is difficult to treat with conventional antibiotics [98]. Reviews on microorganisms causing nosocomial infections list *P. aeruginosa* as one of the top five pathogenic bacteria [99, 100]. Experimental data show that *P. aeruginosa* becomes a MDR pathogen after multiple mutations decreasing permeability of its outer membrane and changing the regulation of efflux pumps [101]. Two major features of *P. aeruginosa* are contributing to high mortality rates of its infections: an intrinsic and acquired resistant phenotype as well as an extraordinary ability to form “biofilms” in order to protect itself from unfavorable environmental factors such as heavy metals and antibiotics [102, 103]. There is a long list of ineffective antibiotics against this persistent pathogen, particularly pronounced in the clinical settings. Because of an increased spread of carbapenem-resistant *P. aeruginosa* strains, WHO has now listed it as one of the three bacteria with critical priority as target of antibiotic therapy research. After having discussed the main reasons why carbapenem-resistant *P. aeruginosa* is listed as one of the three pathogens that require urgent action, the search for an alternative to the current inefficient treatment of infections, caused by carbapenem-resistant *P. aeruginosa*, will be discussed in the following sections.

3.4 The Description of Present Therapy

P. aeruginosa is a common cause of nosocomial infections worldwide. Both intrinsic and acquired adaptive mechanisms made it phenotypically and genetically resistant to most currently prescribed antibiotics. Several classes of antibiotics are routinely used to treat *P. aeruginosa* infections, such as beta-lactams (monobactam, cephalosporin or carbapenem), polymyxin, and aminoglycoside. Currently, piperacillin is the only effective antibiotic against *P. aeruginosa*. The mechanisms of resistance against antibiotics of *P. aeruginosa* are complex and multifactorial, related to different chromosomal and plasmid modifications [104]. Only in the USA, CDC reported that over 14% of MDR infections are caused by *P. aeruginosa*, which resulted in 405 in 1 year. *P. aeruginosa* infections with globally increasing rates of antibiotic resistance are characterized by high mortality. Limitations in development and design of new antimicrobial agents mean that there is a limited choice of available alternative treatments [105]. Phages, probiotics, and phytomedicine are currently the main alternatives used against drug-resistant *P. aeruginosa* infections. Based on the latest WHO report, carbapenem-resistant *P. aeruginosa* requires highest attention of clinicians because of high prevalence of isolates expressing a resistant phenotype. Interestingly, many research groups around the world show an increasing rate of *P. aeruginosa* drug resistance. However, only few are trying to develop new therapeutic strategies.

XDR and MDR phenotypes were the first reported among *P. aeruginosa* clinical strains. Further analysis showed that *P. aeruginosa* strains, which are resistant to all available antibiotics, belong to lineages called ST235 and ST111 [106, 107]. Efflux system-mediated genes and mutations were found responsible for the resistant phenotype in the clonal strains. Polymyxin is used in therapy against *P. aeruginosa*, but some reports showed an emerging resistance to this treatment as well. It seems that medical world is losing all available options for treatment of *P. aeruginosa*. This is the starting point of the crisis in management of *P. aeruginosa* infections. Naturally, an economic reason is decisive, but it is crucial to fund intensively the study of antibiotic resistant *P. aeruginosa* if the current treats created by its infections are to be defeated. Finally, even if the main goal were to control merely the distribution of antibiotic resistant *P. aeruginosa*, it is imperative to find ways to fight against carbapenem-resistant *P. aeruginosa*.

3.5 Enterobacteriaceae: Carbapenem-Resistant, ESBL-Producing Bacteria

Even though *E. coli* is the most prevalent intestinal anaerobic bacteria and a part of normal human micro flora, some of its strains are pathogenic. Hence, they are considered to be

clinically dangerous [108, 109]. Although it has been known from a long time that this Gram-negative bacteria is the main cause of urinary tract infections [UTI] and life-threatening bloodstream septicemia, our knowledge regarding the antibiotic-resistant *E. coli* is quite fragmentary. Alarming last year, WHO report urged to take a closer look at the present state of antibiotic therapy against *E. coli* [110]. It has been established some time ago that *E. coli* is resistant to ampicillin. However, recent findings report an increasing amount of resistant phenotypes among isolates from the TEM2 β -lactamase producing communities [111, 112]. Carbapenems are usually prescribed as part of a treatment of *E. coli* infections, but with an increased rate of resistance to these antibiotics, the deadlock of therapy against this microorganism, especially for nosocomial and community-acquired infections, is very serious. The knowledge of biologic phenomena of *E. coli* resistance can be helpful in understanding antibiotic resistances of other microorganisms such as salmonellae. This could be a starting point in developing novel clinical interventions [113, 114]. Antibiotic resistance, especially against third-generation cephalosporins and fluoroquinolones, has increased among the majority of clinical *E. coli* isolates [115, 116]. The major concern is that many of these resistant *E. coli* isolates are found in communities rather than in hospitals or in healthcare centers [53, 117]. The growth of resistances of *E. coli* isolates is also reaching the highest rate compared to other bacterial pathogens. All this stimulated WHO to include the carbapenem-resistant *E. coli* as a critical priority pathogen in its last report. Another obstacle to the efficient control of spread of resistances against antibiotics in human communities is the fact that drinking water and foods are the main vectors of *E. coli* infections in humans [118, 119]. Gagliotti et al. reported that the frequency of bacteremia caused by *E. coli* has increased in recent years solely due to the antibiotic resistance [120]. *E. coli* isolates from hospital and communities mutated into new strains of extended spectrum β -lactamase (ESBL)-producing bacteria must be considered as a critical problem worldwide. Moreover, current reports show that the presence of *bla*NDM-1 gene which produces the New Delhi metallo- β -lactamase (NDM-1) induces high resistance to carbapenem among *E. coli* strains [121–124]. An improved management is required to better control the NDM-1-producing *E. coli* isolates particularly among the clinical samples. It is clear that carbapenem should be used as a before last option in treating *E. coli* infections. In such a case, colistin might be an alternative against the carbapenem-resistant *E. coli*. The recent WHO report presented the need for an urgent change in current administration of carbapenem against *E. coli* associated infections. Without the new policy to modify ongoing strategies, we may be left with no antibiotics to treat the *E. coli* in the nearest future.

3.6 Farms and Antibiotics: Uncontrolled Use of Magic Bullets

During the last decades, a sharp increase of ovine, bovine, poultry, and fish meat production has occurred almost in all countries of the developed world. Around 70% of all antibiotics administered are used for not only livestock fighting animal infectious diseases but also growth stimulators. The overuse of antibiotics in animals (pets, livestock, and companion animals) has contributed greatly to the rise of MDR strains and problems of healing of antibiotic-resistant infections in humans. Since a great part of benefits of animal meat production is dependent on addition of antibiotics (penicillin, tetracycline and cephalosporins) into the animal food, it is difficult to convince farmers to abandon current procedures. Antibiotics have been used in animal production for decades worldwide. Supplemented in low doses to the feed of farm animals, they improve their growth performance. However, due to the emergence of microbes resistant to antibiotics, which are used to treat human and animal infections “antimicrobial resistance,” the European Commission decided to phase out, and ultimately ban, the sale and use of antibiotics as growth promoters in feed. Antibiotics will now only be allowed to be added to animal feed for veterinary purposes. Initially, The EU has banned antibiotics used in human medicine from being added to animal feed. Since 2006, EU has introduced the ban of use of antibiotics as growth promoters [125, 126]. Another side of this problem is that many of farmers are living outside developed countries in countries which are not really aware on how to use properly the antibiotics even for ill animals and do not introduce any legislative or other measures to stop these practices. The USA and China are the main global antibiotics users in industrial scale. Current evidences are showing that more than 75% of this ration is used in pig farm, and it calls for urgent intervention. Pig meat is popular in both countries, and any change in these patterns takes a time. However, we think that revisited policy in meat industry in these countries is required. In other words, worldwide education of all farmers and veterinarians about how to apply antibiotics on their farms can be a key step in our mission to prevent emergence of antibiotics originating on farms [127].

3.7 Strategies Against Overuse of Antibiotics in Animal Farms

It is more than half a century long that people were using antibiotics in animal farms in order to reduce chance of diseases and increased product yields. It is clear that overuse of many antibiotics as growth promoting agents in animals is the main cause of emergence of bacterial resistances against antibiotics in humans worldwide. It is evident that all parties including clinicians, healthcares, and veterinarians should stop using antibiotics for nontherapeutic cases. Public media

should propagate this attitude. In other words, as in EU, antibiotic use should be only allowed for therapeutic treatment of sick animal farms. In the case of sick animals, the antibiotics should be prescribed only after correct diagnosis of disease! Unfortunately, developing countries are still quite far away from such a disciplined behaviour. Taking together, it is likely that most of countries will stop the growth stimulating antibiotic use on animal farm soon. We also suggest to increase the funding for the development of animal vaccinations reducing the incidence of bacterial infections in animal farms.

3.8 Phage Therapy in the Fight Against the Antibiotic Resistances

Description of the bacterial antibiotic resistances against all prescribed antibiotics induced to analyze all alternative approaches including phage therapy. Although the first reports of phage therapy is supported from experiments in 100 years ago, but the clinical trials backing its widespread application are to close. Of course, new methods are the most desirable. Hence, phage therapy even being known from almost a century rapidly started to be considered as novel potential approach in the battle with antibiotic resistant infections. The main concern and limitation about phage therapy is that we faced with the high chance of quick spread of phage resistance factors among the other bacteria using horizontal transfer. Given the importance of fight against resistant bacteria in the intensive care units (ICUs), some experts are recommending to intensify the application of phage therapy to reduce outbreaks of resistant bacteria in ICUs [128, 129]. Following the Herelle groundbreaking discovery, first speculations about the role of phages in recovery of diarrheal illness initiated. Within the first 30 years after phage therapy introduction, the story went really conflicting and controversial. Many of decision-makers were insisting that still antibiotics can compensate the infectious diseases, and we do not need of any other options such as phage therapy. So far, rapid emergence of antibiotic resistance to many of already useful drugs almost changed the minds to now! However, for obvious reasons, the application of phage therapy seems not hard to generalize worldwide.

3.9 Ways to Solve the Crisis

The WHO released a report, showing that there is an urgent need for different strategies in managing bacterial infections. As mentioned before, the golden era of antibiotic treatments is over and we are now facing the crisis, which can still unfold into potentially even more catastrophic dimension. Failure to cure severe infectious diseases sends a clear message to clinicians and microbiologists, saying that we are witnessing a decrease of efficacy of antibiotic therapy. Therefore, new approaches should be developed to conserve the therapeutic efficacies of

currently available antibiotics and to apply new alternative treatments against persistent infectious. Millions of people are dying annually from untreated or untreatable infectious diseases, which are currently the third causes of deadly diseases worldwide. Rapid replication rate in bacteria (for some species less than 20 h) enabled them to adapt to high doses of antibiotics when exposed both in environment and human body. Summarizing, the problem of antibiotic resistance is mainly concerning the Gram-negative bacteria as well as for some opportunist microorganisms like *Acinetobacter baumannii*.

3.10 Possible Solution

The main way out of the current crisis is to start looking for new antibiotics, regardless of the lack of funding. Although polymyxin resistance was reported, we can still count on this novel antibiotic to fight against these microorganisms. *A. baumannii* is another pathogen causing worries in hospitals and environment. Since carbapenem-resistant *A. baumannii* is mostly sensitive to polymyxin, it would be beneficial to add it to the existing therapy after performing susceptibility tests in local laboratories. Phage therapy was also used in some trials against antibiotic resistant bacteria, but controversial results prevent researchers to apply this approach to other bacteria [130–132]; the same happened with research on effects of probiotics [133, 134]. Since it takes at least 3–5 years for developing new antibiotics, we should consider available antibiotics and their better administration in clinic.

4 Conclusion

Since *A. baumannii* and *P. aeruginosa* belong to ESKAPE group (<https://en.wikipedia.org/wiki/ESKAPE>) and meanwhile listed in the WHO report, we call for more in detailed research to find better strategy in management of this nosocomial infections. It is important that everyone who is involved in atmosphere, from young researchers to top officials in government and nongovernment organizations, are well informed about various aspects of the current situation. MDR and XDR *P. aeruginosa*, historically the first pathogens with resistant phenotype, are the main priority in the fight against the three bacteria from the WHO report.

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