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Disease
Narrative review

Antibiotic resistance: current issues and future strategies

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Abstract

The antibiotic resistance (antimicrobial resistance – AMR) and the particular emergence of multi-resistant bacterial strains, is a problem of clinical relevance involving serious threats to public health worldwide. From early this decade, a lot of studies have demonstrated a significant increase in the rates of antibiotic resistance by bacterial pathogens responsible for nosocomial and community infections all over the world. The AMR leads to a reduced drug efficacy in the treatment options available and therefore, to an increase in mortality rates. The original causes of the phenomenon are: environmental factors which favor a mutation of the genetic bacterial inheritance, thereby inhibiting the active ingredient of the antibiotics; unsuitable administering of antibiotics in veterinary, incorrect taking both in hospitals and at home and, lately, lack of investments in the development of new drugs. The alarming epidemiological data prompted the World Health Organization (WHO) in 2011 to coin the slogan "No action today, no cure tomorrow" in order to immediately implement a new strategy to improve the use of available drugs and to accelerate the introduction of new ones through a new phase of research involving private and public institutions. The European Union has stressed that the surveillance is considered an essential factor for an effective response to this problem but it has also highlighted that the results produced have been lower than expectations because of serious shortcomings such as lack of methodological standards, insufficient data sharing and no coordination among European countries. In Italy the situation is much more troubling; in fact, according to the Ministry of Health, 5000-7000 yearly deaths are deemed due to nosocomial infections, with an annual cost of more than 100 million €.These figures explain how the fight against infections is far from being won. The purpose of this review is to analyze the basic causes of the recurrence of the phenomenon, to explain the steps taken by the most important international organizations to face AMR and finally to suggest a possible way to search for new classes of antibiotics.

Keywords

Bacterial pathogens, Antibiotic resistance, Hospitals

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Introduction

The antibiotic resistance (antimicrobial resistance – AMR) is a global health problem that, because of different policies both in the use of antibiotics and their applications not always rigorous in the infection control practices, presents epidemiological differences in several countries. Until the late 50s the international medical community believed that the fight against infectious diseases had been won; unfortunately, in the last 30 years, the increasing rates of AMR revealed how that belief was illusory [1-3]. In 2008, the European Council invited the European Commission to promote cooperation between the Commission, the agencies and the United States against AMR; in 2011the WHO defined it the most serious threat to global public health, since discomforting reality of the loss previously effective drugs in combination with the slow discovery of new antibiotics threatens a post-antibiotic era of infectious incurable diseases [4-6].

The WHO reports that, despite the quality and completeness of the surveillance phase, epidemiological data confirm that in recent years there has been an increase in the rates of AMR and this worrying trend is not limited to specific pathogens or to a specific geographical area [7]. In 2013, it was estimated that in the USA there had been 2 million serious infections, 23,000 deaths and 35 billion $ of social and health costs [8,9]. The European Centre for Disease Prevention and Control (ECDC) has estimated that infections caused by a subset of drug-resistant bacteria are responsible for about 25,000 yearly deaths in Europe and that health care costs, added to the losses of productivity, amount to 1.5 billion € [10]. Today, the AMR remains the second leading cause of deaths worldwide and the third in the USA [11,12]. The WHO, in a report published in 2014, estimated 10 million deaths and 100 billion $ of economic losses due to antimicrobial resistant infections within the year 2050. In the action plan issued by the Commission in 2011, surveillance antimicrobial resistance is considered a sector where measures associated to a proper use of antibiotics are needed, along with the prevention and control of infections and, lately, to the development of new antimicrobials [13-15]. It's requested a close international cooperation in order to preserve both the future antimicrobial effectiveness as well the effectiveness of treatments.

Antibiotic resistance: epidemiology

The ECDC, through the European Antimicrobial Resistance Surveillance Network (EARS-Net), has recently alarmed about multidrug resistance of the pathogens Eskape, an acronym including enterococci, S. *aureus*, K. *pneumoniae*, A. *baumanii*, P. *aeruginosa* and Enterobacteriaceae resistant to cephalosporins, quinolones and carbapenems [16]. The methicillin-resistant *Staphylococcus aureus* (MRSA) is the worldwide most serious cause of resistant infections related to hospitalization; in fact, MRSA infections cause increased periods of hospitalization and mortality, with very high social and economic costs. In 2010, seven European countries such as Austria, Cyprus, Estonia, France, Greece, Ireland and the United Kingdom (UK), have reported a significant decreasing trend for the spread of MRSA as a result of aggressive interventions to control it. In countries like Italy, Hungary, Germany and Slovenia, the spread of MRSA strains was found increasing and the percentage rose to 25% in a quarter of European countries; in Italy the percentage is up to 38%, one of the highest value in Europe with a steady trend in recent years. Such epidemiological condition requires the use of anti-MRSA whenever a possible staphylococcal infection etiology is suspected [17-19]. It is also significant the proportion of pneumococci resistant to macrolides; Italy is among the first in Europe, with 27%, whereas the proportion of pneumococci not susceptible to penicillin is lower, about 10% in the last decade [17]. Among the Gram-negative pathogens, strains of E. *coli* and K. *pneumoniae* resistant to fluoroquinolones and

to third-generation cephalosporins have gone through a rapid and massive spread in Austria, Cyprus, Hungary and Italy where the rates of resistance to fluoroquinolones are respectively of 41% and 46%, whereas to the third-generation cephalosporins are of 20% and 46%. This phenomenon has caused a considerable increase in the consumption of carbapenems which are promoting the spread of resistant strains of the genus Acinetobacter and Enterobacteriaceae. In the case of some Gram-negative bacteria, as the A.*baumanii*, you may find strains resistant to all currently available antibiotics [20]. Some strains of K. *pneumoniae* carbapenem-resistant produce the enzymes responsible for the destruction of the antibiotic; the gene coding for this enzyme is inserted into a plasmid, a DNA fragment which can easily move from one bacterium to another, allowing the rapid spread of this resistance mechanism between different species. Other strains of K. *pneumoniae* have acquired resistance to carbapenems producing enzymes of different type, such as the metallo-beta-lactamase ones [21,22]. The first strain of these microorganisms was identified in January 2008 in Sweden and, within the following three years, other cases have occurred in the UK and the US and, among the microorganisms capable of producing these enzymes, there is also the E. *coli* [10]. Some countries such as Israel, France and the UK have started programs of active surveillance, checking positive findings to carbapenem-resistant Enterobacteriaceae (CRE) in patients who enter hospitals or have been hospitalized in the previous six months, reporting in any national health records the carrier state of pan-resistant microorganisms. Currently, the options for the treatment of infections by CRE are limited: two drugs only are available: tigecycline and colistin. Not all patients reply to these drugs and colistin implies a high risk of kidney damages, therefore, the best means to fight against the spread of these microorganisms is the application of a good practice sanitation inside hospitals [23].

Antibiotic resistance: mechanisms

Antibiotics interfere with the essential functions of the bacterial cells and the mechanisms of resistance exploit every possible strategy to prevent drug to hit its target [24,25]. The main mechanisms by which microorganisms develop their resistance are well known and include: destruction of antibiotics (e.g., through the beta-lactamase), modification of the target (e.g., mutation of the protein rpsL of the 30S ribosomal subunit, which confers resistance to streptomycin), extrusion using efflux pumps (by means pumps AcrAB-TolC which confer multidrug resistance) (Table I) [26-28].

The mechanisms of tolerance are still the subject of studies and it has been proved that the persistent bacteria are mainly responsible for the antibiotic tolerance as they can survive. These are sleeping cells tolerant of the bactericidal antibiotics which need active targets to kill the cell. The mechanisms underlying the formation of persistent cells are not fully known as, besides having important implications in the clinical manifestations of infection, they favor the emergence of resistance. The persistent cells, in fact, are destroyed more slowly by antibiotics and resume growing when the concentration of the drug decreases, so facilitating the onset of relapses [29-31].

Antibiotics	Mechanism of action
Bacitracin Cephalosporins Cycloserine Penicillins	Synthesis inhibition of bacterial membrane components
Amphotericin b Nystatin Polymyxin	Irreversible alteration of bacterial membrane permeability
Chloramphenicol Eritrocin Kanamycin Neomycin Tetracyclines	Alteration of protein synthesis
Dactinomycin Rifampin	Alteration of bacterial nuclear DNA

Table I. Mechanisms of action of antibiotics

Environmental factors in antibiotics resistance

Recent studies have shown how, in the environment, microorganisms never come in contact with certain antibiotics, including certain of more recent introduction into clinical and have resistance to these same molecules: an observation that led to the definition of the term bacterial resistoma [32]. It has been observed, in fact, that the genes which confer resistance to these environmental organisms are similar, but sometimes identical to those observed in their clinical omologous pathogens, among which the same ones producing antibiotics and lately those ones bearing the genes of the resistance [33]. Molecular studies have demonstrated gene transfer between microorganisms, even belonging to different genes; it is therefore plausible that the transfer of genes of AMR could also involve the human microbiota, even in the absence of selective pressure made by the use of antibiotics [34]. Such hypothesis cannot explain whether these products can select resistors, moreover the absolute absence of antibiotic sensitivity of microorganisms in the stationary phase of growth in vitro, if demonstrated in vivo, could justify the various therapeutic failures [35].

Use of antibiotics in veterinary medicine

Over the past three decades there has been an abnormal use of antibiotics in farm animal and this phenomenon is mainly due to two factors: growth in consumer's demand for animal products in middle-income countries and the spread of large herds, where antibiotics are not administered for therapeutic purposes, but both for preventive purposes and for the promotion of growth, that is, at low doses and for long periods [36]. At the level of health care, there has been a higher incidence of zoonotic diseases, of which 56 are responsible for 2.5 billion cases of infections in humans every year [37]. According to the WHO, a half of all antibiotics produced in the world is for animals and the percentage rises to 80% in the US, where farm animals, according to a recent report by the FDA (Food and Drug Administration), consume yearly 13,000 tons of antibiotics [7]. Each year, 100,000 people in the USA die in hospitals for bacterial infections, 70% of these infections are resistant to treatments established by the protocol [38]; moreover, MRSA is responsible for the death of 19,000 patients and causes seven million visits both at the doctors' premises or emergency rooms. The AMR in the USA has an estimated yearly cost of 20 billions $ [39]. The European Union (EU) reacted in 2006, prohibiting the use of antibiotics to boost animal growth; however, a study has evaluated the presence of antibiotics in 67.7 mg per kilo of meat produced in farms and French are still consuming more than a thousand tons of antibiotics each year [40]. Stated the widespread use of antibiotics, some bacteria responsible for ordinary intestinal or respiratory tract infections in animal species, have a higher resistance to the drugs most commonly used in veterinary medicine. The reasons leading to these practices are several: to avoid rapidly spreading infections in factory farms with a large numbers of young animals confined in limited areas and to speed production keeping in effective costs and times; however, rather than improving the hygienic conditions of breeding and the amount of food available for the animals, it's preferred to use massive quantities of antimicrobials with an exponential increase in the selection pressure of resistant pathogens. Antibiotics allow a reduction of one-third of the production costs and without their use 175,000 tons of food in addition would be required [8,39]. A lot of studies have shown that an excessive use of antibiotics in livestock can facilitate the development of food infections because of antibiotic resistant strains that pass from the gastrointestinal tract of animals to humans through ingestion of meat or dairy products. This practice has led to the emergence of new multi-resistant strains of bacteria including those of the genus Campylobacter, Salmonella, E. *coli* and MRSA, mainly identified in pig farms, which may be transmitted to humans through contact with animals or with the ingestion of contaminated food [40,41]. It's inte-

resting to note that the spread of resistance to antimicrobials in livestock, for example salmonella and campylobacter resistant to fluoroquinolones, is a phenomenon that goes side by side with the same phenomena found in hospitals since similar antibiotics are also used in both environments. A study in 2011 revealed that half the beef, chicken, pork and turkey sold in department stores in the USA contains germs resistant to antibiotics, particularly MRSA [42]. Some studies carried out in South America, have shown that children, never treated with antibiotics, have contracted food infections, due to the consumption of chicken meat contaminated with bacteria resistant to antibiotics [43-45]. The preventive administration of enrofloxacin, belonging to the family of fluoroquinolones, to treat infections of respiratory type in poultry, cause resistance to ciprofloxacin, an antibiotic from the same family, which is administered to humans to treat infections from Campylobacter and Salmonella spp. Tylosin, belonging to the family of macrolides, used in the past in the EU countries as a growth promoter and today for the prevention and control of infections in pigs is liable for the emergence of strains resistant to erythromycin, an antibiotic administered to humans in the treatment of infections of respiratory type [46,47]. The results of these studies prove that zoonotic infections are difficult to treat because of the limited number of therapeutic options, wherefore Europe, to reduce the risk of cross-resistance to antibiotics used in human medicine, by means of the EC Regulation 1831/2003 banned antibiotics for non therapeutic uses and let them be administered upon veterinary prescriptions to be reported to health authorities [48].

Irrational use of antibiotics in hospitals and communities

Each year more than 4 million patients in the EU are affected by infections related to health care with an estimate of 147,000 deaths. The most frequent infections are pneumonia, mainly those related to communities and hospitals, which are 19.4% of all infections, post surgical (19.6%) and urinary tract infections (19%). Bloodstream infections (10.7%) and gastrointestinal ones (7.7%) are particularly frequent too [7,40]. The phenomenon of multidrug resistance to antibiotics is of particular concern because of the risk of infection in hospitals, both Italian and European, where the rate of infection is very high especially for enterobacteria that commonly colonize the intestine without causing serious consequences. Unfortunately, some of them, because of the excessive use of antibiotics become resistant and among these especially *E.coli* (15.9%) and *K. pneumoniae* (8.7%), the latter with high resistance to most or all antibiotics [10]. Italy is at fifth place in Europe for excessive use of antibiotics for human health, the average European consume out of hospitals during 2014 is of 21.6 daily doses per 1.000 inhabitants and varies from 10.6 in Netherlands to 34.6 in Greece. Italy, with 27.8 doses, is at the fifth place, behind France, Romania and Belgium. As to the consumption of antibiotics in hospitals the European average is steady at 2 daily doses every 1.000 inhabitants. Again, the most virtuous are the Dutch, with one dose a day, while the worst are the Finns with 2.6, while Italy remains above the European average with 2.2 and, apart from the Finnish exception, Southern Europe prevails in consumption [49]. In Table II are summarized the main cause of abuse in antibiotics administering.

Improper use of antibiotics

- Late administration in critically sick patients
- Broad-spectrum antibiotics used too often or narrow-spectrum antibiotics used incorrectly
- Antibiotics doses lower or higher compared to the ones suitable for specific patients
- Antibiotic treatment duration too short or too long
- Antibiotic treatment optimized depending on the results of microbiological culture

A research carried out in Italy showed that 54% of admissions in all the operating units of infectious diseases are caused by bacterial infections, a growing trend in recent decades. In the USA, at least 2 million people are yearly affected by infections of bacteria resistant to antibiotics and there are at least 23,000 deaths as a direct result. The increase of resistance in the hospitals settings which affects particularly departments such as intensive care or other critical departments, is favored in addition to improper use of antimicrobial drugs as well as by surgical and invasive procedures through the horizontal transfer of resistant strains between patients colonized or infected (clonal dissemination mechanism) [50,51]. The epidemic of Enterobacteriaceae resistant to carbapenems, which involved a few years ago 15 hospitals in New York, is an example [52]. Some bacteria such as *C. difficile* can form spores resistant to the action of many biocides and can survive for a long time in the hospital environment so favoring epidemics [53,54]. The acquisition of resistance determinants, the selective pressure of antibiotics and the clonal dissemination of resistant microorganisms are the main factors responsible for the proliferation and spread of antimicrobial resistance in communities, although each of them carries a different impact on the species as to microbial and geographic areas. Community pathogens such as *S. pneumoniae* have become more and more resistant to traditional antibiotics, and community infections from MRSA are associated with a high morbidity and mortality even in young or adults not immune-compromised. Finally, the presence of strains of *Mycobacterium tuberculosis* XDR (extensively drug resistant) resistant to isoniazid, rifampin, fluoroquinolones, is a matter of concern [41,42,55]. The control of resistance does not obviously depend on good policies of antibiotic therapy only, but also on the rules of hygiene and infection control measures; in this regard lack of logistics in hospitals are proved; in fact, the single rooms are 24.2% in Europe, 10.5% in Italy [56,57].

Causes of the decline in the development of new antibiotics

Over the past 50 years two classes of synthetic antibiotics have been developed: fluoroquinolones and oxazolidinones, the former being broad-spectrum, whereas in the last 40 years three compounds of natural origin have been introduced: daptomycin, quinupristin-dalfopristin and fidaxomicin. No doubt that the development of antibiotics has dramatically dropped in the last 25 years; in fact, since 2004 five new antibacterial molecular entities were discovered. A recent survey conducted by IDSA the Task Force Antimicrobial confirmed the reluctance to start a new phase of research for new generation of antibiotics [58]. Antibiotic therapy is effected for a short period of time, usually not longer than two weeks, in contrast with the drugs used to treat chronic diseases, which are taken for a long time even for the whole life of the patient. Clinical trials designed to test the effectiveness of new antibiotics involve some difficulties as the need to evaluate their effectiveness against resistant pathogens and the impossibility to insert a placebo group for ethical reasons. In addition, the ability of bacteria to develop resistance to antibiotics shortens the period of time wherein these drugs can show the maximum of their effectiveness. Unfortunately, antibiotics provide a lower return on investments than other drugs, such as antiretrovirals [59,60]: before the expiry of the patent, a torvastatin, which is taken daily, generated yearly takings of 12 billion $, whereas the best-selling antibiotic, that levofloxacin, is taken only few days and grants yearly sales of 2.5 billion $. The development of antibiotics is facing increasing challenges, because of the high costs, currently estimated between 400-800 million $ for each approved agent [61]. For these reasons, research and development of new antibiotics have met a clear decline and many pharmaceutical companies have completely abandoned this sector finding it not profitable. In recent years, thanks to the changed economic conditions, the legislators of the USA and EU have removed some of the obstacles which have slowed the development of antibiotics granting a priority review for innovative medicines. The FDA has launched in 2012 the Generating Antibiotics Incentives Now (GAIN) Act, which provides incentives for companies that invest in research and development of new antibacterial molecules intro-

ducing at the same time new business models which may solve the problem of low sales volumes [62]. In March 2015, it was proposed to the USA Congress to double funds for the fight against the antibiotic resistance from 600 million to 1.2 billion $, strengthening the public research of new molecules and new diagnostic tests along with the promotion of a responsible use of these in both human and veterinary areas, including international co-operations, too. The Action Plan was published with detailed indications of the specific objectives to be achieved within 2020 with specific actions to be implemented [63]. In 2013, the EU announced to have financed a 800 million € research against both drug resistant bacteria and the use of last generation of antibiotics and additional 91 million € for 15 research projects involving 44 medium-size enterprises for the realization of new antibiotics to be used in food chains and consequently develop nanotechnologies useful to provide new antimicrobial drugs [64].

Another disincentive factor for the start of a new phase of research is the use of broad unsuitable-spectrum antimicrobials because they are considered a panacea against all infections and their use has reduced the effectiveness [65]. On the regulatory hand, the pharmaceutical companies have expressed their concern about the lack of formal guidance documents and the inconsistencies and the requirements of the protocol required to develop drugs as well as the uncertainty that the process currently required by the FDA will be accepted in the future, when a new drug will be tested. The availability of these guidelines by the FDA would remove this regulatory uncertainty, greatly increasing the ability of the companies to carry out the development of new antibiotics. The FDA, after collecting the proposals, has published a clinical protocol with the guidelines in five areas, so to carry out clinical trials for the development of new anti-infective agents [66].

Research and development of new antibiotics

The pharmaceutical industry has opposed to the spread of antibiotic resistance by focusing on the development of synthetic antibiotics using approaches based on high-tech genomics, recombinant chemistry and high-throughput screening (HTS). It was thought that a promising approach was to use as a target essential proteins and preserved bacteria, identified through genomic studies, but pharmaceutical companies have not been able up today to synthesize drugs with a spectrum of activities as appropriate. In fact, although in vitro studies have identified inhibitors of specific targets, these compounds did not possess the properties necessary to overcome the membrane of the bacterial cell, especially Gram-negative bacteria [67]. The international medical community has come to the conclusion that the new most promising antibiotics are the species-specific ones as they involve a lower risk of toxicity, since they are addressed against specific bacteria targets and do not damage the normal bacterial flora [68,69]. The species-specific antibiotics have also promising properties in relation to the potential development of resistance: while resistance against broad-spectrum compounds may emerge in any bacterium, including the commensal bacteria and then be transferred to the pathogen, this possibility is much lower in the case of a narrow-spectrum antibiotic, which acts against the target pathogen only [70,71]. The development of this class of antibiotics, however, will require the introduction of diagnostic tests able to quickly identify the bacterium responsible for the disease, in order to administer the drug indicated for the MRSA [72,73].

The antibiotics addressed against Gram-negative bacteria should be developed taking into account the fact that these pathogens are equipped with a membrane hardly accessible and of efflux pumps able to eject a large number of drugs. To overcome this, the new antibiotics should be relatively hydrophilic compounds, with a mass lower than 600 Da and include atoms which are not often found in natural compounds, such as fluoride and boron [74,75]. The hope for the introduction of new classes' antibiotics in next years is linked to development of effective platforms allowing the development of drugs' combination. As we learned from the use of drugs addressed against the tubercular micro-bacterium,

a therapy based on the combination reduces greatly the ability of pathogens to develop resistance. Therefore, with the possibility to develop a combination of new drugs to put on the market in an only pill should considerably slacken the development of the bacteria antibiotic resistance. The new platform should also permit the development of new drugs able to contemporarily act against more bacterium targets [76]. Lately, a promising approach for the development of new antibiotics consists in making them as pro-drugs, being activated by a specific enzymes of the bacterium of the compounds reactant against non-specific molecules to be linked to in a covalent bond [77]. Some current antibiotic present some features very similar to this ideal pro-drug: isoniazide, pirazinamide, etonamide and metronizadolo, the first three used in the therapy against the tubercular bacterium and the fourth as a broad-spectrum antibiotic against anaerobic bacteria; they all are drugs turned into active molecules inside the bacterium cells and linked to the target by a covalent bond. However, these drugs targets are specific molecules of the bacterium, whereas the ideal pro-drug should link to the molecule of the bacterium cell in a not-specific way so to increase the reactivity [78].

Conclusions

An increasing number of bacteria acquires resistance to use antibiotics actually used and are available very few new drugs to tackle the problem. Nowadays, antibiotic resistance causes about 700.000 deaths worldwide every year and within 2050 it is estimated that 10 million people will be at risk of death. The excessive and unsuitable use of antibiotics in farms along with their misuse and overuse at home even to treat diseases for which they are useless, makes it necessary to develop new drugs and then use them consistently on both humans and animals [79]. Since the targets affected by antibiotics, to slow the growth of the microorganism or kill it belong to a restricted set of chemical molecules, the resistance acquired through mutations tends to protect the bacterium against entire classes of antibiotics, rather than of a single one. Pharmaceutical companies have faced this problem by studying the genetics of bacteria and carrying out studies to identify new targets for antibiotics; from these studies new classes of compounds were created as inhibitors of leucyl-tRNA synthetase that, according to preliminary data, should not be subject to resistance mechanisms that affect the current antibiotics in use [80,81]. The new targets include enzymes from fatty acid synthesis, filamentous proteins sensitive to temperature (fts), DNA polymerase IIIa (dnaE), UDP-3-ON-acetylglucosamine deacetylase (LpxC) and deformilasi. Most antibiotics in advanced stages of development include now drugs referable to existing classes, such as glycopeptides. However, among the drugs both in pre-clinical and phase I of development, there are 8 drugs with innovative action mechanism and if this will take extensive validation studies, these new therapeutic approaches are promising [82]. Most governments in the industrialized world devote approximately 1% of their GDP to research and development of drugs what gives rise to intellectual property, but each country should allocate a fixed percentage of its GDP to research and development of new antibacterial drugs. Other stakeholders, such as health insurance private companies could financially contribute and achieve long-term savings through reduced stay in hospitals of their customers. It's essential to reduce the cost of drugs' development and risks for companies that carry out research; today, more than 10 years are needed to bring a new drug on the market and the costs exceed one billion $ of which more than half incurred during the phase III of clinical trials [83,84]. Stated that in phase II are tested the safety and efficacy of antibiotics, there is the need to replace part of a phase III with a larger phase II of large clinical trials, in order to provide patients with antibiotics in shorter times and at lower costs. This protocol has been successively achieved in the fight against AIDS through the quick approval of ARVs [85]. The development of new antibiotics is of global importance and must be sustained and intensified since the microbial evolution will non-stop continue, and drug resistance will emerge because of a natural selection. A way forward is to implement systems of antimi-

crobial stewardship, that is of guidance of antibiotic therapies, based on a greater involvement of infectivologists and a strict application of prevention and infection control measures [86, 87]. In this way next generations will be granted a better future.

Questions for further research

- Awaken the public to the suitable use of antimicrobials
- Strengthen prevention and control of nosocomial infections
- Reconsider end points for marketing authorization of new antibiotics
- Prepare follow- up reports
- Strengthen and coordinate research activities and clinical trials
- Tax incentives for industries and an establishment of public-private partnerships
- Train doctors on good practices

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The review in brief	
Clinical question	Antibiotic resistance has become a problem of global concern. The purpose of this review is not only to analyze the basic causes of the resurgence of antibiotic resistance but also to explain the steps taken by the most important international organizations in the fight against the phenomenon and then suggest a possible way to search for new antibiotics.
Type of the review	Narrative
Search of the literature	A number of full text articles published in English from 2000 to 2014 have been reviewed. The first search on the site PubMed allowed initially to collect 126.150 articles. The PubMed database has been considered for the bibliographic research and the following keywords were applied: antibiotic resistance bacteria, antibiotic resistance mechanism and evolution, research study of new antibiotics class.The exclusion criteria were: comments, letters to publishers, reviews and studies carried out before 2000. From each selected study, the following data were collected: year of publication, study period, type of study.
Conclusions	Due to the number of antibiotic resistant bacteria, very few effective drugs against infections are left. Therefore, this drove both pharmaceutical laboratories as well public agencies and universities to start a new phase of research based on leucyl-tRNA synthetase inhibitors and glycopeptides. Tests have shown good pre-clinical results.
Limitations	Clinical studies concerning patients with infections only, and not with other concomitant diseases, have been considered in order to prevent the non-statistical significance of epidemiological data.

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