Review Article

Antimicrobial Resistance Crisis and Combating Approaches

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Abstract:

Antimicrobial resistance is a major global public health challenge threatening the utility of antibiotics. Inappropriate antibiotic prescribing and sales, using outside of the health sectors, and genetic factors are mainly influencing the development of antimicrobial resistance (AMR). Antibiotics abuse in human, wildlife, and farming practices have an enormous health impact. Recently approved antibiotics are anticipated to help stem this crisis. To fight against antibiotic resistance crisis, development of collaboration among concerned stakeholders to establish policies, initiatives, and investments for new agents can be auspicious. New methods of antibacterial drug identification and strategies, neutralize virulence factors, are the substitute approaches to address the AMR threat. Some novel approaches have also been taken to develop alternatives to typical antibiotics for bacterial infection. Here, we tried to highlight some of the key reasons behind antibiotic resistance, management, and burden. Moreover, this paper also discusses recent developments in this area and a brief overview of future antibacterial agents.

Key words: AMR; Public Health; Antibiotic abuse; Bacterial infection.

Introduction:

Antibiotics have been substantially reducing mortality and morbidity in acute bacterial infections for many years. But, resistance of microorganisms to antibiotics threatens the effectiveness of one of the most important interventions in healthcare sector and there is convincing evidence that the consumption of antibiotic drugs incites resistance.[1] In recent years antibiotic resistance problem in bacteria has reached the exigency level developing the rates of bacterial resistance to traditional antibiotics at an ever-increasing rate. A relatively common occurrence of antibiotic resistance, multidrug-resistance and extensively drug-resistance are

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happening because development of novel-acting antibiotics has been reduced. Recently, the WHO (2014) reported "a post-antibiotic era- in which common infections and minor injuries can kill - far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century", thus poses unimaginable risks to animal health.[2,3] As systematic surveillance towards antibiotic resistance is absent, some leading organizations and governments have taken coordinated action plans to effectively control and conduct the risks involved. Though it is a complex and multidimensional task in global scale, there have been incentive developments in last few years.[4,5] The CDC has classified a number of bacteria many of which are already responsible for placing an effective clinical and financial burden on health care system, patients, and their families presenting as urgent, serious and concerning threats.[6,7]

Though the developing world is yet to assert a stable line systematic approach fighting against ABR, the developed world seems to have woken to the perils of ABR, formulated stiff policies and stimulated surveillance methods. Reports have estimated annual death rate in the USA, EU, and India from various drug-resistant bacterial infections are 23,000,

25,000 and 58,000 respectively.[2,4,5] In 2013, WHO[8] report was the ûrst comprehensive and closest to ground-zero analysis on ABR endorsing an action plan on antimicrobial resistance with five strategic goals. The reports of the European Union and the CDC also provide their territorial over-view of the situation. The latest of all is a report of 2015 by Global Antibiotic Resistance Partnership (GARP).[2-4]

1. Drivers Antibiotic Resistance

Intrinsic resistance is commonly found in the genome of the bacterial species. Resistance can be acquired by means of new genetic material or through sporadic mutations of intrinsic genes.[9] On mobile genetic elements, such as plasmids, genes can be inherited and acquired from relatives and nonrelatives respectively. The horizontal gene transfer (HGT) allows antibiotic resistance among different species of bacteria.[10] Genes for resistance to antibiotics, like antibiotics themselves, are ancient.[11,12] The genes that give in resistance are well-known as the environmental resistome and can be transferred from non-disease-causing bacteria to those that cause disease, moving forward to clinically significant antibiotic resistance.[13] As of natural selection, antibiotics withdraw drug-sensitive competitors, leaving resistant bacteria back to reproduce.[10]

Epidemiological studies have clearly indicated the relation of origination and dissemination of resistant bacteria to antibiotic consumption. Many studies have also found that increasing bacterial resistance is linked with the volume of antibiotic prescribed.[14,15] Antibiotics contribute to the development of resistant bacteria when they are prescribed incorrectly.[6] Studies have shown that treatment in 30% to 50% of cases, drug selection, or duration of antibiotic therapy is incorrect. Interestingly, 30% to 60% have been found as redundant, inappropriate, or suboptimal prescribed in ICUs.[6,16,17]

Self-medication, by antibiotics, is very usual in many parts of the world. In many countries of Asia, Africa, South and Central America, and even in Southern European countries, such as Italy, Spain, Greece and Malta, antibiotics are sold illegally.[18-21] Deficiency in controlling results cheap, easy and profuse access of antibiotic and promotes overuse.[22] Sometimes human ingests antibiotic by consuming livestock that is treated with it. Moreover, resistant bacteria in farm animals reach clients through meat products.[7,16] Antibiotic resistance is a rising problem among humans and wildlife in terrestrial or aquatic environments. The spread and contamination of the environment, particularly through "hot spots" such as hospital wastewater and untreated urban wastewater, are a serious public health problem.[23,24] Pollution

of the environment, by human waste, animals, and the pharmaceutical industry, enhances the antibiotic-resistant bacteria into the environment.[25]

Antibacterial products may also contribute to this problem when they are used for hygienic or cleaning purposes restraining the improvement of immunities to environmental antigens in both children and adults. Therefore, the versatility of immune-system can be endangered by increasing morbidity and mortality.[7,22] Antibiotic development is no longer considered as an economically wise investment for the industry because it is used comparatively short time and is often ineffective. Antibiotics are not as profitable as drugs treating chronic conditions such as diabetes, psychiatric disorders, asthma, or gastroesophageal reflux.[13,16,26] Physicians retain new antibiotics in reserve for only the worst cases due to fear of developing drug resistance rather than prescribing it immediately.[7,27] When new agents are finally used, the emergence of resistance is nearly inevitable thus the profits of the manufacturer, invests a huge amount of money into antibiotic development, are reduced.[2]

Regulatory authorization is mostly an obstacle for companies those are optimistic pursuing the discovery of new antibiotics.[7,27] Bureaucracy, the absence of limpidity, differences in clinical trial requirements among countries, changes in regulatory and licensing rules, and ineffective channels of communication are some of the difficulties in pursuing regulatory approval.[27]

2. Drug-Resistant Pathogen Listed by CDC and WHO

In 2013, CDC published[28] a list of top 18 drug-resistant threats to the USA and categorized it under 3 level of concern: urgent, serious, and concerning. Three of those threats were assigned as urgent threat category and twelve were assigned as serious threats. Threats which required relatively less monitoring and prevention activities assigned in the concerning category. Following CDC, WHO published its first ever list of antibiotic-resistant entitled "priority pathogens" - a catalog of 12 families of bacteria, posing the greatest threat to human health, on 27th February 2017. The list is divided into three categories according to the urgency of the need for new antibiotics: critical, high and medium priority.[29]

3. Burden Due to Antibiotic Resistance

The burden of antibiotic resistance is highly challenging and arguably not a comprehensible objective with current health data. For estimation of this burden, frequency and clinical impact of failures of antibiotic treatment are considered as two key quantities.[30] In most cases, data indicate that patients with resistant infections require

significantly longer hospital stays, more doctors' visiting, lengthier recovery and a higher chance of long-term disability. It is also a burden to families and communities for low wages and health care costs.[7,22]

4. Checkpoints to Manage Antibiotic resistance

Antibiotics are sold, illegally, without any prescription in several countries as well as self-medication with antibiotics is common in many parts of the world. This illegal sale at pharmacies should be prohibited by law enforcement.[19,31] Several factors may impact the decision of prescribing an antibiotic, such as the patient presentation and wishes, the true outcome of whether a prescription is written or not depends on the doctor's decision. The prescription should also be driven by knowledge of resistance.[32] A reduction in resistance happens when a reduction in antibiotic consumption occurs.[33] In the UK, delayed antibiotic prescribing is an extensive practice and its use is enforced by national guidelines, but it has been difficult to implement in other countries. However, similar to the UK delayed antibiotics prescribing is practiced in Norway and recent evidence shows that it may eventually lead to a reduction in application of antibiotic for sinusitis and otitis media predominantly.[34,35] A coordinated program of antimicrobial stewardship enhances the right use of antibiotics, improves patient outcomes, minimizes microbial resistance, and also decreases the spread of infections caused by multidrug-resistant organisms. This program covers building an assurance to use antibiotics only when needed, chooses the appropriate drug and administers the medication inappropriate dose and duration. It also demonstrates the improvement in patient care, shortening hospital stays, and reduction of healthcare facilities.[6,36]

The major contribution of point-of-care tests seems to decrease doctors' uncertainty. As all of the rapid tests are not necessary for primary care, only those are perfect, precise, simple to use and illustrate, rapid and affordable for a primary care setting are acceptable.[37] However, several point-of-care tests have been proven to be effective in reducing the number of antibiotics prescribed such as CRP rapid testing that gives the result within 3 minutes. Without compromising the clinical evolution of the patients, it has been shown the reduction of antibiotic prescribing in lower respiratory tract infections significantly.[38] Transmission of pathogens from one patient to another via the hands of HCPs or objects used in health care placed the patients at risk for antibiotic-resistant infections.[6] Careful hand hygiene, before and after all patient interactions during the delivery of healthcare, is critical to release the risk of transmitting both antibiotic susceptible and resistant bacterial pathogens. Asepsis of the healthcare

environment, as well as patient-care materials, should also be required.[39] Modernization of infection-prevention approaches, through utilization of robotic and automated sterilization technologies, would help with these efforts. Automated hand-washing disinfection technology improves hand-washing rates and self-cleaning hospital rooms can minimize the risk of HAIs.[36]

Recently, the National Healthcare Safety Network (NHSN) has been implemented by Advance Tracking Approaches for use by healthcare facilities to electronically report infections, antibiotic use, and resistance. These data allow regions, states, and facilities to identify and track antibiotic-resistant bacteria that are responsible for many HAIs. This public health surveillance system tracks antibiotic infections and resistance in humans and animals that are usually transmitted through foods, such as Salmonella, Campylobacter, and other bacteria.[6]

Antibiotics are normally prescribed according to a fixed regimen comprising a specific dose, dosage frequency, and length of treatment.[22] However, current evidence shows that elongated regimens may be useless since many clinical trials have shown that longer courses of therapy are often less effective than shorter ones.[17,36] Prolonged antibiotic therapy may facilitate the colonization of antibiotic-resistant bacteria, which might cause a recurrent occurrence of infection.[17] Clearly defined, intelligible, and national action plans need to be set up to manage the antibiotic resistance crisis.[36] It would comprise measures to collect data to inform decisions, minimize antibiotic abuse in medicine and agriculture, foster antibiotic stewardship, optimize the use of newer molecular diagnostic techniques, support resistance-related research, and promote the development of new antibiotics.[16]

The British Society has launched a global initiative entitled "Antibiotic Action" for antimicrobial chemotherapy which is a worldwide alliance of groups including the Infectious Diseases Society of America (IDSA), React, charities, and nonprofit agencies.[26] The objective of Antibiotic Action is to apply pressure and raise the profile of the antibiotic resistance threat with policy-makers whole over the world.[40] To address the lack of development of new antibiotics, Public-private partnerships (PPPs) are a potentially important resource.[26,36] For example, Biomedical Advanced Research and Development Authority (BARDA) and the U.S. government have participated in PPP initiatives for antibiotic research.[16]

Enactment has been signed into law or is under consideration to address challenges met by the pharmaceutical industry regarding antibiotic development.[27,39] Inspiration has been proposed to encourage pharmaceutical companies to

antibiotic drug development field; these include measures to streamline regulatory approval, promote economic viability, and provide alternative or supplemental funding in this area.[26,27]

5. New Agents for the Treatment of Bacterial Infections

Pharmaceutical industries have been prompted to revamp its antibiotic discovery and development programs because of thriving awareness of the antibiotic resistance crisis.[41]

While only five new antibiotics approved between 2000 and 2010 by FDA, this pace has been accelerated with four new antibiotics approved in 2014 alone and only one approved in 2015. However, after February 2015, no antibiotic was approved until May 2017. After a long gap on 19th June 2017 FDA approved Baxdela (delafloxacin) by Melinta Therapeutics; for the treatment of acute bacterial skin and skin structure infections. Recently on 29th August 2017, Vabomere (meropenem and vaborbactam) approved for the treatment of complicated urinary tract infections.[42] (Table I)

Table I: *Drug approved by FDA between 2011 and 2017*

Drug Name	Company (year)	Drug Class	Indication
Vabomere (meropenem and vaborbactam)	The Medicines Company (August 2017)	beta-lactamase inhibitor	Vabomere addresses gram-negative bacteria that produce beta-lactamase enzymes, particularly the Klebsiella pneumoniae carbapenemase (KPC) enzyme
Baxdela (delafloxacin)	Melinta Therapeutics (June 2017)	Fluoroquinolone	Delafloxacin is used to treat acute bacterial skin and skin structure infections caused by designated susceptible gram negative and gram positive bacteria
Avycaz (ceftazidime–avibactam)	Actavis (February 2015)	non-betalactam beta-lactamase inhibitor	For complicated intra-abdominal and urinary tract infections caused by *E. coli, K. pneumoniae, C. koseri, E. aerogenes, C. freundii, Proteus spp.* and *P. aeruginosa*
Orbactiv (oritavancin)	The Medicines Company (August 2014)	semisynthetic lipoglycopeptide	For acute bacterial skin and skin structure infections caused by *S. aureus* (including MRSA), *S. pyogenes, S. agalactiae, S. dysgalactiae, S. anginosus* group, and *E. faecalis.*
Sivextro (tedizolid phosphate)	Cubist Pharmaceuticals (June 2014)	Oxazolidinone	For acute bacterial skin and skin structure infections. *S. aureus* (including MRSA), *S. pyogenes, S. agalactiae, S. anginosus*, and *E. faecalis.*
Dalvance (dalbavancin)	Durata Therapeutics (May 2014)	semisynthetic lipoglycopeptide	For acute bacterial skin and skin structure infections caused by S. *aureus* (including MRSA), *S. pyogenes, S. agalactiae*, and *S. anginosus.*
Metronidazole 1.3% Vaginal Gel	Actavis, Inc. (April 2014)	Nitroimidazole	For the treatment of bacterial vaginosis caused by anaerobic bacteria and protozoa
Sirturo (bedaquiline)	Janssen Therapeutics (December 2012)	diarylquinoline	For multi-drug resistant tuberculosis
Abthrax (raxibacumab)	Glaxo SmithKline (December 2012)	monoclonal antibody	For Anthrax
Dificid (fidaxomicin)	Optimer Pharmaceuticals (May 2011)	Macrolide *antibiotics*	For *C. difficile*-associated diarrhea

6. Current Antibiotics in Clinical Development

Antibiotics such as new-generation aminoglycosides, beta-lactamase inhibitors, quinolones, ketolides, tetracyclines, and oxazolidinones are involved in the research pipeline.[27] Since September 2016, an estimated 40 new potential antibiotics, to treat severe bacterial infections, are in clinical development for the USA market and at least 11 are in phase 3 of clinical trial.[43]

7. Next Generation Approaches to Combat Antibiotic Resistance

The ubiquity of antibiotic resistance instructs that the drug development pipeline must include proactive screens for existing environmental resistance threats to new drugs and should look for substitute strategies for combating resistance besides the conventional antibiotic pipeline.[44] Lately, the pharmaceutical industries have been screening large libraries of synthetic molecules for antibiotic activity. New techniques in the invention of antibiotic, resistance and virulence inhibition, new goals and culturing techniques, and novel drug combinations are looking forward to conserving natural products as a non-stoppable source of new antibiotics.[45]

Marine bacterial samples, tropical rainforests, myxobacteria, and extremophilic bacteria are actively being observed.[26] The teixobactin discovering as foremost of a new class of antibiotics was reported in January 2015 by the use of a new technique called isolation chip or ichip to grow Eleftheria terrae in the laboratory and in soil.[46] Without killing the microbes new approaches treating infections are also being investigated.[36] Moreover, in last two years, significant progress has been obtained in the field of antibacterial nanodrugs having absolute properties, mode of action and activity against MDR bacteria and biofilms.[47,48] The genomes of organisms, produce natural antibiotics and biosynthetic pathways, have been investigated and identified respectively.[26] Besides, for producing a hybrid molecule with antibiotic activity, molecular techniques are being applied to clone genes accountable for antibiotic biosynthesis into a different strain. Analytical chemistry, synthetic biology, and bioinformatics are overcoming obstacles to antibiotic drug discovery[26,45] In January 2016, Czaplewski and his colleagues published a review of the alternatives currently under investigation, and found at least 19 different approaches, of which they decided, 10 should be given top priority.[49] (Table II)

Table II: *Alternatives to antibiotics that might be available soon*

Approach	Highlights	Mechanism	Probable use	Anticipated registration (49)
Antibodies [50-53]	Have strong science basis with history of safe use and a high degree of technical feasibility	Antibodies that bind to and inactivate a pathogen, its virulence factors, or its toxins	Prevent gram-positive and gram-negative bacterial infection;	Soon
Probiotics [54-56]	Probiotics are the functional food ingredients, which beneficially affect the host by improving its intestinal microbial balance.	Administration of adequate amount of live microorganisms offer health advantages by possibly therapeutic and prophylactic therapies	Prevent or treat *Clostridium difficile*-associated diarrhea or antibiotic-associated diarrhea	2018
Vaccines [57-59]	Vaccine-resistant bacteria have never been reported	Inactivated bacteria or bacterial proteins that stimulate the immune system	More gram-positive prevention than gram-negative bacterial infection	2019
Immune stimulation [60-62]	Successful antimicrobial therapy depends on an appropriate immune response.	Innate proteins or bacterial extracts that boost the immune system	Prevent or provide adjunct therapy for gram-positive and gram-negative bacterial infection	2021
Lysins [63,64]	Have direct antibacterial action, act to reduce bacterial burden, weaken biofilms, or both	Enzymes used by bacteriophages to destroy the cell wall of a target bacterium	Treat gram-positive bacterial infection	2022
Antimicrobial peptides [65-68]	Have broad spectrum activity, bactericidal and rapid action, low target - based resistance, and low immunogenicity	Small proteins that have direct antibacterial activity	Treat or adjunct for gram-positive and gram-negative bacterial infection	2022

Conclusions

Now it is clear that the alarming situation of global antibiotic resistance problem reflects the unregulated use of antibiotics and lack of importance of pharmaceuticals companies towards new antibiotic agents. Infectious disease specialists and institutional antibiotic stewardship program can play a great role against the development of further resistance. Pharmaceuticals companies should take an eye on this site instead of looking towards benefit only. Coordinated efforts of Public-private partnerships (PPPs), Legislation, HCPs, researchers, and representatives of the pharmaceutical industries can play a significant role against antibiotic resistance crisis. It is a matter of concern that only 10 antibiotics have been approved from 2011 to 2017 by FDA. However, about 40 antibiotics are in different stage of clinical trial and more drugs are anticipated to be available soon. Moreover, investigation is ongoing to develop effective alternatives to antibiotics which may protect us in WHO reported 'post-antibiotic era'.

Conflicts of interest: None.

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