Acta Scientific Microbiology (ISSN: 2581-3226)

Volume 7 Issue 3 March 2024

Review Article

Antibiotic Resistance in India: Counteractive Consequences Using Antibiotics During the COVID-19 Pandemic

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DOI: 10.31080/ASMI.2024.07.1360

Received: January 09, 2024

Published: February 22, 2024

Abstract

The rapid appearance and spread of antibiotic resistance is due to increased use of antibiotics inappropriately. Over the last 80 years, it has become more and more complex to get rid of it. The ability to track epidemics and study how resistance develops through experimental evolution is made possible by Whole-genome sequencing. Despite the fact that in vitro and experimental evolution studies on antibiotic resistance will benefit from the power and accuracy of genomic technologies, there is still much to learn, particularly about the relative significance of different environmental compartments that contribute to the phenomenon of resistance. In low and middle income countries, it is unfortunately difficult to identify bacterial pathogens during the COVID-19 pandemic since there aren't any easily accessible, affordable clinical or molecular indicators that can reliably distinguish between bacterial and viral infections. And that is how we came across a scenario in which antibiotic-resistant bacteria discovered a means to flourish more and bacterial super-infection became prominent in COVID-19 patients. In this review, we will therefore discuss about the severe situation of emergent antibiotic resistance during the COVID-19 pandemic in India as a result of increased antibiotic consumption.

Keywords: Antibiotic Resistance; Superbugs; Inhibitors; COVID-19; Pandemic and Genetic Evolution

Introduction

Antibiotic resistance is one of the most threatening public health problems in the world, and it has now become a more serious health risk after a pandemic in India [1]. Although it affected people prior to the COVID-19 pandemic, it took on a disastrous form after heavy misuse consumption of antibiotics during the pandemic. Bacteria have the common ability to easily transfer their genetic material within their population, by horizontal gene transfer (HGT) through plasmid. This ability helps bacteria to easily develop antibiotic resistance (AR) and spread it rapidly among every nearby cell [2]. Disease that were once easily treated with antibiotics can become untreatable due to antibiotic resistant bacteria, which can result in serious infections. Unaware individuals occasionally treat viral illnesses with antibiotics. Some people use it needlessly to treat all infections, such as sore throats, coughs, colds, flu, acute sinus infections, etc., despite the fact that it does not treat viral illnesses and is only advised by doctors because it reduces the risk of contracting additional bacterial infections caused by weakened immunity. Consequently, this made it possible for microbes to utilize all sources of resistance genes and antibiotic resistance is constantly increasing.

In the last three years, SARS-Cov-2 undoubtedly become the major problems over any other problem worldwide. Ultimately, in the health care system demand for acute care beds and the number of COVID-19 patients in the intensive care unit (ICU) has increased dramatically. When bacterial super-infection was a significant issue in patients admitted to the ICU and the main cause of disease severity was the inflammatory response there were no effect of antimicrobial stewardship (AMS) whose objective is to monitor better patient care, reduced antibiotic use, and cost-effective health care are favorable side effects. Surprisingly, we overlooked a large number of the antimicrobial stewardship (AMS) initiatives that were created and put into place in the previous decade as the pandemic spread but unfortunately there is no proof of its proper implementation during pandemic [3]. During the second wave of the COVID-19 pandemic in India, it was also reported that novel corona viruses and resistant *Salmonella Typhi* strains were frequently found simulta-

neously in patient diagnoses. Because the antibiotics which were commonly used by patients in a varying manner for viral infection which effect minimal inhibitory concentrations (MIC) of resistant strains might be causing co- presence in diagnostic report.

Discussion

The global situation of antibiotic-resistant infections since their discovery prior to the pandemic: Alexander Fleming developed penicillin in 1928, and two of the penicillin discovery team members identified a bacterial penicillinase in 1940, several years before penicillin was made available as a treatment [4]. The emergence of particular mechanisms of resistance has hampered the therapeutic use of the first potent antimicrobials, the sulfonamides, since their debut in 1937. The same mechanisms that caused sulfonamide resistance in the late 1930s still exist today, around 86 years later [5]. According to estimates from the World Health Organization, India had one of the highest rates of age-standardized infectious illness mortality in South Asia in 2008, at 377 per 100,000 people. Despite having a lower per capita use than many other nations, India had the greatest consumption of antibiotics in 2010 with 10.7 units consumed per person. As an illustration, the United States has 22 units per person [6]. In 2016, the acute infectious illness mortality was 416.75 per 100,000 people, which is twice the rate in the United States before the use of antibiotics (roughly 200 per 100,000 persons) due to a combination of inadequate public health systems, cheap drugs, untreatable newborn sepsis, and healthcare-associated infections, as well as hospital infections [1]. In tertiary care facilities, prescription audits reveal substantial usage of cephalosporins, penicillins, and fluoroquinolones [6].

According to a 2011 study, MRSA and other antibiotic-resistant bacteria are present in 50% of the beef, chicken, pork, and turkey sold in department shops in the United States. The eating of chicken meat tainted with bacteria resistant to antibiotics resulted in food infections in children who had never received antibiotic treatment, according to certain South American research [7-9]. However, pharmaceutical corporations have not been able to create medications with a variety of activities as appropriate up to this point. It was assumed that a potential strategy was to use as a target critical proteins and preserved microorganisms, found through genetic studies. In fact, irrespective of the fact that in vitro investigations have discovered inhibitors of particular targets, these substances lacked the qualities required to pass through the bacterial cell membrane, particularly in the case of Gram-negative bacteria. The international medical community has concluded that species-specific antibiotics are the most promising new ones since they have a lower risk of toxicity because they only target particular bacteria targets and do not harm the normal bacterial flora [10].

Effectiveness of novel antibiotics on superbugs and re-emerging of different antibiotic resistant strains

WHO's the list of priority pathogens or superbugs for the R&D of novel antibiotics in 2017 is summarized in (Table 1).

Priority1: CRITICAL	Priority2: HIGH	Priority3: MEDIUM
Acinetobacter baumannii, carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing	*Enterococcus faecium*, vancomycin-resistant *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant *Helicobacter pylori*, clarithromycin-resistant *Campylobacter* spp., fluoroquinolone-resistant *Salmonellae*, fluoroquinolone-resistant *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant	*Streptococcus pneumoniae*, penicillin-non-susceptible *Haemophilus influenzae*, ampicillin-resistant *Shigella* spp., fluoroquinolone-resistant

Table 1: List of WHO priority pathogens for research and development of novel antibiotics.

Plazomicin, eravacycline, sarecycline, omadacycline, and rifamycin (2018) and imipenem, cilastatin and relebactam combination, pretomanid, lefamulin, and cefiderocol (2019) are novel antimicrobial drugs that the US FDA has approved in the past two years. Regardless of their best efforts, doctors must constantly deal with the threat of bacterial resistance around the world [11]. There are various examples of such studies when it comes to using natural remedies in addition to antibiotics to treat AMR.

Given the current situation in combating AMR, innovative methods to pinpoint and priorities the genetic causes of AMR that are still unidentified are urgently required [12]. To mitigate bacterial resistance to antibiotics, novel antimicrobial methods and medications are therefore urgently needed [11]. Globally, in various stages of clinical development of new antibiotics combinations, some of them are already approved by FDA among total 43 new antibiotics at the end of 2019. Iclaprim which inhibit bacterial dihydrofolate reductase with diaminopyrimindine structure molecule where it is tested successfully in a randomized controlled trial (REVIVE-1) of phase 3 to treat ABSSI. Because it was found to be non-inferior to vancomycin and due to its lack of nephrotoxicity and capacity to suppress bacterial exotoxins, soon it will be approved by FDA and

proven to be the most helpful in combat Gram positive bacteria [13]. However, the quantity and effectiveness of these new medications fall far short of what is required to completely combat highly adaptive microorganisms. When it comes to re-emergence resistance, bacteria basically use these tricky adaptive mechanisms like to translation of new protein (enzyme) that can inactivate drug or by changing its cell permeability to reduce the uptake of drug and sometimes structural modification in the cell membrane that leads to drug efflux outside [14].

Recently, Nanotechnology-based approaches rang from the engineering and material sciences to biology and medicine. Due to the fact that nanomaterials are typically composed of carbon-based, emulsion-based, metal and metal oxide nanoparticles (NPs), they have been devised to combat harmful microbes and are cost-effective and capable of battling germs resistant to antibiotics. Researchers can create unique composite antimicrobial compounds for use in diverse applications through a variety of procedures that can vary with different qualities, such as size, morphology, electrical charge, and surface coatings [15-20]. Numerous studies have been conducted to determine the mechanism of action of metal-based nanoparticles. For instance, silver nanoparticles influence the permeability of the cell membrane and aid in inhibiting energy transfer by the transport chain of electrons by producing large quantities of silver ions. DNA damage caused by microbes to cells has also been discovered. Another form of nanoparticle that develops in cells and releases Zn^{+2} ions there are zinc oxide nanoparticles. These necessitate the creation of hydrogen peroxide and the breakdown of cell membranes. Titanium dioxide nanoparticles contribute to the synthesis of reactive oxygen, which in turn affects the cell membrane's structural integrity (Table 2) [21-28].

The drawback of this innovative technique is that it still has a challenging delivery system for clinical applications. Inhaled NPs can reach the liver, brain, spleen, heart, and lung because of their small size and potent cell absorption. Effective clinical translation requires the presence of nanoparticle toxicity. In the bone marrow, spleen, liver, and lung, NPs can build up as a result of NP administration. Recent research has mostly concentrated on delivering targeted bacteria to particular bodily sections but not to other parts of the body as a whole [29-34].

Spontaneous unexpected mutations with their adverse effect of using excessive antibiotics during pandemic

Total world estimates indicate that by 2021, the pandemic will have significantly increased morbidity and mortality worldwide. Global estimates indicate that as of the last week of October 2021, more than 46 lakh deaths have occurred out of 22.6 crore cases [49]. In India, out of more than 3.3 billion COVID-19 instances, more than 4.3 lakh people have died [50]. Nevertheless, as a result of COVID-19-related preventative and control measures like lockdowns, curfews, closures, travel restrictions, etc., a significant negative impact has been observed globally on the economy, socio-milieu, and health programs. A number of variants, notably Delta-plus, a sub-lineage of the Delta variant, have emerged as a result of the etiologic virus's exceptional capacity to undergo mutations [35]. Since its initial discovery in India, the Delta variant has been found in 132 nations and territories. It spreads more quickly, results in more terrible diseases, and is becoming the prevalent variant in many areas. The Delta Plus is thought to be even more contagious and dangerous. In the early stages of the infection, it was unclear if the infection was COVID or bacterial-related (pneumonia). Also delay in receiving the COVID test results. Concern of a co-infection with a multidrug-resistant (MDR) bacterial infection in complex cases, particularly when a combination is present. In individuals with COVID-19, microbial coinfection is likely to worsen the processes of occurrence, progression, treatment, and outcome of medical diagnosis and therapy were some of the obvious causes of antibiotic overuse and the reappearance of superbugs [36].

Human attempts to regulate bacterial development ultimately lead to the fixation of resistance determinants in human pathogens and commensals [37]. As we can see from the outset, antibiotics are a heterogeneous collection of compounds with the shared ability to inhibit bacterial growth at high concentrations. They are not a natural chemical group [5,51]. As a result, far lower concentrations than those employed in antibiotic therapy are necessary for them to have biological effects [52]. We should think about antibiotic resistance on account of the strong possibility that the compounds we employ as antibiotics today will never reach clinical quantities in their natural surroundings. It is not unexpected that bacteria express a huge number of genes involved in making or reacting to small molecules given the variety of secondary metabolites they create and the number of bacterial species present in the biosphere [53-55]. Therefore, it's achievable that certain genes could be utilized by bacteria in humans to develop resistance to the medications we use.

There is an important anthropocentric concept of "resistome", which is the pool of genes that could potentially confer an antibiotic resistance phenotype [38,39]. The resistome concept is helpful because it draws attention to the facts that environmental bacteria

Nanoparticles	Targeted Antibiotic Resistant Bacteria	Antibacterial Mechanisms	Factors Affecting Antimicrobial Activity
Fe_2O_3 NP	MRSA Klebsiella *pneumonia* MDR Escherichia *coli*	Disruption of cell walls through ROS	Dispersibility High chemical activity Air oxidation leading to magnetism Aggregation occurs
Ag NP	MDR Escherichia *coli* *Staphylococcus epidermidis* MRSA *Pseudomonas aeruginosa* *Vancomycin-resistant Enterococcus* *Acinetobacter baumannii, carbapenem resistant* *Pseudomonas aeruginosa Carbapenemandpolymyxin B-resistant* *Carbapenem-resistant* *Enterobacteriaceae* *Klebsiella pneumoniae* *Extended-spectrum betalactamase-producing organisms*	Lipid peroxidation Intercalation between DNA bases ROS generation Inhibition of cell wall synthesis Inhibition of cytochromes in the electron transport chain Ribosome destabilization Dissipation of proton gradient resulting in lysis Increase in membrane permeability Cell surface binding which causes lipid and protein deterioration Bacterial membrane disintegration	Shape Particle size
ZnO NP	*Klebsiella pneumoniae, Enterobacteraerogenes, ESBL-producing* Escherichia *coli* MRSA *Klebsiella pneumonia* Escherichia *coli* *Klebsiellaoxytoca*	Lipid and protein damage Adsorption to cell surface ROS production, disruption of membrane	Concentration Particle size
Cu NP	*Acinetobacter baumannii* MDR Escherichia *coli*	DNA degradation ROS generation, Cell membrane potential dissipation Protein oxidation Peroxidation of lipid	Concentration Particle size
Au NP	MRSA	Bacterial membrane disruption Respiratory chain damage, Reduced activity of ATPase The generation of cell wall apertures. Loss of membrane potential Decline in tRNA binding to ribosome subunit	Particle size Roughness
TiO_2 NP	*Staphylococcus aureus* Escherichia *coli* *Enterococcus faecium* *Pseudomonas aeruginosa*	Adsorption to the cell surface ROS generation	Particle size Shape Crystal structure
Si NP	MRSA	Disruption of cell walls through ROS	Particle size Stability Shape
MgO NP	*Staphylococcus aureus* Escherichia *coli*	Alkaline effect ROS generation Electrostatic interaction Lipid peroxidation	pH Particle size Concentration
Al NP	Escherichia *coli*	Disruption of cell walls through ROS	Particle size
SPIONS	*Staphylococcus aureus* Escherichia *coli*	NO release Production of ROS.	Particle size

Table 2: List of Nanoparticles and their targeted antibiotic resistance bacteria**.**

can produce pathogens with resistance phenotypes that affect humans and animals, and that the resistance genes found in clinical isolates make up a very small portion of all the potential resistance genes in ecosystems [40-41]. The strength of the selection pressure that humans apply to bacterial populations, which gives an advantage to those rare cells in populations that can express a resistance phenotype through gene mutation or through the introduction of new genes through lateral gene transfer (HGT), is thus one of the main factors causing the fixation of resistance genes. However, the development and administration of databases and bioinformatics tools is crucial for this attempt, especially given how quickly our understanding of the factors influencing resistance is expanding as more whole genome and next generation sequencing data become obtainable [37].

Current action plans and implementation on the control of antibiotic resistant infections

Public health concerns influenced the development and application of measures for prudent antibiotic usage and for preventing the spread of resistant bacteria, sometimes known as "antibiotic stewardship." Optimizing antibiotic use while employing affordable strategies to reduce antibiotic resistance and control *Clostridium difficile* is a key component of antimicrobial stewardship**.** For all US hospitals, the Centers for Disease Control and Prevention (CDC) recently established and standardized ASPs. Antibiotic stewardship has demonstrated its effectiveness, but it is not without constraints and difficulties. But the search for novel, effective compounds must go on, staying a cornerstone of the campaign against drug-resistant bacteria. Hospitals vary in size, location (rural, suburban, or urban), teaching vs. community focus, staff antibiotic prescribing practices, availability of full-time ID physicians, resistance patterns, and other factors. As a result, ASPs must vary amongst hospitals. One size definitely does not fit all [11,42].

Initiating antimicrobial stewardship programme AMSP activities by creating AMSP curricula, holding workshops, and creating AMSP research projects, the Indian Council of Medical Research (ICMR), New Delhi, India, has recognized the significance of constructing AMSP structures in health care institutions across the nation in 2018 (revised guidelines). An effective AMSP implementation requires a multidisciplinary strategy incorporating a range of specialists. Nevertheless, AMSP structure and procedures are lacking in the majority of Indian institutions. Effective methods for managing antimicrobial stewardship are like proper antibacterial treatment, enhancing the use of antibacterial prophylaxis before surgical procedures, creating and executing antimicrobial policy and standard treatment guidelines (STG), the prescriptions for antibiotics can be made more efficient through prospective audits, feedback, and prompt intervention, pre-authorization or formulary limitation and enhancing antibiotic prescriptions by administrative and instructional measures. In order to achieve these, a comprehensive strategy through a hospital policy on the sensible use of antibiotics is necessary. Hospitals that provide primary, secondary, and tertiary care are under the AMSP programme [56]. But when it comes to pandemic, health professionals' anxiety about contracting COVID-19 infection and refusal to enter COVID-19 ICUs and wards caused the healthcare system to collapse and fall into unintended neglect, which ultimately risked the programme of antimicrobial stewardship policy [43]. Although there was little evidence that bacterial superinfection was a substantial problem in patients admitted to the ICU and that the primary factor contributing to the severity of the disease was the inflammatory response, antibiotics were effectively monitored broadly [3]. While 15% of secondary bacterial infections after hospitalization are reported under AMR surveillance in India, studies have found that 3.1-3.5% of COVID-19 patients have bacterial co-infections. However, these patients' mortality rates have been as high as 56.7%, compared to 10.6% for all COVID-19 patients [43,44]. Experts in both high- and low-income nations agree that the following factors are necessary for efficient AMS implementation and operation: hospital leadership commitment, accountability, knowledge of pharmacy and infection control, education, hands-on training, monitoring, and surveillance, as well as consistent providing information and recommendations [57]. As the survey was done during a time when the environment was constantly changing due to the pandemic, their personal knowledge gaps about the function of AMS in emergency outbreaks were acknowledge by the AMS committee members.

Knowledge and skill gaps (individual-level factors) that hinder the application of AMS protocols were reported by participants (both AMS committee members and non-members). An ongoing need to improve the implementation of AMS was highlighted in a literature analysis from 2021 by emphasizing the need to create a culture of trust "by offering mutual assurance for action." According to the objective measurements gathered from the case questions and information from qualitative data, India and France perceived the greatest gaps between present and ideal levels, in comparison to the USA and Mexico [45-47].

A systematic approach to AMR was developed by Kerala and become the first state in India which included the implementation of empirical clinical guidelines for infection management, an apprenticeship training for under- and post-graduate medical trainees, and a strong State-wide training programme covering 50,000+

general practitioners. In low and middle income countries LMICs, where budgets are perhaps restricted, the commercial and governmental sectors can successfully collaborate to develop public health policies, including AMR. The lessons learned from Kerala's AMR approach can help other states and countries execute AMR action plans [48].

Conclusion

Antibiotic resistance mechanisms have been in place since the late 1930s and continue to exist today. In 1937, sulfonamides were the most potent antimicrobials, but later they became resistant to their targeted microbes. Later on, from veterinary to aquacultural zones, agriculture to other livestock farming, the use of heavy antibiotics for large-scale production of food sources causes different antibiotics' resistance to spread widely among other organisms, too. Many alternates were discovered from plants that have proven to be helpful in treating AMR but cannot produce systemic concentrations high enough to meet the required MIC concentrations. The re-emergence of this resistance is due to genomic mutational modification, which causes mechanical changes to either tolerate or efflux antibiotic drugs. The reason for this is antibiotic overuse. Nanoparticles are another useful technique for combating AMR, but their small size has a negative impact on various organs of the body. COVID-19 infection exacerbated the situation the most, and refusal to enter COVID-19 ICUs and wards harmed the healthcare system as well. Inadequate surveillance and negligence allow bacterial and viral co-infections to thrive during the pandemic.

Highlights

- The global situation of antibiotic-resistant infections since their discovery prior to the pandemic.
- Effectiveness of novel antibiotics on superbugs and re-emerging of different antibiotic resistant strains.
- Spontaneous unexpected mutations with their adverse effect of using excessive antibiotics during pandemic.
- Current action plans and implementation on the control of antibiotic resistant infections.

Future Perspective

We must understand threatening pathogens like COVID-19, Ebola, swine flu, and other roughly comparable viruses that enter our environment right away and spread susceptible infections among people and in society. It would undoubtedly affect other human pathogens specifically AMR bugs if the wrong medication was taken, which would worsen the situation most. Also, recognizing the importance to create AMSP structures in health care institutions and their implementation in the country in situation like pandemic.

Acknowledgment

This work was supported by Head, Department of Microbiology, Barkatullah University Bhopal (M.P.).

Conflict of Interests

The authors declare they have no conflict of interest.

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