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Antimicrobials and antimicrobial resistance: Causes and remedies – A short review

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The residuals of pharma wastes have been found to be present in wastewater, surface water, aquifers and even in potable water from treatment plants. The antimicrobial resistance (AMR) has been observed to increase and spread, primarily because of misuse and overuse of antibiotics, thereby threatening our public health, global economy and development. Furthermore, the mechanisms by which microbes are getting resistant, are changing and evolving continuously in an uninterrupted manner. If necessary actions are not taken soon enough to attenuate and arrest the antimicrobial resistance, it can lead to a situation where even the common diseases can become fatal. An attempt has been made in the present review to combine the reported causals (like release of active antibiotics from aquaculture and pharmaceutical companies, human and animal wastes etc.) and carriers (bacteriophages, imported animals, livestock insects, birds etc.) of AMR. In addition, this review also discusses some of the proposed tools, steps and methods (Re-sensitizing resistant bacteria to antibiotics, microfluidics, use of alternatives for antimicrobials) to fight AMR.

Keywords: Antibiotics, antimicrobials, resistance, pharmaceuticals, pharma wastes.

Introduction

The existence of antimicrobials can be traced back to 350-550 AD. However, their effective usage began in mid-1940s. Over the last decade the use of antimicrobials has increased by 40%. The pharma wastes are not properly degraded in the environment, which is why their presence has been detected in ground and surface water, and potable water. Both misuse and overuse of the antibiotics are considered as main drivers of antimicrobial resistance. It seems that the Golden Age of the antibiotics is coming to an end as alarming reports of AMR have flooded the scientific fraternity. AMR, if left unchecked, would not only affect the health sector but would also pose a great threat to the achievements made hitherto in poverty reduction and economic growth.

India is the numerouno consumer of antibiotics, and is also home to MDRTB (Multi-drug resistant tuberculosis) which is affecting 2 million people each year. Some of the greatest amounts of antibiotic residues ever detected were found in India. The causals and carriers of AMR are many. Due to this many have tried to develop strategies and methods to fight this threat. Microfluidics is an emerging discipline which can be a great tool to fight AMR. Use of alternatives like phyto compounds (having antimicrobial property), probiotics, prebiotics, synbiotics, bacteriocins, antimicrobial peptides, phage therapy etc. can also help in fighting AMR.

The main objective of the study is to combine many of the reported causals and carriers of AMR, some proposed tools, steps and methods to fight it.

Antimicrobials

Antimicrobials are the medicines used for inhibiting the growth of microorganisms or for destroying them[1]. Some reports have traced back the antimicrobial existence to 350-550 AD[2,3] but the effective usage of them began in mid-1940s. The last decade has seen 40% increase in global antibiotics consumption[4]. 63151 tons of antimicrobials were used in food animals in 2010 globally and is estimated to increase by 67% by 2030[5]. Recently, 3821 and 8927 tons of antimicrobials were used for humans and animals respectively in European Union[6].

Many reports have shown that the pharma wastes are not properly eliminated during WWTPs. Since the half-life of most of the pharmaceuticals are greater than the sludge retention time[7], more than 70% of the FQs are not removed by bioremediation, thus turning activated sludge into reservoir

for FQs[8] and when this sludge is released into the environment it facilitates towards AMR[9]. They are also not properly degraded in the environment[10]. Leaching of pharma wastes into the aquifers have also been reported[11]. Their presence has been detected in ground and drinking water samples[12–14], surface water, influent and potable water[15–17]. There is plethora of methods available for estimation of pharmaceuticals using chromatographical methods like gas chromatography, liquid chromatography, mass spectroscopy etc. Further reading materials on this can be found elsewhere[18]. Even plants are not spared from becoming the victims of the antibiotics. The effect of uptake of antibiotics by plants can be found from literature[19].

Antimicrobial resistance (AMR)

Microbes are believed to gain resistance through conjugation, transformation or transduction and mutation[20]. Antimicrobial resistance (AMR) is a natural phenomenon[21] and a survival strategy[22]. It is an example of Darwinian evolution in which the drug obstructs the biological processes of the microbe without killing it resulting in the development of the mechanism that resist the drug[23].

Some of the common antimicrobial resistance mechanisms through which microorganisms gain resistance are intrinsic resistance,mutation,inactivation of antibiotics, horizontal gene transfer, efflux pumps, biofilm resistance and quorum sensing[24].

The emergence of AMR was observed and reported since 1950s[25]. Reports suggest that antibiotics are still being overprescribed[26]. Doctors receive regular compensation from pharma industries for prescribing antibiotics[27]. The ability of bacteria to evolve and the overuse and misuse of antibiotics have encouraged them to adapt, resulting in the development of resistance against the antibiotics[28]. As per WHO the AMR is one of the greatest challenges to public health and can lead to 'post-microbial period' where common infections can become fatal[29]. The data available throughout the world was recently combined by WHO on AMR in common pathogens (*Escherichia coli*, *Staphylococcus aureus* and 5 others)[29].

The AMR has impacts on population health[30], world economy[31] and global development at large[32]. In fact, if the AMR spreads then it can cause (in 2050) the global GDP reduction comparable to the global financial crisis of 2008-2009 and may also widen the gap of economic inequalities between nations[31]. The current loss in GDP due to AMR is 0.4 to 1.6%[33]. The projected global loss due to AMR by 2050 is expected to be around USD 100 trillion which is about 3.5% decrement in global GDP[34]. The current mortality associated with AMR is estimated to be 700,000[35]. If the AMR is not contained, then by 2050 the death counts may exceed 10 million deaths annually[34]. Most of the victims will be from developing countries. Recently, UN General Assembly (2016) called for global plans to fight AMR[36]. If AMR continues to increase then it can lead to costly antibiotics/medicines, negation of achievements made against deadly diseases like HIV, tuberculosis etc. and can also make the complex interventions like organ transplant, cancer chemotherapy etc. dangerous and risky[37]. It can also result in prolonged illness, disability and death[38].

The "Golden Age" of the antibiotics seems to be coming to an end[39] as alarming reports of AMR has flooded the surface. Resistance against almost all major categories of antibiotics have been reported[40]. Even the last resorts are not safe now from AMR[41]. The spread of AMR through gene transfer has complicated the situation further[42]. AMR is turning the situation at present into a troublesome one as in some cases diseases (like gonorrhea) are reported to be untreatable because of resistance developed to even the last resort antibiotics[43]. Cases of drug-resistant TB (from 100 countries)[44] and rise in drug-resistant malaria (in Southeast Asia)[45] are also increasing the worry. Not only that, drug resistance to HIV medicines have also been reported[46]. The alternatives to antibiotics are very few and some of them are still in experimental stages. This also necessitates the immediate need to tackle AMR[47].

AMR if goes unchecked and if necessary actions are not taken soon enough to contain this threat then it will not only affect the health sector but also threatens the achievements made so far in poverty reduction and economic growth[48].

Antimicrobial resistance in India

Antibiotic resistance is a severe threat to the world and especially to India[49]. India is the top consumer of antibiotics in the world followed by China and USA[50]. India is also the home for MDRTB (Multi-drug resistant tuberculosis) affecting 2 million people each year i.e. a death in every 2 min (approximately)[51]. Moreover, around 58,000 neonatal sepsis deaths per year is also attributed to AMR[52].

Some of the greatest amount of antibiotic residues ever detected, were found in Hyderabad, India[53]. In Assam, antibiotic residues as high as 5 μg/ml equivalent of penicillin were detected in pooled milk samples[54]. In some food animals, 100% resistance against some drugs have also been reported[55]. Enteric pathogens are reported to be continuously evolving and developing resistance because of their genomic plasticity (remarkable plasticity of their genome). Moreover, the resistance mechanisms are also shifting from target modification to mobile resistant trait acquisition[56]. A detailed review on occurrence of antibiotics and antibiotic resistance in India can be found elsewhere[57].

Causals and carriers

The greatest causals of AMR are the use of antibiotics in livestock production[58] and massive use of antibiotics in humans and animals[6]. Use of livestock manure[59], extensive use of antimicrobials in aquaculture sector[60] are some of the input sources of resistant bacteria into the environment. Therapeutic use of antibiotics in veterinary and human medicines is one of the main drivers of acquisition/selection of resistant bacteria[61]. The release of active antibiotics from aquaculture and pharmaceutical companies, human and animal waste also increase the risk of AMR[62,63]. Reclaimed water is also a potential source of veterinary antibiotics[64,65]. AMR is also affected strongly by environmental regulator factors[66,67]. Moderately prudent and faulty antibiotics usage by medium and small dairy farmers[68] are also contributing to the spread of AMR.

Resistant genes and bacteria are transmitted to humans through intake of contaminated food and water, by coming in contact with contaminated soil, water and animals[57,69]. Overall risk is the highest in the South East Asia regions. Risk assessment approach and definitions can be found elsewhere[70].

One of the important drivers of AMR is horizontal gene transfer[71,72]. Bacteriophages are the prime molecular carriers for ARG transfer[73]. Levels of metals and antimicrobials in animal feedlot also effects the horizontal transfer of ARGs[74]. In a recent study, factors such as microbial adaptation, ecosystem, international travel etc. were attributed to the development of resistance against antibiotics[75]. Imported animals[76,77], livestock insects from animal farms[78] and even the birds have been reported to carry and spread AMR[79].

Methods and steps to fight and contain AMR

A global health treaty[80] with a legally binding governance mechanism[81] along with an ethical approach[82] can have positive effects in controlling this threat. Prevention and control of infection[83,84], making the general public aware of the potential loss of anti-infective drugs[85] and AMR situation, along with Global collaboration and accountability distribution for action against AMR[30] have also been suggested by many.

Reducing antimicrobial use i.e. AMU[1,86] (though some study suggests that reduction in AMU may not always lead to decline in AMR[87]), proper monitoring system for AMUs, use of digital data on AMU studies and tracking of antibiotics from production to its utilization to its ultimate fate in nature[88], understanding the social and behavioral drivers of AMU and AMR[89] can also be of great help. Limiting the use of critically important antimicrobials[86] and termination of antimicrobial use as growth promoters[90] is the need of the hour.

Re-sensitizing resistant bacteria to antibiotics[91,92] can be a valid method for treating AMR, electron beam irradiation of VA's[93] can also be used to fight it. SNAPPs (structurally nanoengineered antimicrobial peptide polymers) a new class of antimicrobials – having multimodal antimicrobial mechanism can be very much effective against Gram-negative resistant bacteria[94]. Microfluidics can also be a great tool to fight AMR (like knowing more about bacteria, improving susceptibility tests and developing new antibiotics)[95].

Optimization of the therapy through a good indication, adequate dosage, timely initiation and avoidance of too long therapy[37] and proper stewardship practices in hospitals and communities can also help in fighting AMR. More incentives should be provided for research to find new drugs, vaccines etc.[82]. Development of new antimicrobials cannot be seen as the only promising tool to fight AMR as sooner or later, bacteria may develop resistance against them too[96]. Use of alternatives like vaccination, phytocompounds (having antimicrobial property), probiotics, prebiotics, synbiotics, bacteriocins, phage therapy, CRISPR-Cas, immuno stimulants, cytokines, quorum quenchers, feed enzymes, nanoparticles and chicken egg yolk antibodies (IgY) should be explored more to fight AMR[97,98].

Treatment of wastewater containing antibiotics

Membrane filtration and ozonation were reported to be

effective in removal of antibiotics in various water matrixes[99]. Significant amount of degradation of antibiotics have been reported during storage in lagoons, composting or fermentation in anaerobic digesters[100,101].

Conclusions

The growing number of reports on AMR has necessitated urgent attention and action towards it. The failure of medicines against treatment of diseases has worsened the situation. There is an immediate need for development of new antibiotics and more so ever there is a need of strict regulations to limit the use of medically important antibiotics in animal food production. Moreover, alternatives like probiotics, prebiotics, synbiotics, bacteriocins, antimicrobial peptides, phage therapy, CRISPR-Cas, immuno stimulants, cytokines etc. should be explored more so that in case of total failure of antibiotics in future, we would be prepared.

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