



History:

Received: May. 2, 2020
Accepted: Nov. 17, 2020
First Published: Dec. 14, 2020
Collection year: 2020
Status: Published

Identifiers and Pagination:

Year: 2020
Volume: 12
First Page: 69
Last Page: 81
Publisher ID: 19204159.12.81
DOI:
<http://dx.doi.org/10.21065/19204159.12.81>

Corresponding author:

Noor-ul-Ain Department of Pharmacy,
The University of Faisalabad, Pakistan.T.:
+923367744654, Email:
ananoorkhan105@gmail.com

Citation:

Noor-ul-Ain, Saad bin Nawaz, Auj Mustafa
and Madiha Khan. Prevalence of antibiotic
resistance and its challenges for health
care providers. J App Pharm. Vol. 12:
2020. p. 69-81

Review Article

PREVALENCE OF ANTIBIOTIC RESISTANCE AND ITS CHALLENGES FOR HEALTH CARE PROVIDERS

Noor-ul-Ain^{1*}, Saad bin Nawaz², Auj Mustafa³ and Madiha Khan⁴

1. Department of Pharmacy, The University of Faisalabad, Pakistan.
2. Faisalabad Medical University, Faisalabad, Pakistan.
3. National Institute of Food Science and Technology, University of Agriculture Faisalabad, Faisalabad, Pakistan.
4. Department of Horticulture, Huazhong University of Science and Technology, China

Abstract

The load of antibiotic resistance has been prevailing worldwide which is deteriorating health and human development. Antibiotics also called antimicrobial are the wonder drugs used to act against the microbes. It can be bactericidal or bacteriostatic in action thus acting by either killing or slowing down the activity or growth of bacteria respectively in human body. Abuse of such drugs lead to amalgamation of bacterial cells in the body which makes bacterial cell wall prone to mutations and develop resistance against the drugs. The various lethal adverse effects lead to the clinical conditions challenging healthcare providers. Certain strains secrete enzymes that inactivates the antibiotics and decreases permeability of the cell membrane along with strengthening their efflux pumps. The most concerned organisms of this era are *E. faceium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and *Enterobacter spp* (ESKAPE) recorded by World Health Organization (WHO). Multifaceted interventions are required to mitigate the challenge of antibiotic resistance. Prohibiting the over the counter sale of antibiotics, clinical audits, utilization of valid diagnostic tests can be helpful in precise prescription of drugs. Public awareness about the poisonous use of antibiotics can decrease improper self-medication Clinicians.

Key words: antibiotic resistance. challenges, prohibition of bacterial growth, ESKAPE, mechanism of antibiotic resistance

Introduction:

The resistance of antibiotics is a major concern to the human development as it effects the capacity to treat infectious diseases. Antibiotics are known to have toxic effects on cells by inhibiting the growth of cells of micro-organisms [1]. The ribosomal part of the bacteria has the capacity to synthesize several new bacterial cells within few minutes. Antibiotics degrade the ribosomal part of the bacteria by crossing over the external walls of the microbe. It crosses the threshold of outer cell wall of microbes by an energy dependent mechanism which transfers it to the ribosomal part of the bacteria [2].

The antimicrobial resistance within pathogens like bacteria has become a worldwide concern leading to the towering level of mortality and morbidity. WHO (World Health Organization) has described it as 'global threat' [3]. According to WHO global surveillance report the consumption patterns of the antibiotics is 4.4-64.4 Defined Daily

Funding:

The authors received no direct funding for this research.

Competing Interests:

The authors declare no competing interests

Additional information is available at the end of the article.

Dose (DDD)/ 1000 inhabitants/day. Moreover, amoxicillin and clavulanic acid were recorded to be the most frequently consumed [4].

The main driver of antibiotic resistance is the use of antibiotics. It involves the wrong prescription or wrong diagnosis of the infection by practitioner. The easy availability of the OTC (over the counter) drugs and self-medication has also lead to the toxic load on human health [3]. However multidrug resistance has been recorded to have patterns regarding nature of organism such as Gram positive bacteria and Gram-negative bacteria [5].

Shortcomings of health care system increase the antibiotic load. Poor practitioner practices, before time recognition of the causative agent, less information about the susceptibility of the antimicrobial agents present in patients by means of bacteremia and broad spectrum of the antibiotic activity needs to be addressed [6] and the some chances of the people as they prefer self-medication and this leads to lethal effects on their body as well as augment the load of the resistance against some antibiotics which then increase the cost of the country for the health facilities and to cope up with these infections caused by the resistant species of bacteria [7].

The acquired resistance appears because of vulnerable types of bacteria which have its gene encoded with the confrontation. It replicates by transformation and it may include the transmit of material related to genes of other kinds of bacteria [6].

Origin and evolution:

All the way through the last almost two decades the amalgamation of the bacterial cell and haphazard way of using antibiotics in humans, animals and in agriculture has been occurring [8]. The main reason behind antibiotic resistance is the irregular practice and mismanagement [9]. Researches have a lot of gears to be deem throughout this appraisal in adding together to those of discriminating as well as corollary effects [10].

In the course of the possession of impulsive mutations that are present predominantly pertinent in favor of some mostly used drugs, like those of quinolones as well as those of rifamycins type of drugs which are intended for confrontation and transmutation [11]. For instance the type of bacteria *Salmonella typhimurium* is transmuted by summit alteration in those of gene as *henC*. The confrontation present in the bacteria to increase protamine [12].

Comparable consequences were represented within *Salmonella enterica*, wherever changes present throughout the isolate gene of tRNA bestow confrontation towards the mupirocin however by means of a diminution in augmentation [13]. Considering the intention of progress throughout the accretion of manifold chronological changes the mutation has not just by solitary spot mutations but it is also accountable to the elevated levels as it seems to have increased the resistance capacity [14]. Currently a number of bacterial genus, pathogenic species have grown to possess more presence of resistance due to the wrong way of using them in wrong practice as well as in the treatment with broad spectrum types of antibiotics [15].

These consequences always revealed that the microorganisms may have a very brawny discriminating strain (high concentrations of antibiotics), have those that are presented in the recent era; comparable to those which have offered at present, particularly in the treatment of the infections in humans [16].

The use of antibiotics in clinical aspects discriminating strain on to the pathogen that have evolved a growing level in the resistance against the antibiotics hastily compromising towards the effectiveness of the antibiotic [17]. The appearance of the resistance to the process of use of antibiotics in lot of vituperative pathogens in human appears to be a mushrooming worldwide crisis of health [16]. In recent times, WHO is focusing towards the more resistant types of bacteria which are making to treat the infections very difficult [18]. However, most of the resistance species come out transversely to be bacterial as well as those of fungal organisms which are pathogenic in nature which poses a particular challenge for health care professionals [19]. To treat the infections caused by the Gram negative strains as they possess cell wall that is more resistant to their entry and in addition to the huge fraction of the unique cell wall physiologies of the envelope present in their cells [20].

Invasion in bloodstream of the host through bacteria appears to be the mainly rigorous penalty towards the contagion, the most common isolate organism as those Gram-negative type of organism *E.coli* conscientious in favor of a propos of 1/3rd of the infections like this globally [21].

Moreover, presentation of a sturdy augments in occurrence. The resistance in using the antibiotics as in all of these isolate is extensive as well as increasing [22]. As a meticulous apprehension is Increase in occurrence due to the fact of the presence of the enzymes as lactamases and other enzymes Which act to inactivate the antibiotics which provide defenses against the infection as in both treatment and prophylaxis [23].

Antibiotic resistant strains of bacteria:

The spread as well as the emergence of the pathogens like bacterial, which are defiant to numerous types of antibiotics, is perhaps consider the main issue regarding health of patient public. Although the innovation of novel substances appropriate in favor of therapy of lethal infections [24]. Main community authorities related to or dealing with the health issues like WHO and other health care authorities strappingly alerted meant for the growing death rates attributed to the resistance of multidrug in most of the pathogens [25].

Resistance in many strains of bacteria and other pathogens towards the substances use to combat their effect is a topic of recent concern worldwide that is causing an alarming increase in the mortality as well as morbidity issues. The researchers are aiming for the invention of the treatment that is effective and does not cause resistance [24].

If we take it as an instance via vulnerable as well as defiant strains the *P. aeruginosa* media as LB moreover the appearance of the culture like broth or else on the agar media [26]. Opposing strains that are having closely similar genotypes in the midst of vulnerable strains through the exemption they must have distorted by means of the medical and the resistance in multi drugs.

The gene as *blaA* provides resistance to the carbenicillin, in the type like those of class constitutive of β -lactamase. And the most concerned organisms of this era are (ESKAPE) *E.faceium*, *S.aureus*, *K.pneumoniae*, *A.baumannii*, *P.aeruginosa* and *Enterobacter spp* [27].

This enhance is steady by means of the verdict that augmentation beneath biofilm surroundings increase in opposition flanked by the strains. [28]. *E. coli* is amongst the

majority recurrent isolates as of the urine of various patients through UTI which is also resistant to mostly used drugs as antibiotics foremost worldwide health predicament [29]. The resistant strains of bacteria of different species is due to the fact of the presence of mutation in the bacterial strains which make them resistant to various antimicrobials as the genetic mutation as well as the presence of the enzymes that leads to the decrease activity of these antibiotics [30].

P. aeruginosa a type of the resistant strain of bacteria that have in cooperation intrinsic as well as those of the adaptive confrontation towards the broad assortment of antibiotics as well as repeatedly cause the condition known as bacteremia [31].

Pneumonia and the Urinary tract infection (UTI) related to *P. aeruginosa* organism is the main species of bacteria infecting the patients with cystic fibrosis causing respiratory related infections.. In adding together, *P. aeruginosa* willingly produce biofilms, microbial communities that are surface-associated that are tremendously broadminded to the antibiotics as well as effectors of immune systems [32]. The aptitudes of *P. aeruginosa* cells to produce the biofilms throughout contagion facilitate its perseverance within the patient. In conclusion, *P. aeruginosa* hastily develops confrontation throughout anti-pseudomonal drug therapy. All the way through over appearance of efflux pumps, porins that cause loss, modification of targets of drug or modification of enzymes that act on antibiotics [33].

Mechanism of antibiotic resistance:

Antibiotic resistance mechanism is ancient and may be acquired due to change and mutated chromosomal gene pattern and receiving of foreign DNA coding for resistance determinants by the progression of parallel transfer of gene or lateral transfer of genes [34].

Sometimes the resistance developed in the bacteria is due to their intrinsic mechanism. The easiest instance of fundamental confrontation in the species that is due to as of the lack of the vulnerable target of the unambiguous antibiotic, as the biocide triclosan has wide efficiency alongside the Gram-positive type of bacteria along with most of the Gram-negative type of bacteria, but it is not able to block the augmentation of some members of the type of most lethal infections causative Gram-negative class *Pseudomonas*. Even though it was in the beginning it was contemplated that the direction of cause is due to an energetic efflux. In recent times it has been depicted that it is instead of caused because of the cart of an inconsiderate type allele of the *fabI* that codes enoyl-ACP reductase enzyme, the intention in favor of the triclosan in susceptible species. Built-inconfrontation of various Gram-negative type of bacteria to the most of the drugs is caused due to incapability of these compounds to cantankerous the external membrane, like the vancomycin antibiotic which is glycopeptide in nature that inhibits.

The crosslinking of the peptidoglycan via obligatory to the target d-Ala-d-Ala amino acids however are merely valuable in the Gram-positive type of bacteria as, in the Gram-negative type of organisms, as it cannot cantankerous the surface membrane as well as reach to those of the peptides within the periplasm [35]. Certain other mechanisms that are implicated in ESKAPE of drug confrontation are of various categories. They include the inactivation/alteration of the drug, alteration in the binding sites/targets or receptor, modification in permeability of the cell which results in the decreased drug accumulation intracellular, along with biofilm development [36].

Chemical modification of the antibiotic:

The synthesis of enzymes which are really able of inculcate chemical alterations in the antibacterial molecule is a well-recognized process of acquired resistance to the antibiotics in those of the Gram-negative as well as Gram-positive types of bacteria. As it is very interesting point to be noted, many of the antibiotics which are altered by these enzymatic regulated changes alter their action of mechanism by blocking protein formation at the level of ribosomes. Most of the altering enzymes types have been explained, moreover the mainly of the biochemical reactions they catalyze are following: [35]. Adenylation (aminoglycosides, lincosamides).

- Acetylation (streptogramins, aminoglycosides chloramphenicol)
- Phosphorylation (aminoglycosides, chloramphenicol)
- Adenylation

Irrespective of the reactions of biochemical nature, result is frequently linked to the process of steric interference which diminish efficacy of the medicine for its receptor, as a result, is depicted in higher bacterial minimal inhibitory concentrations [37].

Destruction of antibiotic:

One of the diverse mechanisms and well-known inactivation mechanisms is the hydrolysis or breakdown of β -lactam antibiotics, which includes penicillin, cephalosporins, and carbapenems. The β -lactamases are a family of more than thousands specific and unique individuals, with most groups relying on a serine residue to behave like a nucleophile essential for the ring opening of the β -lactam structure through a deacylation reaction [38].

Decreased permeability of antibiotic:

The external membrane of the Gram-negative type of bacteria is a rare structure that is made up of lipopolysaccharides, phospholipids, lipoproteins, and β -barrel porins. The outer membrane functions as an increased barrier for inhibiting the movement of toxic compounds across the membrane such as bile acid and antibiotics. Chemicals with weight of more than 600Da cannot generally permeable to the envelope of the Gram-negative bacteria. Therefore, antibiotics having a molecular weight more than 1400Da, such as vancomycin and daptomycin, cannot cross or transported through the external membrane of the Gram-negative type of bacteria. This characteristic of the outer membrane is one of the best obstacles or hindrance in the formation of novel antimicrobial potent agents targeting the Gram-negative pathogens [39].

Alteration in antibiotic binding site:

Sometime cells that are sensitive to or are exposed to prolonged administration of the drug in increased amount during treatment, the most beneficial and prominent mutational alteration occur in the multiple peptide resistance factor (*mrpF*) gene. The multiple peptide resistance factor gene protein is an integral cell membrane protein that have a positively charge lysine residue to phosphatidylglycerol forming lysyl-phosphatidylglycerol. This is formed in the cytosol and is then translocated to the outer face of the cell membrane. The multiple peptide resistance factor alterations associated with Dap occur in hotspots. They result in attain of functional alterations in the protein which increase the level of lysyl-phosphatidylglycerol in the cell membrane. It increases

the charge which is present in the outer face of the cell membrane which opposes the Ca-Dap and as well as decrease the amount of negatively charged phosphatidylglycerol needed for antibiotic binding to begin the membrane damage [40].

Efflux Pumps:

The probability that bacteria can attain resistance by exporting out antibiotics was firstly described in detail something around in 1980 when the person McMurry and his colleagues working along with him described the presence of proteins which are plasmid encoded have the ability of eliminating tetracycline and award resistance to this antibiotic in *Escherichia coli*.

Because of their part in resistance developed in antibiotics, efflux pumps are regarded to be as potentially most effective antibacterial prey, and the formation of bacterial efflux pump inhibitors can assist to improve the curative apparatus against resistant microorganisms. But, efflux pumps differ from other process of resistance such as beta-lactamases that act on a specific family of antibiotics, but in the case of efflux pumps any single efflux pump may eliminate a broad range of several families of antibiotics, so if we inhibit only bacterial efflux pump it will definitely enhance the bacterial sensitivity to different antimicrobials.

There are different ways and chances for blocking the action of Multi Drug Resistant determinants. One is the blocking or putting an impediment to the energy supplier essential for the action of efflux pump. There is one more possibility to block efflux pumps action by formation of compounds able to make competition with the antibiotics for their expulsion [41].

Biofilm Formation:

Biofilms that are organized group of various bacterial items which are mainly involved mainly in the chronic, serious along with repeated infection. Infections which are related to or caused by bacterial films are recurrent in nature in round about 65–80% of cases. Bacteria which are related to the biofilm formation are greatly resistant to antibiotics and related drugs. Information related to biofilm development, its progress and the resistance developed with it, is insufficient and a transdisciplinary effort which is look forward for understanding the reason and develop plans to address this complication.

Biofilm related infection is a three-dimensional and organized colony of the bacteria through complex architectonics which resides on the surfaces as well as is covered by capsule in the mesh of the hydrated type of polysaccharides, proteins along with DNA. Steady infection of bacteria in addition to raised resistance to the antibiotics is mostly caused by biofilm formation on target tissues [42].

Effects of antibiotic resistance:

Superbugs the antibiotic resistant organisms are the major concern. It is not just a concern related to laboratory although they have turn into a worldwide hazard accountable in favor of towering mortality as well as those of the infections which are life-threatening in nature [43].

Table1. Mechanism of resistance of different antibiotic classes

Antibiotic class	Example	Mode of resistance
Glycoprotein	Teicoplanin , vancomycin	Reprogramming of the synthesis Ofpeptidoglycan
Lipopeptides	Daptomycin	Alteration in the target
Macrolides	Erythromycin , azithromycin	Phosphorylation, glycosylation ,efflux system , alteration in target, hydrolysis
Beta-lactams	Cephalosporins, penicillins, monobactams and penems	Efflux system, hydrolysis, alteration in the target molecules
Lincosamides	Clindamycin	Efflux system, altered target molecule, nucleotidylation
Oxazolidinones	Linezolid	Altered target, efflux system
Quinolones	Ciprofloxacin	Altered target, efflux, acetylation process
Sulfonamides	Sulfamethoxazoles	Altered target, efflux system of bacteria
Cationic peptides	Colistin	Efflux system, alteration in the target
Rifamycins	Rifampin	Efflux system, alteration of the target molecule, ADP-ribosylation
Phenolics	Chloramphenicol	Altered target, efflux system, acetylation
Tetracyclines	Tigecycline, minocycline	Efflux system, target alteration, monooxygenation
Aminoglycosides	Gentamicin, streptomycin, spectinomycin	Nucleotidylation, efflux system, acetylation, phosphorylation, altered target

More than 70,000 patients in (USA) the United States of America expire almost every year as due to the hospital acquired infections of bacterial in nature. Almost every year, a predictable more than 20,000 patients pass on owed to the presence of the (MDR) multi drug resistance due to the act of infections from bacterial as in Europe. A lot of countries are in front of the saddle to the infections originating from hospitals (nosocomial) like that of (S. Aureus) infection as effect of the clonal propagation. (MRSA) Methicillin resistant S.aureus strains that are hurriedly scattering worldwide [44]. Infection due to the resistant strains of microorganism in additional costs to the healthcare facilities as well as loss of efficiency. It is considered to be atypical practice intended for the mainly related to the pharmacy companies to allocate antibiotics which may no longer be effectual or deficient of the authoritarian endorsement [45]. The re-administration of the antibiotics as of the preliminary cycle accelerates the mechanism of resistance [46].

Antibiotics persuade discriminating strain in favor of the bacteria to develop while administered recurrently or else absurdly. Persons as well as states engage in recreation a responsibility in the development of antibiotic confrontation. For instance Clarithromycin

use as well as its confrontation likewise augmented in Japan flanked by 1993 and 2000 in comparison to other countries [47]

Resistance in the unethical use of antibiotics has crooked to the rigorous worldwide health disaster as well as the people have no knowledge about their consequences that it poses onto the personal level and community type of level [43].

The expenses are reasonably towering in those emergent countries wherever the healthcare organization is not as highly developed as well as economy is also not like influential. India predictable that additional > 50,000 infants die as a consequence of resistance of antibiotics opposed to infections [48].

The researchers along with physicians as of the whole world concur leading the sternness regarding this disaster; though, the causes well as solution towards the antibiotic exploitation are convoluted. A lot of emergent countries encompass the deprived antibiotic provision laws. Furthermore, the contributor as well as patient role along with assistance are entwined in a number of gear that provide increase to necessitate to the appreciate dissimilar stirring factor in diverse populations, in an improved approach to resolve this condition [49].

Anticipation strategies:

If confrontation of the gene occurrence can be decreased by the side of the restricted echelons well as those of the use of antibiotics must be synchronized, it would be able to avert the worldwide crisis regarding the antibiotics as of mounting in this era [50].

Curtailed acquaintance as well as the misperceptions regarding employ of the antibiotics in addition to the ensuing penalty of maltreatment regarding these types of drugs have to be tinted effectively undertakes the matter [51]. The prevention of this global concern can be only possible by educating the community individuals regarding their use, misuse and the abuse concerning with this issue. The health professionals must guide them regarding the pros and cons of the use of antibiotics in an unusual manner as the people are supplementary liable to conviction as well as deem the advice regarding therapeutic purposes and knowledge related to medical concern [52]. While if the patient is diagnosed by means of contagion which have the requirements that it must undergo be treated antibiotic drugs for therapy professional ought to endow with the appropriate information regarding the convention like the dose given, regularity of the dose of drug, course of treatments well as the detrimental effects regarding its misuse [53]. Be short of conformity towards the antibiotic action itinerary as well as indecent self-medication is the major concerning favor of the augment in the diseases induced by the use of medications along with expansion of the resistance to antibiotics [50].

There must be the stop in the availability of the antibiotics especially the broad spectrum must not be available as OTC (Over the counter). Only the physicians or the health professionals must be allowed to give the drugs only on prescription Rx [54].

Future aspects:

In recent era there is much awareness about the developing resistance against the antibiotics and this is due to various researches. As the Researchers explored the uttered apprehension in mounting number of patients who are not curable due to omnipresent

infections owing to the process of (MDR) as multidrug-resistant bacteria every next year, as well as the boost in the death toll consequential as of the conditions like this. Hence, there is need to develop the antibiotics which have less resistance by combining the other compounds that are useful in decreasing the resistance of the antibiotics like Sulbactam, avibactam and vaborbactam which can decrease the resistance regarding the beta-lactamase enzymes. The combination of other such molecules with other classes of antibiotics to decrease the process of resistance [55].

Conversely, there must be an additional face towards the debate because the echelon of the confrontation in the direction of various antibiotic classes that have the appearance towards the phenotype of the MDR have been established to subsist constantly steady as well as comparatively stumpy. Furthermore, a number of the options that are accessible on behalf of the older types of antibiotics. A number of experts avow that those of the presently accessible types of antibiotics that are adequate intended for the tackling the hazard of rising resistance of the anti- bacterial stipulation to the disease that must be manage like that is without concern of profit base as well as on intercontinental convention [56].

Conclusion:

The speedy up-and-coming resistance to the antibiotics leads to the catastrophe as well as threatens to the unusual health reimbursement to the antibiotics production. This calamity is not just the health menace but a momentous confrontment for those like pharmaceutical along with the healthcare manufacturing, however in addition to the monetary load on behalf of the mutually developed as well as developing economy. The main rationale accountable in favor of the resistance to antibiotic that leads to disaster is self-medication as well as the over-dosage. Factors that influence is inadequate education relevant to health, scarcity along with derisory access in the direction of the treatment by the doctor all these are the reason meant for the people headed for to look for recommendations of the quack and to be coddle in the self-medication in its place of getting recommendation as of the expert health care member. Government desires to put into practice novel policies that can be helpful in tackling this concern. Also the need for more collaborative researches to manage the crisis like this. The contribution of the every individual for these concerns and also the development of resistance free drugs is need of the hour to cope up this issue.

Reference

1. Ekwanzala MD, Dewar JB, Kamika I et al. Systematic review in South Africa reveals antibiotic resistance genes shared between clinical and environmental settings. *Infect Drug Resist* 2018; 11:1907-20.
2. Zaman SB, Hussain MA, Nye R. A review on antibiotic resistance: alarm bells are ringing. *Cureus* 2017; 9(6):e1403.
3. McCullough A, Rathbone J, Parekh S, et al. Not in my backyard: a systematic review of clinicians' knowledge and beliefs about antibiotic resistance. *J. Antimicrob Chemother* 2015; 70(9):2465-73.
4. Limmathurotsakul D, Sandoe JA, Barrett DC et al. 'Antibiotic footprint' as a communication tool to aid reduction of antibiotic consumption. *J of Antimicrob Chemother* 2019; 74(8):2122-7.

5. Wong WF, Santiago M. Microbial approaches for targeting antibiotic-resistant bacteria. *Microb Biotechnol* 2017; 10(5):1047-53.
6. MacGowan A, Macnaughton E. Antibiotic resistance. *Medic* 2017; 45(10): 622-8.
7. Azzam MI, Ezzat SM, Othman BA *et al.* Antibiotics resistance phenomenon and virulence ability in bacteria from water environment. *Water Sci* 2017; 31(2):109-21.
8. Torres-Caycedo MI, Castro-Gutiérrez LT, Prada-Quiroga CF *et al.* Antibiotic Resistance: Origins, evolution and healthcare-associated infections. *Salud Uninorte* 2018; 34(2):494-505.
9. Oh H-S, Lee C-H. Origin and evolution of quorum quenching technology for biofouling control in MBRs for wastewater treatment. *J Membr Sci* 2018; 554:331-45.
10. Hamidian M, Hall RM. The AbaR antibiotic resistance islands found in *Acinetobacter baumannii* global clone 1–Structure, origin and evolution. *Drug Resist Updates* 2018; 41:26-39.
11. Edet U, Antai S, Brooks A, *et al.* Metagenomic assessment of antibiotics resistance genes from four ecosystems in the Niger Delta Area of Nigeria. *Asian J Biotechnol Genetic Eng* 2018; 1-10.
12. Rolo J, Worning P, Nielsen JB, Bowden R, *et al.* Evolutionary origin of the staphylococcal cassette chromosome mec (SCCmec). *Antimicrob Agents Chemother* 2017; 61(6):e02302-16.
13. Buultjens AH, Lam MM, Ballard S, *et al.* Evolutionary origins of the emergent ST796 clone of vancomycin resistant *Enterococcus faecium*. *Peer J* 2017; 5:e2916.
14. Bell G, MacLean C. The search for ‘evolution-proof’ antibiotics. *Trends Microbiol* 2018; 26(6):471-83.
15. Vikesland PJ, Pruden A, Alvarez PJ *et al.* Toward a comprehensive strategy to mitigate dissemination of environmental sources of antibiotic resistance. *Environ Sci Technol* 2017; 51:13061-13069.
16. Chevrette MG, Currie CR. Emerging evolutionary paradigms in antibiotic discovery. *J Ind Microbiol Biot* 2019; 46(3):257-71.
17. Richter DJ, Levin TC. The origin and evolution of cell-intrinsic antibacterial defenses in eukaryotes. *Curr Opin Genet Develop* 2019; 58:111-22.
18. [18] Calero-Cáceres W, Ye M, Balcázar JL. Bacteriophages as environmental reservoirs of antibiotic resistance. *Trends Microbiol* 2019; 27(7):570-577.
19. Wagglechner N, McArthur AG, Wright GD. Phylogenetic reconciliation reveals the natural history of glycopeptide antibiotic biosynthesis and resistance. *Nature Microbiol* 2019; 4(11):1862-71.
20. Windels EM, Michiels JE, Fauvart M, *et al.* Bacterial persistence promotes the evolution of antibiotic resistance by increasing survival and mutation rates. *The ISME J* 2019; 13(5):1239-51.
21. Goswami C, Fox S, Holden MT, *et al.* Origin, maintenance and spread of antibiotic resistance genes within plasmids and chromosomes of bloodstream isolates of *Escherichia coli*. *Microb Genom* 2020; 6(4):mgen.0.000353.
22. Merlin C. Reducing the Consumption of Antibiotics: Would That Be Enough to Slow Down the Dissemination of Resistances in the Downstream Environment.

- Frontiers Microbiol 2020; 11:33.
23. Liu J, Gefen O, Ronin I, *et al.* Effect of tolerance on the evolution of antibiotic resistance under drug combinations. *Sci* 2020; 367(6474):200-4.
 24. Bispo PJ, Ung L, Chodosh J, Gilmore MS. The Challenge of Antibiotic Resistance in Corneal Infection. *Foundations of Corneal Disease* 1st ed. Springer Cham, 2020; 277-88.
 25. Chee E, Brown AC. Biomimetic antimicrobial material strategies for combating antibiotic resistant bacteria. *Biomater Sci* 2020; 8:1089-1100.
 26. Lazar V, Martins A, Spohn R, *et al.* Antibiotic-resistant bacteria show widespread collateral sensitivity to antimicrobial peptides. *Nature Microbiol* 2018; 3(6):718-31.
 27. Frost I, Smith WP, Mitri S, *et al.* Cooperation, competition and antibiotic resistance in bacterial colonies. *The ISME J* 2018; 12(6):1582-93.
 28. Kortright KE, Chan BK, Koff JL, *et al.* Phage therapy: a renewed approach to combat antibiotic-resistant bacteria. *Cell Host Microbe* 2019; 25(2):219-32.
 29. Vignaroli C, Pasquaroli S, Citterio B, *et al.* Antibiotic and heavy metal resistance in enterococci from coastal marine sediment. *Environ Pollut* 2018; 237:406-13.
 30. Torres-Barcelo C. The disparate effects of bacteriophages on antibiotic-resistant bacteria. *Emerg Microbes Infect* 2018; 7(1):1-12.
 31. Ferrer-Espada R, Shahrour H, Pitts B, *et al.* A permeability-increasing drug synergizes with bacterial efflux pump inhibitors and restores susceptibility to antibiotics in multi-drug resistant *Pseudomonas aeruginosa* strains. *Sci Rep* 2019; 9(1):1-12.
 32. Go S-h, Kim S-h, Kang I-C, *et al.* The susceptibility of antibiotics for intracanal bacteria removal using *E. faecalis* biofilm model. *Oral Biol Res* 2017; 41(3):114-9.
 33. Caspar Y, Maurin M. *Francisella tularensis* susceptibility to antibiotics: a comprehensive review of the data obtained in vitro and in animal models. *Front Cell Infect MI* 2017; 7:122.
 34. Cui L, Iwamoto A, Lian J-Q, *et al.* Novel mechanism of antibiotic resistance originating in vancomycin-intermediate *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2006; 50(2):428-38.
 35. Khameneh B, Diab R, Ghazvini K, *et al.* Breakthroughs in bacterial resistance mechanisms and the potential ways to combat them. *Microb Pathog* 2016; 95:32-42.
 36. Santajit S, Indrawattana N. Mechanisms of antimicrobial resistance in ESKAPE pathogens. *BioMed Res Int* 2016; 2016.
 37. Munita JM, Arias CA. Mechanism of antibiotic resistance. In: Kudva IT, Zhang Q, Eds. *Virulence mechanisms of bacterial pathogens*, 5th ed. Wiley-Liss: Hoboken, NJ 2016; pp. 481-511.
 38. Yin K, Deng L, Luo J, *et al.* Destruction of phenicol antibiotics using the UV/H₂O₂ process: kinetics, byproducts, toxicity evaluation and trichloromethane formation potential. *Chem Eng J* 2018; 351:867-77.
 39. Weng X-D, Ji Y-L, Ma R, *et al.* Superhydrophilic and antibacterial zwitterionic polyamide nanofiltration membranes for antibiotics separation. *J Membr Sci* 2016; 510:122-30.
 40. Zhang Q, Liu H, Liu X, *et al.* Discovery of the first macrolide antibiotic binding

- protein in *Mycobacterium tuberculosis*: a new antibiotic resistance drug target. *Protein Cell* 2018; 9(11):971-5.
41. Blanco P, Hernando-Amado S, Reales-Calderon JA, *et al.* Bacterial multidrug efflux pumps: much more than antibiotic resistance determinants. *Microorg* 2016; 4(1):14.
 42. Nandakumar K, Jain AK. Biometric template protection: Bridging the performance gap between theory and practice. *IEEE Signal Processing Magazine* 2015; 32(5):88-100.
 43. Cooke K, Browning DF, Lee DJ, *et al.* Position effects on promoter activity in *Escherichia coli* and their consequences for antibiotic-resistance determinants. *Biochem Soc Trans* 2019; 47(3):839-45.
 44. Blaser MJ. Antibiotic use and its consequences for the normal microbiome. *Sci* 2016; 352(6285):544-5.
 45. Ogren MLSB. In vitro antimicrobial activity of liposomal ceftriaxone and liposomal amoxicillin and clavulanic acid against clinical isolates of companion animals with urinary tract infections. MSc dissertation. Lisboa: University de Lisboa 2020.
 46. Guillard T, Pons S, Roux D, *et al.* Antibiotic resistance and virulence: Understanding the link and its consequences for prophylaxis and therapy. *Bioessays* 2016; 38(7): 682-93.
 47. Tang KL, Caffrey NP, Nóbrega DB, *et al.* Restriction in the use of antibiotics in food animals and antibiotic resistance in food animals and humans– A systematic review and meta-analysis. *The Lancet Planet Health* 2017; 1(8):e316-e327.
 48. Kędziora A, Wernecki M, Korzekwa K, *et al.* Consequences Of Long-Term Bacteria's Exposure To Silver Nanoformulations With Different Physico Chemical Properties. *Int J Nanomed* 2020; 15:199.
 49. Deo SK, Rijal S, Kunwar SD, *et al.* Knowledge of Use of Antibiotic, Its Resistance and Consequences Among Students in Private Schools. *Cough. J Nepal Med Assoc* 2018; 56(212):740-4.
 50. Gentry EM, Kester S, Fischer K, *et al.* Bugs and Drugs: Collaboration Between Infection Prevention and Antibiotic Stewardship. *Infect Dis Clin* 2020; 34(1):17-30.
 51. Acevedo R, Bai X, Borrow R, *et al.* The Global Meningococcal Initiative meeting on prevention of meningococcal disease worldwide: epidemiology, surveillance, hypervirulent strains, antibiotic resistance and high-risk populations. *Expert Rev Vaccines* 2019; 18(1):15-30.
 52. Fridkin SK. Advances in Data Driven Responses to Preventing Spread of Antibiotic Resistance across Healthcare Settings. *Epidemiol Rev* 2019; 41(1):6-12.
 53. Peel A, Zangori L, Friedrichsen P, *et al.* Students' model-based explanations about natural selection and antibiotic resistance through socio-scientific issues-based learning. *Int J Sci Edu* 2019; 41(4):510-32.
 54. Tomczyk S, Lynfield R, Schaffner W, *et al.* Prevention of antibiotic-nonsusceptible invasive pneumococcal disease with the 13-valent pneumococcal conjugate vaccine. *Clin Infect Dis* 2016; 62(9):1119-25.
 55. Ruddaraju LK, Pammi SVN, sankar Guntuku G, *et al.* A review on anti-bacterials to combat resistance: From ancient era of plants and metals to present and

- future perspectives of green nano technological combinations. Asian J Pharmaceut Sci 2020; 15(1):42-59.
56. Varaldo PE, Facinelli B, Bagnarelli P, *et al.* (2020). Antimicrobial Resistance: A Challenge for the Future. In: Longhi S, Monteriu A, Freddi A, *et al.* Eds. The First Outstanding 50 Years of "Università Politecnica delle Marche", Springer, Switzerland 2020; pp. 3-29.



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