Review Article

Efficacy of some commonly used Antimicrobial agents against Pathogenic Bacteria

R.C. Lalhmangaihsangi, Anshu Kumar Singh*, Pankaj Kishor Mishra and Umesh Kumar
Department of Paramedical Sciences, Subharti Medical College, Swami Vivekanand Subharti University, Meerut, India 250005

Abstract

The most important global threat to human health is antimicrobial resistance. It is evident that Asia's nations are the epicentres of resistance, where bacterial infections are responsible for the rapid rise in antimicrobial resistance. Drug-resistant infections are mostly caused by the improper and excessive use of antibiotics. In addition to the spread of bacteria that are resistant to antibiotics, poor sanitation and access to clean water all contribute to the problem. Antimicrobial resistance has the potential to have an impact on people at any stage of life, including those working in the medical, veterinary, and agricultural fields. The use of antimicrobial medications, such as carbapenems, linezolid, and vancomycin, which are crucial for human treatment, has begun among veterinarians. The most recent discovery has a positive effect on the continued emergence of animal resistance as well as the risk that veterinary use and unauthorised drug use provide to the public's health. The veterinary profession needs to communicate more, provide better suggestions for how to utilise medications, and be proactive in order to reduce any potential harm to human health.

Keywords: Antimicrobial resistance, *Staphylococcus aureus*, *Streptococcus pyogenes*, Awareness, Betadine (Povidone iodine), Lysol (Benzalkonium chloride)

Introduction

Antimicrobial resistance has grown to be a serious issue for worldwide public health[1]. When bacteria, viruses, fungi, and parasites adapt over time and stop responding to antibiotics, illnesses become more difficult to treat and the risk of disease transmission, life-threatening sickness, and death increases. This phenomenon is known as antimicrobial resistance[2]. Also,

due to the involvement of several microbial populations, antimicrobial resistance is an ecological problem that has an impact on the health of people, animals, and the environment[3]. The resistance problem is resolved using One Health, a coordinated and multi-sectoral strategy, which considers an ecological perspective[45].

One health is defined as "the combined effort of numerous health science professionals, together with their allied disciplines and institutions-working locally, nationally, and internationally" in order to attain optimal health for people, domestic animals, wildlife, plants, and our environment[6]. The mutual dependence of humans and animals living in the same habitat, as well as a number of infectious diseases, served as the foundation for one health[7].

Since medicines are more readily available and consumed on a larger scale in developing nations like India, such countries are more likely to experience antibiotic resistance than other nations due to higher rates of inappropriate antibiotic usage[8]. Due to its inadequate sanitation and malnutrition, India is noted for having the highest antibiotic resistance[9]. Also, India's health sector dealt with inadequate public funding, which can create the conditions for the emergence of medication resistance[10]. A recent study underlined the significance by claiming that the use of antibiotics has helped to reduce antibiotic resistance in India. Antimicrobial resistance will make it harder to treat and control infections and diseases and will reduce the effectiveness of health care services[11].

Development of antimicrobial resistance

Target modification or Mutation

Target site is required for antibiotics to utilize antibacterial effect, in which the mutation or modification of the target site will interfere with the normal combination, thus affecting the effect of antibiotics. The frequency of mutation is 10^8 - 10^9 in which bacteria will develop resistance through mutation[12]. The mutations occur bound to the DNA replication process in

which most of them are harmful to the bacteria and thus it will not inherited at the cellular or population level. A related example of target site modification is the structural alteration of Penicillin Binding Proteins (PBP) [13] in methicillin resistant *Staphylococcus aureus*, PBPs are located on the bacterial cytoplasmic membrane having roles in the synthesis of cell wall peptidoglycan, acting as the target of β-lactam antibiotics. When the mutation occurs, the affinity between β-lactam antibiotics and the target PBPs will disappear resulting in the failure of the antibiotics to bind to the target including bacterial resistance.

Permeability reduction

In Gram negative bacteria, the cell wall constitute of proteins and lipopolysaccharides, in which the hydrophilic compounds are hard to pass through lipid bilayer therefore, facilitated by porin channels[14]. Omps is one of the sources for bacterial resistance. Exposure to antibiotics, the drug resistance can be produced by changing their properties and quantity of porin to reduce the membrane permeability of bacteria. The channels protein OmpF and OmpC allow antibiotic and other drug molecules to enter the bacteria. When bacteria are exposed to antibiotics, the mutations will be induced in the structural gene encoding OmpF protein, resulting in reduction or loss of OmpF channels. Thus, preventing the antibiotics such as β-lactams or quinolenes to enter the bacteria[15]. The inactivation of the structural gene of the OmpF protein can decrease the membrane permeability of bacteria, in which the β-lactams, quinolenes and other drugs can enter the bacteria in the acquired drug resistance.

Efflux Pumps

Efflux is the most rapid and effective resistance mechanism in the bacterial range of stress responses[16]. Bacterial efflux pumps are located in the plasma membrane of bacteria that serve as the transporters for substrates in the cytoplasm[17]. Various types of transporters are involved in which Resistance Nodulation and cell division (RND) are especially crucial in bacteria; other types of transporters are Small Antimicrobials Resistant, Multi - drug

resistance and Cytotoxic Substance Extraction and Main Facilitator Superfamily (MFS) ATP-binding cassette (ABC) [18].

In Gram positive bacteria, the efflux pumps transported involves are MATE family and MFS family whereas, in Gram negative bacteria, all the transporters family are involved where RND family is the most significant[1920]. The RND efflux families are involved in in the efflux of antibiotics, heavy metals, toxins and other substrates. A lot of active efflux systems are non-specific which leads to multidrug resistance, for example *E. coli* can extract resistance to tetracycline, florfenicol, erythromycin, etc.[21].

Hydrolase or Inactivating Enzyme

The antibiotic hydrolases or inactivating enzymes can hydrolyze the antibiotics by entering the cell and making it inactive before reaching the target site. There are many enzymes exist in bacteria which includes N-acetyltransferase, O- phosphotransferase and O-adenosyltransferase which transform the structure of antibiotics by acetylate, phosphorylate[22]. The β-lactamase can bind to the antibiotic by disrupting the cyclic structure and inducing degradation before reaching the target. β-lactamase are secreted by many bacteria up to eight different types in which each of them are capable of hydrolyzing specific β-lactamases[23]. Enterobacteriaceae bacteria can produce carbapenem enzymes and mostly destroy β-lactam antibiotics.

Metabolic Alteration or Auxotrophy

Metabolism is demonstrated by contributing the antibiotic lethality, resistance mutations are entirely identified in metabolic genes and metabolic dysregulation do not serve as mechanism of antibiotic resistance. In 2021, James's team found that mutations in core genes can induce antibiotic resistances, which are present in pathogenic *E. coli* including the genes of metabolic pathways, such as the sucA gene involved in catalyzing the tricarboxylic acid cycle. The metabolic toxicity inhibiting by killing effect of antibiotics, and eventually leading

to antibiotic resistance. The metabolic pathways synthesize amino acids, nucleotides, vitamins, fatty acids. However, metabolic coenzymes at the genetic level are found to be lacking in auxotrophs[2425].

The auxotrophs lack essential metabolic pathways, the growth of auxotrophs depend on the extracellular availability of the metabolites[26]. In 2022, Markus Ralser's team had revealed the metabolic mechanism that links the presence of auxotrophs to enhancement in metabolic interactions and gains in antimicrobial drug tolerance. The elevated efflux activities reduce the intracellular dug concentrations, allowing cells to grow above minimal inhibitory concentrations. The results indicate that the auxotrophy is beneficial to lighten the sensitivity of bacteria to antibiotics, thus reducing the antibacterial effect of antibiotics[27].

Target Protective Proteins (TPPs)

Combination of antibiotics protects antibiotic targets by eliminating their bacteriostatic effects. Daniel N. Wilson's team had divided the target into three types according to their mode of action[28]. In type I target protection, tetracycline ribosomal protection proteins (TRPPs) binds with ribosomes resulting in reverse of ribosomal structure, changes in ribosome configuration, and directly interfering with the interaction of tetracycline D-ring and 16S rRNA base C1054. Tetracycline drugs cannot bind to it and dissociate from the 30S subunit of the binding site by protecting the ribosome[29].

In type II target protection, antibiotics are indirectly removed by changes in target conformation. Antibiotic resistant ABC-F group of proteins is the source of clinical antimicrobials of ribosome 50S subunits, including lincomycins, macrolides, azadones, and phenols etc[30].

In type III target protection, proteins induce changes in target which can lead to binding of antibiotics. In recent years, clinically isolated *S. aureus* and other staphylococcus resistance

to fusidic acid has increased significantly, mainly due to the level of genes encoding the FusB-type protein.

Initiation of Self-Repair Systems

The *E.coli* multiple antibiotic resistance locus was recognized as a determinant for cross-resistance to tetracyclines, quinolones and β-lactams. Studies have shown that the active efflux mechanism is controlled by the global operon is one of the primary reasons for the multiple antibiotic resistance of bacteria. As the prototype of a multiple antibiotic resistance, *E. coli* MarR protein has a negative regulatory function on MarRAB operon which inhibits the expression of related drug resistance genes[31]. The initiation of self-repair systems reduces the rate of antibiotics by entering the cells and impact on cell structure and metabolism through gene regulation of the expression of related genes. This method cannot fully eliminate the bacteriostatic effect of antibiotics thus, enhancing the bacteria to tolerate the antibiotics.

Changes of Cell Morphology

The mechanism of antibiotics is dependent between cell growth and morphology by altering uptake efficiency of modulating relative body area. Increase in cell volume contributes in diluting the antibiotics by entering the bacteria, which include reducing of bending and widening of the surface volume ratio so that fewer antibiotics pass through the surface. In 2021, Aaron's team found that cells of the commonly used organism *C. cresentus* could regain the growth rates which had prior to antibiotics. Once when the antibiotic was removed, the cells returned to their original shape after a few generations[32].

Biofilm Protection

In the real world, the majority of bacteria coexist as communities that collectively resist the effects of antibiotics, with biofilm acting as a crucial type of defence. Bacterial biofilm is a

unique form of survival developed by bacteria adhering to the surface of the body's mucosa. It consists of a protein that is encased in an autocrine polymer matrix. In order to prevent antibiotic diffusion into the population and improve the protection offered by antibiotic inactivation, dense biofilms are used to give protection by building physical barriers[33]. The metabolic activity of biofilms decreases as a result of food and oxygen gradients, and biofilms can also increase drug resistance by changing the expression of pre-existing ARG[34]. By changing the spatial structure of the biofilms and encouraging the expression of resistance mechanisms, biofilms in single species biofilms might further benefit the collective.

Bacterial communities can survive antibiotic exposure by- (1) Collective drug resistance, the interaction in the community can enhance the capability of the members to resist antibiotics to continue to grow, thus increasing the MIC of the community. (2) Collective tolerance which includes interaction of community to reduce the rate of cell death during antibiotic treatment without increasing the MIC. (3) Contact protection to protect the interaction of its sensitive members by reducing the effective concentration of antibiotics in the community[35]. In the mixed biofilm, *P. aeruginosa* can react against the metabolic transformation of *S. aureus* by inhibiting the growth and provide *S. aureus* with protection against vancomycin[36].

Campaigns to aware about the antimicrobial resistances

Infections caused by drug-resistant organisms could lead to increase in mortality rate and causing a huge financial burden to the affected persons and health care systems[37]. Understanding the situation, the World Health Assembly (WHA) organized the Global Action Plan (GAP) on AMR in 2015 which is followed my many countries[38]. The Indian Ministry of Health and Family Welfare published the National Action Plan of AMR in April 2017. The National Action Plan equally focuses on human, environment, food and animal[39].

Antimicrobial Resistance Overview in India

The selection of resistant bacterial strains is influenced by the use of antibiotics in the human and animal health sectors[40]. Resistance development is a natural process. Both Gram-positive and Gram-negative bacteria are antibiotic-resistant. Examples include Neisseria gonorrhoeae, Klebsiella pneumoniae, Escherichia coli, Enterococcus species, Pseudomonas aeruginosa, Acinetobacter species, and Staphylococcus aureus. Multi-drug resistant tuberculosis and extremely drug-resistant (XDR) tuberculosis strains have emerged as a result of Mycobacterium tuberculosis's antibiotic resistance (XDR-TB)[41]. In terms of the ways they produce antibiotic resistance, bacteria form. Antibiotic resistance has been noted throughout the previous few decades. Examples include Vancomycin-resistant Enterococci (VRE), AmpC-mediated drug resistance in Enterobacteriaceae, New Delhi metallo-beta-lactamases in Gram-negative bacteria, and XDR Mycobacterium TB. Of late, drug-resistant mechanisms for carbapenems and colistin have been identified among Gram-negative organisms, and cases of colistin resistance are being reported[42]. Studies have shown that resistance to antibiotics is directly linked to their usage which would therefore be important to briefly review the patterns of antibiotic use (Figure 1)[43].

Staphylococcus aureus

Among the infectious disorders that Staphylococcus aureus can cause are bacteremia, skin and soft tissue infections, endocarditis, osteomyelitis, and pneumonia. It is a frequent human pathogenic bacterium. Methicillin-sensitive Staphylococcus aureus (MSSA) and methicillin-resistant Staphylococcus aureus are two types of Staphylococcus aureus based on their susceptibility to antibiotics (MRSA). Staphylococcus aureus is a common cause of infections in hospitals and the general population and has a high level of drug resistance[44]. The frequent use of anti-staphylococcal drugs has contributed to an increase in resistance rates due to community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) and the significant severity of Staphylococcus aureus infections[45].

Streptococcus pyogenes

Streptococcus pyogenes is an exclusive human bacterial pathogen which causes pyogenic infections that have a characteristic tendency to spread, opposed to Staphylococcal lesions, which are typically localized. *Streptococcus pyogenes* are responsible for non - suppurative lesions, acute rheumatic fever and glomerulonephritis[46]. Person - to - person transmission of *Streptococcus pyogenes* infections occurs in oral cavity, skin and wounds. In healthy person, it causes mild and self-healing purulent infections of mucosal membranes and skin, such as pharyngitis, impetigo and pyoderma[47].

Methicillin – resistant *Staphylococcus aureus*

MRSA is a hazardous and adaptable bacterial pathogen that can be virulent, resistant to antibiotics, and live for a very long time. Health care workers' hands can spread disease and enable cross-transmission. Hence, locating individuals who are MRSA carriers may help with MRSA infection prevention without clinical infection[48]. The control of hospital acquired surgical site infections and the identification of patients with infections by multi-drug resistant germs like MRSA should be prioritised. According to the recommendations of the Infectious Diseases Society of America[49], therapy with vancomycin or daptomycin is advised. Vancomycin has poor bactericidal activity, little tissue penetration, and rising reports of resistance and failure[50]. Daptomycin is effective against MRSA bacteraemia, treatment-emergent non-susceptibility is concerning[51].

Vancomycin has traditionally been used as a first-line agent for treating methicillin-resistant *Staphylococcus aureus* (MRSA) and other Gram-positive beta-lactam–resistant bacteria which are frequent etiologies of severe health-related infections[52]. Methicillin-resistant *Staphylococcus aureus* (MRSA) had become the most frequent causative agents of *S. aureus* disease in both hospitals and communities. In spite of the availability of several structurally different antibacterial agents, the therapy most frequently used for treatment of

MRSA infections has remained the glycopeptide antibiotics, primarily vancomycin[53] (Table 1)[54].

Antiseptics and disinfectants

Most microorganisms develop antimicrobial resistance, which is utilised to kill or suppress the microbes; Betadine (Povidone iodine) and Lysol (Benzalkonium chloride) were chosen as the two antimicrobial agents for decolonization to test their efficacy. Contrary to the widespread use of disinfectants such benzalkonium chloride and povidone iodine; the overuse of antibiotics has undoubtedly led to the creation and spread of resistant bacterial infections, with serious health repercussions[55].

Betadine (Povidone iodine)

Povidone iodine is the common use for antisepsis and wound healing due to their favorable efficacy and tolerability[56]. Povidone iodine is water soluble consists of a complex of iodine and a solubilizing polymer carrier polyvinylpyrrolidone. In aqueous solution, it occurs between the bactericidal agent and the povidone iodine complex[57]. Chemical composition of Betadine (Table 2)[58].

Mechanism of action and antimicrobial spectrum

Povidone iodine enters bacteria quickly, dissolving nucleotides, proteins, and fatty acids before ultimately causing cell death. Gram positive and Gram negative bacteria, as well as strains that are resistant to antibiotics and antiseptics, as well as fungi and protozoa, are all susceptible to the antibacterial properties of povidone iodine. With decreasing exposure duration, povidone iodine is also effective against enveloped and non-enveloped viruses, as well as bacterial spores. Also, povidone iodine is effective in vitro and ex vivo against mature bacterial and fungal biofilms[5960].

Side effects of Povidone iodine in environment and health

Povidone iodine contains a high concentrations which can be harmful for human beings causing itching, redness of skin, swollen, peeling skin with our without fever, trouble breathing or talking, swelling of the mouth, face, lips, tongue or throat. Povidone-iodine is considered to have the broadest spectrum of antimicrobial action compared with other common antiseptics such as chlorhexidine, octenidine, polyhexanide and hexetidine showing efficacy against Gram-positive and Gram-negative bacteria, bacteria spores, fungi, protozoa and several viruses[61].

Uses:

i). in small burns, scrapes, and cuts, betadine is applied directly to the skin to cure and prevent skin infection.

ii). In order to assist prevent infection; betadine is also applied in medical settings.

iii). Facilitate wound, pressure sore, or surgical incision healing

Advantages:

i). The broad spectrum bacterial and fungal activity of povidone iodine is quite high.

ii). Povidone iodine does not hurt or irritate the skin.

iii). Simple to apply to the skin and use.

Lysol (Benzalkonium chloride)

As an antiseptic and disinfectant, Lysol is a solution made of a blend of cresols and water. Except for bacterial endospores, benzalkonium chloride is a cationic biocide with broad-spectrum activity[62]. Lysol has been used as a cleaning agent in both homes and businesses. Lysol can also be used as a disinfectant in hospitals. The breakup of cellular membrane lipid bilayers, which causes cellular contents to seep out, has been linked to a modification in

cytoplasmic membrane permeability and bactericidal efficacy[63]. It is yet unclear how exposure to benzalkonium chloride causes bacteria to become more resistant to antibiotics, which has clear implications for public health[64]. Chemical composition of lysol (Figure 2)[65].

Mode of action

Benzalkonium chloride mechanism of antibacterial action involves altering the cell membrane permeability. The exact mechanism varies with the concentration of BKC solution in which ionic and hydrophobic interaction between the positively charged BKC head and negatively charged bacterial cell membrane leads to loss of coherence in membrane. The bacterial cell loses its physical and ionic stability, resulting in the release of cytoplasmic materials and cellular lysis. BKC is also effective in inactivating many viruses such as Herpes simplex virus-1 and Human immunodeficiency virus-1[66].

Side effects of Lysol on environment and health

Lysol can affect in physical and chemical factors which includes temperature, pH, relative humidity and water hardness. The more disinfectant increases the more temperature increase. Prolonged and repeated exposure can cause drying, defatting and dermatitis. Prolonged symptoms of lysol include redness of skin, edema, drying and cracking of the skin. Exposure symptoms include headache, dizziness, tiredness, nausea and vomiting.

Uses:

i). Kills 99.9 % of viruses and bacteria, including cold and flu.

ii). Kills the COVID – 19 VIRUS and emerging variants.

iii). Sanitizes soft surfaces.

Advantages:

i). Lysol helps to control and prevent mold and mildew.

ii).Lysol is useful in any household for killing germs.

iii).Lysol disinfectant kills bacteria, fungi and viruses.

Conclusion

Infectious disorders caused by Staphylococcus aureus include moderate skin and soft tissue infections, infectious endocarditis, osteomyelitis, bacteremia, and surgical site infections. It is one of the most common pathogenic illnesses in both the general public and hospitals. Longer hospital admissions, the prevalence of bacteria that are resistant to antibiotics as a result of antibiotic overuse, and ultimately greater mortality rates are all associated with Methicillin-sensitive Staphylococcus aureus (MSSA) strains. Among other pyogenic disorders, Streptococcus pyogenes, a particular human bacterial infection, also causes non-suppurative lesions, acute rheumatic fever, and glomerulonephritis. According to studies, Lysol (Benzalkonium Chloride) and Betadine (Povidone Iodine) are efficient antibacterial products for halting the spread of Staphylococcus aureus and Streptococcus pyogenes in public areas and clinical settings.

Conflict of interest

Authors declare that there is no conflict of interest.

References

1. Kang CI, Song JH. Antimicrobial resistance in Asia: current epidemiology and clinical implications. *Infect Chemother*. 2013; 45(1): 22-31.

2. World Health Organization. 2021. Antimicrobial Resistance.

3. Tompson AC, Mateus ALP, Brodbelt DC, Chandler CIR. Understanding Antibiotic Use in Companion Animals: A Literature Review Identifying Avenues for Future Efforts. *Front Vet Sci*. 2021; 8:719547.

4. World Health Organization. 2015. Global Action Plan on Antimicrobial Resistance. WHO, Geneva, Switzerland.

5. Torren-Edo J, Grave K, Mackay D. One Health": the regulation and consumption of antimicrobials for animal use in the EU. 2021; 2:14-16.

6. One Health Commission. 2018. What is One Health?

7. Collignon PJ, McEwen SA. One Health-Its Importance in Helping to Better Control Antimicrobial Resistance. *Trop Med Infect Dis*. 2019; 4(1): 22.

8. Kumar SG, Adithan C, Harish BN, Sujatha S, Roy G, Malini A. Antimicrobial resistance in India: A review. *J Nat Sci Biol Med*. 2013; 4(2): 286-291.

9. Taneja N, Sharma M. Antimicrobial resistance in the environment: The Indian scenario. *Indian J Med Res*. 2019; 149(2): 119-128.

10. World Health Organization. 2012. The evolving threat of antimicrobial resistance: options for action. World Health Organization. https://apps.who.int/iris/handle/10665/44812.

11. Ganguly NK, Arora NK, Chandy SJ, Fairoze MN, Gill JP, Gupta U, et al. Rationalizing antibiotic use to limit antibiotic resistance in India. *Indian J Med Res*. 2011; 134(3): 281-294.

12. Davies J, Davies D. Origins and evolution of antibiotic resistance. *Microbiol Mol Biol Rev*. 2010; 74(3): 417-433.

13. Alexander JAN, Chatterjee SS, Hamilton SM, Eltis LD, Chambers HF, Strynadka NCJ. Structural and kinetic analyses of penicillin-binding protein 4 (PBP4)-mediated antibiotic resistance in *Staphylococcus aureus*. *J Biol Chem*. 2018; 293(51): 19854-19865.

14. Chevalier S, Bouffartigues E, Bodilis J, Maillot O, Lesouhaitier O, Feuilloley JG, Orange, et al. Structure, function and regulation of *Pseudomonas aeruginosa* porins, *FEMS Microbiol Rev 2017*; 41(5), 698–722.

15. TorresMoya A, Mulvey MR, Kumar A, Oresnik IJ, Brassinga KC. The lack of OmpF, but not OmpC, contributes to increased antibiotic resistance in Serratia marcescens. *Microbiol Soc* 2014; 160(9).

16. Rahman T, Yarnall B, Doyle DA. Efflux drug transporters at the forefront of antimicrobial resistance. *Eur Biophys J*. 2017; 46(7): 647-653.

17. Blanco P, Hernando-Amado S, Reales-Calderon JA, Corona F, Lira F, Alcalde-Rico M, et al. Bacterial Multidrug Efflux Pumps: Much More Than Antibiotic Resistance Determinants. *Microorganisms*. 2016; 4(1): 14.

18. Li XZ, Plésiat P, Nikaido H. The challenge of efflux-mediated antibiotic resistance in Gram-negative bacteria. *Clin Microbiol Rev*. 2015; 28(2): 337-418.

19. Costa SS, Viveiros M, Amaral L, Couto I. Multidrug Efflux Pumps in Staphylococcus aureus: an Update. *Open Microbiol J*. 2013; 7: 59-71.

20. Reygaert WC. An overview of the antimicrobial resistance mechanisms of bacteria. *AIMS Microbiol*. 2018; 4(3): 482-501.

21. Swick MC, Morgan-Linnell SK, Carlson KM, Zechiedrich L. Expression of multidrug efflux pump genes acrAB-tolC, mdfA, and norE in Escherichia coli clinical isolates as a function of fluoroquinolone and multidrug resistance. *Antimicrob Agents Chemother*. 2011; 55(2): 921-924.

22. Tooke CL, Hinchliffe P, Bragginton EC, Colenso CK, Hirvonen HA, Takebayashi Y, et al. β-Lactamases and β-Lactamase Inhibitors in the 21st Century. *J Mol Biol*. 2019; 431(18): 3472-3500.

23. Ghafourian S, Sadeghifard N, Soheili S, Sekawi Z. Extended Spectrum Beta-lactamases: Definition, Classification and Epidemiology. *Curr Issues Mol Biol*. 2015; 17: 11-21.

24. Sieuwerts S, Molenaar D, van Hijum SA, Beerthuyzen M, Stevens MJ, Janssen PW, et al. Mixed-culture transcriptome analysis reveals the molecular basis of mixed-culture growth in Streptococcus thermophilus and Lactobacillus bulgaricus. *Appl Environ Microbiol*.2010; 76(23): 7775–7784.

25. Zelezniak A, Andrejev S, Ponomarova O, Mende DR, Bork P, Patil KR. Metabolic dependencies drive species co-occurrence in diverse microbial communities [published

correction appears in Proc Natl Acad Sci U S A. 2015 Dec 22;112(51):E7156]. *Proc Natl Acad Sci U S A*. 2015; 112(20): 6449-6454.

26. Seif Y, Choudhary KS, Hefner Y, Anand A, Yang L, Palsson BO. Metabolic and genetic basis for auxotrophies in Gram-negative species. *Proc Natl Acad Sci U S A*. 2020; 117(11): 6264-6273.

27. Wilson DN, Hauryliuk V, Atkinson GC, O'Neill AJ. Target protection as a key antibiotic resistance mechanism. *Nat Rev Microbiol*. 2020; 18(11): 637-648.

28. Sharkey LK, Edwards TA, O'Neill, AJ. ABC-F Proteins Mediate Antibiotic Resistance through Ribosomal Protection. *American Soc Microbiol*. 2016; 7(2).

29. Mee MT, Collins JJ, Church GM, Wang HH. Syntrophic exchange in synthetic microbial communities. *Proc Natl Acad Sci U S A*. 2014; 111(20): E2149-E2156.

30. Su W, Kumar V, Ding Y, Ero R, Serra A, Lee BS, et al. Ribosome protection by antibiotic resistance ATP-binding cassette protein. *Proc Natl Acad Sci USA*. 2018; 115 (20): 5157- 5162.

31. Prajapat MK, Jain K, Saini S. Control of MarRAB Operon in Escherichia coli via Autoactivation and Autorepression. *Biophys J*. 2015; 109(7): 1497-1508.

32. Mickiewicz KM, Kawai Y, Drage L, Gomes MC, Davison F, Pickard R, et al. Possible role of L-form switching in recurrent urinary tract infection. *Nat Commun*. 2019; 10(1): 4379.

33. Roy R, Tiwari M, Donelli G, Tiwari V. Strategies for combating bacterial biofilms: A focus on anti-biofilm agents and their mechanisms of action. *Virulence*. 2018; 9(1): 522-554.

34. Bottery MJ, Pitchford JW, Friman VP. Ecology and evolution of antimicrobial resistance in bacterial communities. *ISME J*. 2021; 15(4): 939-948.

35.Orazi G, O'Toole GA. *Pseudomonas aeruginosa* Alters Staphylococcus *aureus* Sensitivity to Vancomycin in a Biofilm Model of Cystic Fibrosis Infection. *mBio*. 2017; 8(4): e00873-17.

36. Beaudoin T, Yau YCW, Stapleton PJ, Gong Y, Wang PW, Guttman DS, et al. *Staphylococcus aureus* interaction with *Pseudomonas aeruginosa* biofilm enhances tobramycin resistance. *NPJ Biofilms Microbiomes*. 2017; 3: 25.

37. Friedman ND, Temkin E, Carmeli Y. The negative impact of antibiotic resistance. *Clin Microbiol Infect*. 2016; 22(5): 416-422.

38. World Health Organization 2016. Global action plan on antimicrobial resistance.

39. World Health Organization. Financing of health in India. Available from: http://www.whoindia.org/LinkFiles/Commision on Macroeconomic and Health Financing of Health in India.pdf.

40. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect Dis*. 2014; 14: 13.

41. Terreni M, Taccani M, Pregnolato M. New Antibiotics for Multidrug-Resistant Bacterial Strains: Latest Research Developments and Future Perspectives. *Molecules*. 2021; 26(9): 2671.

42. Santajit S, Indrawattana N. Mechanisms of Antimicrobial Resistance in ESKAPE Pathogens. *Biomed Res Int*. 2016; 2016: 2475067.

43. Ponnusankar S. Need for the implementation of antibiotic policy in India: An Overview. *Int J Cur Res Rev*. 2020; 13(05):168.

44. Guo Y, Song G, Sun M, Wang J, Wang Y. Prevalence and Therapies of Antibiotic-Resistance in *Staphylococcus aureus*. *Front Cell Infect Microbiol*. 2020; 10: 107.

45. Ahmad-Mansour N, Loubet P, Pouget C, Dunyach-Remy C, Sotto A, Lavigne JP, et al. *Staphylococcus aureus* Toxins: An Update on Their Pathogenic Properties and Potential Treatments. *Toxins (Basel)*. 2021; 13(10): 677.

46. Ananthanarayan, Paniker's, 2022. Systematic Bacteriology. Textbook of Microbiology. Universities Press (India) Private Limited., p. 42.

47. Fiedler T, Köller T, Kreikemeyer B. Streptococcus pyogenes biofilms-formation, biology, and clinical relevance. *Front Cell Infect Microbiol*. 2015; 5: 15.

48. Sganga G, Tascini C, Sozio E, Colizza S. Early recognition of methicillin-resistant *Staphylococcus aureus* surgical site infections using risk and protective factors identified by a group of Italian surgeons through Delphi method. *World J Emerg Surg*. 2017; 12: 25.

49. Hassoun A, Linden PK, Friedman B. Incidence, prevalence, and management of MRSA bacteremia across patient populations-a review of recent developments in MRSA management and treatment. *Crit Care*. 2017; 21(1): 211.

50. Han JH, Edelstein PH, Lautenbach E. Reduced vancomycin susceptibility and staphylococcal cassette chromosome mec (SCCmec) type distribution in methicillin-resistant Staphylococcus aureus bacteraemia. *J Antimicrob Chemother*. 2012; 67(10): 2346-2349.

51. Kullar R, Casapao AM, Davis SL, Levine DP, Zhao JJ, Crank CW, et al. A multicentre evaluation of the effectiveness and safety of high-dose daptomycin for the treatment of infective endocarditis. *J Antimicrob Chemother*. 2013; 68(12): 2921-2926.

52. Álvarez R, López Cortés LE, Molina J, Cisneros JM, Pachón J. Optimizing the Clinical Use of Vancomycin. *Antimicrob Agents Chemother*. 2016; 60(5): 2601-2609.

53. Gardete S, Tomasz A. Mechanisms of vancomycin resistance in Staphylococcus aureus. *J Clin Invest*. 2014; 124(7): 2836-2840.

54. Kim M, Weigand MR, Oh S, Hatt JK, Krishnan R, Tezel U, et al. Widely Used Benzalkonium Chloride Disinfectants Can Promote Antibiotic Resistance. *Appl Environ Microbiol*. 2018; 84(17): e01201-18.

54. Sganga, Gabriele T, Carlo S, Emanuela C, M C, Pierre C, et al. Focus on the prophylaxis, epidemiology and therapy of methicillin-resistant Staphylococcus aureus surgical site infections and a position paper on associated risk factors: The perspective of an Italian group of surgeons. *World J Emer Surg*. 2016; 11. 10.1186/s13017-016-0086-1.

55. Kim M, Weigand MR, Oh S, Hatt JK, Krishnan R, Tezel U, et al. Widely Used Benzalkonium Chloride Disinfectants Can Promote Antibiotic Resistance. *Appl Environ Microbiol*. 2018; 84(17): e01201-18.

56. Bigliardi PL, Alsagoff SAL, El-Kafrawi HY, Pyon JK, Wa CTC, Villa MA. Povidone iodine in wound healing: A review of current concepts and practices. *Int J Surg*. 2017; 44: 260-268.

57. Lepelletier D, Maillard JY, Pozzetto B, Simon A. Povidone Iodine: Properties, Mechanisms of Action, and Role in Infection Control and *Staphylococcus aureus* Decolonization. *Antimicrob Agents Chemother*. 2020; 64(9): e00682-20.

58. *U.S. Pharmacopeia 35/National Formulary*. Rockville, MD: U.S. Pharmacopeial Convention, Inc. 2012; 334-386, 1140, 4381-4383.

59. Hoekstra MJ, Westgate SJ, Mueller S. Povidone-iodine ointment demonstrates in vitro efficacy against biofilm formation. *Int Wound J*. 2017; 14(1): 172-179.

60. Johani K, Malone M, Jensen SO, Dickson HG, Gosbell IB, Hu H, et al. Evaluation of short exposure times of antimicrobial wound solutions against microbial biofilms: from in vitro to in vivo. *J Antimicrob Chemother*. 2018; *73*(2): 494–502.

61. Kanakalingam J, Feliciano R, Hah JH, Labib H, Le TA, Lin JC. Practical use of povidone-iodine antiseptic in the maintenance of oral health and in the prevention and treatment of common oropharyngeal infections. *Int J Clin Pract.* 2015; 69(11): 1247-1256.

62. Leggett MJ, Setlow P, Sattar SA, Maillard JY. Assessing the activity of microbicides against bacterial spores: knowledge and pitfalls. *J Appl Microbiol*. 2016; 120(5): 1174-1180.

63. Knauf GA, Cunningham AL, Kazi MI, et al. Exploring the Antimicrobial Action of Quaternary Amines against *Acinetobacter baumannii*. *mBio*. 2018; 9(1): e02394-17.

64. Kim M, Weigand MR, Oh S, Hatt JK, Krishnan R, Tezel U, et al. Widely Used Benzalkonium Chloride Disinfectants Can Promote Antibiotic Resistance. *Appl Environ Microbiol*. 2018; 84(17): e01201-18.

65. Merchel Piovesan Pereira B, Tagkopoulos I. Benzalkonium Chlorides: Uses, Regulatory Status, and Microbial Resistance. *Appl Environ Microbiol*. 2019; 85(13): e00377-19.

66. Shadman SA, Sadab IH, Noor MS, Khan MS. Development of a Benzalkonium Chloride Based Antibacterial Paper for Health and Food Applications. *ChemEngineering*. 2021; *5*(1).

Tables

Table 1. Main characteristics of the antibiotics used for the treatment of SSIs due to MRSA (Sganga *et al*., 2016). Ref. 54.

Antibiotic	**Bactericidal activity; pharmacodynamics;anti-biofilm activity**	**Route of administration**	**Doses**	**Adverse events**	**Interactions**
Teicoplanin	Bactericidal with low MIC; time-dependent; none	IV, IM	7-10mg/ Kg once daily, loading dose	Renal toxicity	None
Vancomycin	Bactericidal with low MIC; time-dependent; none	IV	1g twice daily, 500 mg four times a day	Renal toxicity	Other nephrotoxic drugs
Daptomycin	Bactericidal; concentration-dependent; yes	IV	4-6 mg/ kg	Myotoxicity	Statins
Linezolid	Bacteriostatic; time-dependent; none	IV, oral	1200 mg once daily	Bone marrow toxicity, neuropathy, serotoninergic syndrome	SSRIs

Tigecycline	Bacteriostatic; time-dependent; partial	IV	50 mg twice daily; 100 mg loading dose	Nausea, vomiting, pancreatitis	None
Ceftaroline	Bactericidal; time-dependent; none	IV	600 mg twice daily	Rash	None
Dalbavancin	Bactericidal; concentration-dependent; yes	IV	1000 mg day 1, 500 mg after 7 days; or 1500 mg one shot	No	None
Cotrimoxazole	Bactericidal; time-dependent; none	IV, oral	800/160 mg 3 times a day	Anemia	None
Rifampin	Bactericidal; time-dependent; yes	IV, oral	600 mg once a day	Liver toxicity	Several

Chemical composition:

Table 2. Chemical composition of Povidone iodine (U.S. Pharmacopeia., 2012). Ref. 58.

Ingredient	
Povidone iodine	10 g
Citric acid 0.1 M solution	36 g
Disodium phosphate 0.2 M solution	18 g
Polyethylene glycol 400	5 g
Mineral oil	10 g
Pluronic F 127	21 g

Legends to figures

Figure 1. Alarming statistics of antibiotic usage in India (Ponnusankar., 2021).

Figure 2. Benzalkonium chlorides chemical composition (Merchel Piovesan *et al*., 2019).

SHOCKING STATISTICS

1

7 Lakh Estimated annual number Deaths due to antibiotic-resistant bacteria worldwide. Predicted to rise to 1 crore by 2050.

75% of Indians in a WHO survey thought incorrectly that colds and flu could be treated with antibiotics.

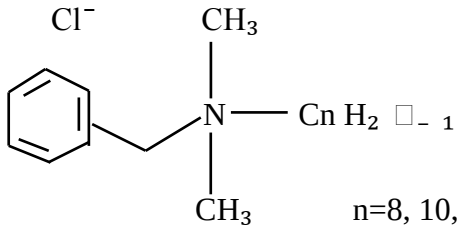
India already has cases of resistance to Colistin, a drug used when all other antibiotics fail.

58% Respondents knew they should stop taking antibiotics only when they finish the course prescribed.

Figure 1. Ref. 43.

Chemical composition:

Benzalkonium chlorides (BACs) C_9 H_{13} CINR (R=C_8 H_{17} to C_{18} H_{37})



n=8, 10, 12, 14, 16, 18

Figure 2. Ref. 65.