REVIEW ARTICLE

Current scenario of antibiotic resistance and latest strategies to overcome it

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Abstract	Introduction	Conclusion	References	Citation

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Abstract

Antibiotic resistance in microorganisms has become a critical health issue these days and has evolved to become a worldwide health threat. Over a decade, the resistance level of bacteria has increased many folds due to various factors, accounting to the added pressure on the environmental resistome. Infections that are resistant to these antibiotics show potentially devastating effects on public health, often affecting developing countries. This review focuses on the present scenario of antibiotic resistance and enlists some of the strategies to combat this global community threat.

Key Words

Antibiotic resistance; Superbugs; Antimicrobial resistance; Drug resistant bacteria; MDR bacteria; Resistome.

Introduction

Antibiotic resistance in microorganisms, especially in bacterial species, has become an eminent and serious concern in the field of healthcare and medicine. Decrease in new antibiotic research permitted a rise in bacterial drug resistance. Antibiotic resistant bacteria have been found in the initial stages of antibiotic use, but over the time, they have become resistant to more than one antibiotic, termed as multidrug resistant organisms (also called "superbugs"). Bacteria now are frequently resistant to many if not all of the antibiotics. Inappropriate use and misuse of antibiotics are significant factors for the increase in antibiotic resistant bacteria and thus evoked counter attack. Hence, we are now experiencing a rapid increase in the number of alternative approaches to combat these antibiotic resistant bacteria.

Antibiotic Resistance and its Current Aspects: Antibiotic resistance has become a major concern in the present-day world. Most of the antibiotic resistant bacteria may have attained resistance to the first-line antibiotics. This has necessitated the development of second-line antibiotics. With a slowdown in the development of antibiotics in the past decade, the resistance level of bacteria has increased many folds, which demand the development of new drugs. Currently, newer classes of compounds, including antimicrobial peptides, bacterial biosynthetic inhibitors, etc., have given an upper hand against antibiotic resistance. The recently developed carbapenem family of beta-lactum antibiotics exhibit broad-spectrum activity. A number of next-generation fluoroquinolones currently are in developmental stages. Moreover, the use of lytic bacteriophages to manage bacterial infections is accelerating the current research developments. However, just like a bacteria, bacteriophages can also acquire resistance to phages that attack them. Thus, phages can evolve resistance and adapt to resistant bacteria. Looking at the current situation, there does seem to be a necessity to identify and develop compounds that can address the problem of antibiotic resistance. The threat of resistant bacteria is a critical public health issue that requires a coordinated and multifaceted response.

New and Alternative Approaches: Prevention is (always) better than cure. Avoiding infections will reduce the use of antibiotics, further inhibiting the incidence of resistance development in bacteria. A closer look at antibiotic resistant infections and the causes and analysing them will help the scientific community to develop new and specific strategies to prevent them. Avoiding inappropriate use and misuse of antibiotics would slow down the spread of resistant bacteria. As bacteria always evolve and can develop more and more resistance, new antibiotics are needed to fight against them. WHO recommends guidelines and some global strategies to fight and overcome this serious issue [1]. Latest strategies and approaches to tackle antibiotic resistant bacteria are described in the following sections.

Photodynamic Therapy (PDT): PDT uses the interaction of light with a photosensitiser to inactivate bacteria. Photosensitiser binds to the target cell and is activated by irradiation with a light of suitable wavelength. During this process, reactive oxygen species are generated that will produce bactericidal effect by damaging multiple cellular structures [2]. It has been found that anaerobic bacteria that lead to periodontal diseases can be suppressed using PDT [3]. In a research by Minnock et al. [4], it was concluded that chlorine e6 and BLC 1010 is able to suppress periodontopathogenic bacteria. The efficiency of PDT can be improved by chemical derivatisation or conjugation of photosensitisers; e.g., introduction of side chains into the dye molecule methylene blue and porphirins has shown optimised results [5, 6]. Although there are some adverse effects such as impairment of benign oral flora that may further develop to a single resistant species [7], scar formation [8] and phototoxic effects [9], PDT has a great benefit when the resistance against antibiotics become worse.

Antimicrobial Peptides (AMPs): Recent findings suggest that AMPs could be used as a therapeutic model for designing new class of antibiotics [10]. AMPs are basically small peptides produced as part of non-specific immune response in many organisms of both animal and plant kingdom. Study of AMPs as novel therapeutic agents is in experimental stages. Hypotheses have been made regarding whether these peptides can interfere with DNA as well, but this is yet to be evaluated for confirmation. McGrath et al. [11] synthesised a low-toxicity Lys-Leu or kloth (KL) peptide called $(KLAKLAK)^2$ toward mammalian cells. A variant of $(KLAKLAK)^2$—known as $_D(KLAKLAK)^2$—has been studied for antimicrobial activity. The study successfully showed the inhibition of several gram-negative bacteria. In another experiment, Barbu et al. [12] showed that $_D(KLAKLAK)^2$ induced apoptosis in mucor. The molecule was also shown to inhibit germination and reduce hyphal activity, yielding a fungicidal effect. With technological advancements, some of the limitations like toxicity, stability, drug delivery mechanism, etc., can be resolved, and then this new class of antibiotics could be a promising antimicrobial in the market.

Use of Platensimycin and Platencin: Platensimycin, a metabolite of *Streptomyces platensis* MA7372 strain, is a potential antibiotic candidate, as it does not exhibit cross-resistance to gram-positive bactera [13, 14]. Platencin—having an analogous structure and profile to platensimycin—has been described as an antibiotic [15, 16]. However, some improvements are needed before they can be made available in the market for clinical use.

Quorum Sensing (QS) Approaches: Quorum sensing (QS) is a cell-density-dependent phenomenon based on the release of low-molecular weight agents that coordinate gene expression in a given cell population [17]. Burn wounds could sometimes be associated with *Pseudomonas aeruginosa* infections. Evidence suggests that 10 % of *P. aeruginosa* genes are controlled by QS regulatory communication system. A group led by Que et al. [18] hypothesised that, using anti-QS inhibitors that target QS system may reduce the infections caused by the bacteria. It has also been found that virulence nature of *P. aeruginosa* in mice was reduced to a great extent when MvfR (multiple virulence factor regulator) was inhibited [19].

Phytotherapy: Phytotherapy is an herbal therapy that uses whole plants and plant extracts as the potential bactericidal agent. Herbal medicine is an old method based on empirical knowledge. Several clinical trials have been performed to treat *Helicobacter pylori* using different plant extracts [20, Table 1]. A focus on this therapy could yield a new strategy to overcome the antibiotic resistance in future.

Aminoglycosides and Derivatives: Aminoglycosides are bactericidal antibiotics that work by interacting with 16S RNA, which results in a conformational change in decoding site A leading to mistranslation of protein synthesis. Aminoglycosides are used to treat staphylococcal infections and enterococcal endocarditis when combined with beta-lactum or vancomycin. Planzomicin (ACHN-490), a novel neoglycoside, has also been shown to have enhanced activity against antibiotic resistant bacteria [21].

Nanoparticles: Nanotechnology can also help in dealing with antibiotic resistant bacteria. The antimicrobial activity of nanoparticles can be used against pathogens for their destruction [22, 23]. The unique characteristic of nanoparticles is that their properties can be altered by changing their size.

Bacterial species like *Eschcerichia coli* and *Staphylococcus aureus* have been shown to have high susceptibility to nanoparticles of ZnO and CuO. Azam et al. [21] have synthesised three nanoparticles ZnO, CuO and Fe_2O_3 to study the bactericidal activity of these particles. It was found that ZnO showed high bactericidal activity rate as compared with other particles.

Other Considerable Issues: Although antibiotic resistance may seem like a challenge of science, in truth, it is a global issue of economics and national security. As antibiotics are rarely used, the drug developing firms do not show much interest in developing new antibiotics because of low monetary returns. This also means that there is a need for new business model that rewards drug firms with good returns.

Another approach is extending patents for antibiotics. Initial patent runs out by the time antibiotics typically reach peak sales after 13 years on the market compared with just 6 years for other drugs.

The threat of resistant bacteria is a critical public health issue that requires immediate counteraction. As discussed earlier, inappropriate use and misuse of antibiotics—usually excessive use—are significant factors for the increase in antibiotic resistant bacteria. The development of antibiotic resistant bacteria accounts for the added pressure on the environmental resistome that, over time will be very difficult for the treatment. Therefore, it is very important to take necessary precautions while administrating antibiotics to any individual. Their inappropriate use may show potentially devastating effects in individuals, e.g. in pregnant women [24].Similarly, a study by Rastogi et al. [25] have isolated bacterial strains from a hospital and found 12.4 % isolates resistant to multiple drugs, thus, highlighting it as an important health issue for both national and international community. Regulation is required to control the poor-quality medicines. This is because; availability of falsified drugs and sub-standard medicines can inadvertently lead to antibiotic resistance. Encouraging rational drug use, reducing misuse of antibiotics, educating and raising awareness among individuals at all levels of community with the help of antimicrobial stewardship programmes; are some of the measures to limit the antibiotic resistance and maintain good community health.

Conclusion

In this regard, new formulations of antibiotics, combination therapies and development of new bioactive compounds might be useful for a better therapeutic outcome. Approaches that can destruct bacteria in single-step attempts are to be preferred rather than multilevel breakdown or destruction of bacteria. At the same time, maintaining safety at community level is also equally important. The approaches described in this review are at various stages of development, and which of them or a new one would emerge as a best therapeutic approach is worth watching with keen interest.

References

1. WHO. The evolving threat of antimicrobial resistance. 240 Options for action. Geneva:WHO;2012.
2. Wainwright M. Photodynamic antimicrobial chemotherapy (PACT). J Antimicrob Chemother. 1998 Jul;42(1):13–28. Review. PubMed PMID: 9700525. [PubMed]
3. Pfitzner A, Sigusch BW, Albrecht V, Glockmann E. Killing of periodontopathogenic bacteria by photodynamic therapy. J Periodontol. 2004 Oct;75(10):1343–9. PubMed PMID: 15562911. [PubMed]
4. Minnock A, Vernon DI, Schofield J, Griffiths J, Parish JH, Brown ST. Photoinactivation of bacteria. Use of a cationic water-soluble zinc phthalocyanine to photoinactivate both gram-negative and gram-positive bacteria. J Photochem Photobiol B. 1996 Feb;32(3):159–64. PubMed PMID: 8622179. [PubMed]
5. Mellish KJ, Cox RD, Vernon DI, Griffiths J, Brown SB. In vitro photodynamic activity of a series of methylene blue analogues. Photochem Photobiol. 2002 Apr;75(4):392–7. PubMed PMID: 12003129. [PubMed]
6. Reddi E, Ceccon M, Valduga G, Jori G, Bommer JC, Elisei F, Latterini L, Mazzucato U. Photophysical properties and antibacterial activity of meso-substituted cationic porphyrins. Photochem Photobiol. 2002 May;75(5):462–70. PubMed PMID: 12017471. [PubMed]
7. Roberts FA, Darveau RP. Beneficial bacteria of the periodontium. Periodontol 2000. 2002;30:40–50. Review. PubMed PMID: 12236894. [PubMed]
8. Fink-Puches R, Soyer HP, Hofer A, Kerl H, Wolf P. Long-term follow-up and histological changes of superficial nonmelanoma skin cancers treated with topical delta-aminolevulinic acid photodynamic therapy. Arch Dermatol. 1998 Jul;134(7):821–6. PubMed PMID: 9681345. [PubMed]
9. Valenzeno DP, Pooler JP. Phototoxicity. The neglected factor. JAMA. 1979 Aug 3;242(5):453–4. PubMed PMID: 448964. [PubMed]
10. Marr AK, Gooderham WJ, Hancock RE. Antibacterial peptides for therapeutic use: obstacles and realistic outlook. Curr Opin Pharmacol. 2006 Oct;6(5):468–72. Epub 2006 Aug 4. Review. PubMed PMID: 16890021. [PubMed]
11. McGrath DM, Barbu EM, Driessen WH, Lasco TM, Tarrand JJ, Okhuysen PC, Kontoyiannis DP, Sidman RL, Pasqualini R, Arap W. Mechanism of action and initial evaluation of a membrane active all-D-enantiomer antimicrobial peptidomimetic. Proc Natl Acad Sci U S A. 2013 Feb

26;110(9):3477–82. doi: 10.1073/pnas.1221924110. Epub 2013 Jan 23. PubMed PMID: 23345420; PubMed Central PMCID: PMC3587187. [PubMed]

12. Barbu EM, Shirazi F, McGrath DM, Albert N, Sidman RL, Pasqualini R, Arap W, Kontoyiannis DP. An antimicrobial peptidomimetic induces Mucorales cell death through mitochondria-mediated apoptosis. PLoS One. 2013 Oct 3;8(10):e76981. doi: 10.1371/journal.pone.0076981. eCollection 2013. PubMed PMID: 24098573; PubMed Central PMCID: PMC3789667. [PubMed]
13. Singh SB, Young K. New antibiotic structures from fermentations. Expert Opin Ther Pat. 2010 Oct;20(10):1359–71. doi: 10.1517/13543776.2010.509347. Review. PubMed PMID: 20653459. [PubMed]
14. Häbich D, von Nussbaum F. Platensimycin, a new antibiotic and superbug challenger from nature. ChemMedChem. 2006 Sep;1(9):951–4. Review. PubMed PMID: 16952137. [PubMed]
15. Wang J, Kodali S, Lee SH, Galgoci A, Painter R, Dorso K, Racine F, Motyl M, Hernandez L, Tinney E, Colletti SL, Herath K, Cummings R, Salazar O, González I, Basilio A, Vicente F, Genilloud O, Pelaez F, Jayasuriya H, Young K, Cully DF, Singh SB. Discovery of platencin, a dual FabF and FabH inhibitor with in vivo antibiotic properties. Proc Natl Acad Sci U S A. 2007 May 1;104(18):7612–6. Epub 2007 Apr 24. PubMed PMID: 17456595; PubMed Central PMCID: PMC1863502. [PubMed]
16. Jayasuriya H, Herath KB, Zhang C, Zink DL, Basilio A, Genilloud O, Diez MT, Vicente F, Gonzalez I, Salazar O, Pelaez F, Cummings R, Ha S, Wang J, Singh SB. Isolation and structure of platencin: a FabH and FabF dual inhibitor with potent broad-spectrum antibiotic activity. Angew Chem Int Ed Engl. 2007;46(25):4684–8. PubMed PMID: 17487925. [PubMed]
17. Ng WL, Bassler BL. Bacterial quorum-sensing network architectures. Annu Rev Genet. 2009;43:197–222. doi: 10.1146/annurev-genet-102108-134304. Review. PubMed PMID: 19686078. [PubMed]
18. Que YA, Hazan R, Ryan CM, Milot S, Lépine F, Lydon M, Rahme LG. Production of *Pseudomonas aeruginosa* Intercellular Small Signaling Molecules in Human Burn Wounds. J Pathog. 2011;2011:549302. doi: 10.4061/2011/549302. Epub 2011 Mar 17. PubMed PMID: 23533774; PubMed Central PMCID: PMC3594954. [PubMed]
19. Lesic B, Lépine F, Déziel E, Zhang J, Zhang Q, Padfield K, Castonguay MH, Milot S, Stachel S, Tzika AA, Tompkins RG, Rahme LG. Inhibitors of pathogen intercellular signals as selective anti-infective compounds. PLoS Pathog. 2007 Sep 14;3(9):1229–39. PubMed PMID: 17941706; PubMed Central PMCID: PMC2323289. [PubMed]
20. Vale FF, Oleastro M. Overview of the phytomedicine approaches against *Helicobacter pylori*. World J Gastroenterol. 2014 May 21;20(19):5594–609. doi: 10.3748/wjg.v20.i19.5594. PubMed PMID: 24914319; PubMed Central PMCID: PMC4024768. [PubMed]
21. Livermore DM, Mushtaq S, Warner M, Zhang JC, Maharjan S, Doumith M, Woodford N. Activity of aminoglycosides, including ACHN-490, against carbapenem-resistant Enterobacteriaceae isolates. J Antimicrob Chemother. 2011 Jan;66(1):48–53. doi: 10.1093/jac/dkq408. Epub 2010 Nov 14. PubMed PMID: 21078604. [PubMed]
22. Tran N, Mir A, Mallik D, Sinha A, Nayar S, Webster TJ. Bactericidal effect of iron oxide nanoparticles on *Staphylococcus aureus*. Int J Nanomedicine. 2010 Apr 15;5:277–83. PubMed PMID: 20463943; PubMed Central PMCID: PMC2865022. [PubMed]
23. Azam A, Ahmed AS, Oves M, Khan MS, Habib SS, Memic A. Antimicrobial activity of metal oxide nanoparticles against Gram-positive and gram-negative bacteria: a comparative study. Int J Nanomedicine. 2012;7:6003–9. doi: 10.2147/IJN.S35347. Epub 2012 Dec 5. PubMed PMID: 23233805; PubMed Central PMCID: PMC3519005. [PubMed]
24. de Tejada BM. Antibiotic use and misuse during pregnancy and delivery: benefits and risks. Int J Environ Res Public Health. 2014 Aug 7;11(8):7993–8009. doi: 10.3390/ijerph110807993. PubMed PMID: 25105549; PubMed Central PMCID: PMC4143845. [PubMed]
25. Rastogi V, Mishra PK, Bhatia S. Emerging antimicrobial resistance in hospital a threat to public health. Ind J Comm Health 2014;24(4):260–263. [Google Scholars]

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