Alternative Approaches and Perspectives of Nanotechnology in Antimicrobial Resistance and Infection Control

Vaso Taleski, Milka Zdravkovska, Zdenka Stojanovska
Faculty of medical Sciences, University "Goce Delchev", Sthip, Macedonia

Introduction

Infection diseases caused by antibiotic resistant bacteria present major global health concern and a great challenge for science and medicine. Over 700 000 deaths worldwide (25 000 in Europe), including 214 000 neonatal sepsis deaths, are caused to resistant bacterial pathogens each year.
Currently, insufficient access and delays in access to antibiotics cause more deaths than antibiotic resistance, but more resistance-related deaths are being reported in all countries irrespective of income level.

Objectives

To present possibilities and limitations of current antimicrobial therapy against resistant Gram-positive and Gram-negative bacteria, and current, new concepts, approaches and methods as very promising to overcome this tremendous problem.

Methods and Discussion

Extensive use and misuse of antimicrobials has led to increased bacterial resistance. Studies have revealed that antibiotic resistance genes existed within the microbial genome prior to the discovery of antibiotics.There is evidence that heavy metals and some pollutants, introduction of antibiotics into the environment through human waste (medication, farming), animals, agriculture and the pharmaceutical industry may select antibiotic-resistant bacteria.

Current concepts in antimicrobial therapy against resistant Gram-positive bacteria imply use of vancomycin, daptomycin, ceftaroline and telavancin, while, against Gram-negative bacteria (*Multidrug-resistant*/MDR, *Extensively drug-resistant*/XDR, *Pandrug-resistant/*PDR) mostly used are colistin, polymyxin B, carbapenems, tigecycline, fosfomycin, aminoglycosides and rifampicin. Limitation of current antimicrobial therapies are due to concerns of side effects such as: the potential of selecting and rapid spread of resistant strains, toxicity, reduction of normal microbiota and high cost.

Therefore, one of the major challenges for scientists and highest priorities of modern medicine and biotechnology has become developing of novel alternative methods. A promising approach seems to be manipulation of microbes using natural or synthetic molecules which have potential to be used in controlling microbial behavior and virulence.

Current approaches includes:

- Anti-infectious Approaches Based on Biological Factors (Bacteriophages, Synthetic Biology);
- Anti-infectious Approaches Based on Physical Factors (Cold Plasmas low-temperature, Photodynamic Antimicrobial Chemotherapy);
- Chemical Virulence Modulators and Alternative Antimicrobial Compounds
    - Natural Virulence Modulators
    - Synthetic Virulence and QS Signaling Modulators
- Increasing the Efficiency of Antimicrobial Compounds Using Nanotechnology
    - Nanostructures Used in Anti-infectious Therapy

        - Zinc Oxide Nanoparticles
        - Silver Nanoparticles
        - Magnetite Nanoparticles such as Fe_3O_4
        - Synthesis of Fe_3O_4 Nanoparticles
        - Functionalized Magnetite Nanoparticles
    - Antimicrobial Nanoshuttles
    - Antimicrobial Nano-modified Surfaces (Anti-adherent Nano-surfaces)

Extremely small size (1-100 nm) enables nanoparticles to enter the human body through cell membranes or cross the blood-brain barrier.

Metal nanomaterials (silver, gold, copper, titanium, zinc, magnesium, cadmium, and alumina) possess advantage of unique antimicrobial activities. Scientists offers also new complex antibacterial and antiviral Nano systems on the basis of metal oxides or intermetallic oxide compounds (such as TiO_2, ZrO_2, SnO and SiO_2). Silver ions showed strongest bactericidal effect, cooper and gold weaker one. Silver ions are non-toxic to human cells in low concentrations.

In our preliminary study on antibacterial activity of several different compositions of nanoparticle coatings (titanium, inox and silver), we found antimicrobial activity of silver, double composition of titanium plus silver against *Staphylococcus aureus* and *Staphylococcus epidermidis,* but not against *E. coli, Pseudomonas aeruginosa, Listeria monocytogenes and Candida albicans.*

The Global antimicrobial resistance crisis alerted WHO to prepare and adopt Global Action Plan (GAP) on Antimicrobial Resistance (2015) which outlines five strategic objectives:

1. to improve awareness and understanding of antimicrobial resistance through effective communication, education and training;
2. to strengthen the knowledge and evidence base through surveillance and research;
3. to reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures;
4. to optimize the use of antimicrobial medicines in human and animal health;
5. to develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions.

The strategic goal of GAP, as a need for an effective “one health” approach is to ensure successful treatment and prevention of infectious diseases with effective and safe medicines accessible to all who need them.

In 2016, EASAC (European Academies Science Advisory Council) and FEAM (Federation of European Academies of Medicine) issued the final report of the Independent Review on Antimicrobial Resistance including recommendations similar to GAP, also suggesting:

- establishment of a Global Innovation Fund for early stage and non-commercial research;
- better incentives to promote investment for new drugs and improvement of existing drugs;
- building of a global coalition for action, via G20 and the United Nations;
- intensify the surveillance activities (antimicrobial resistance and antibiotic use).

Seven new EU research projects on AMR, aim to develop novel antibiotics, vaccines or alternative treatments for drug-resistant microbial infections. Other projects set out to identify better methods to use currently available antibiotics or to study antibiotic resistance within the food chain.

Three projects, funded by the EU Seventh Framework Program (FP7) and the Nano sciences, Nanotechnologies, Materials and New Production Technologies (NMP) Program are working to develop novel nanotechnology-based AMR approaches as follows:

- PneumoNP: Nano therapeutics to treat pneumonia infections
- FORMAMP: Innovative Nano formulation of antimicrobial peptides to treat bacterial infectious diseases
- NAREB: Nano therapeutics for antibiotic resistant emerging bacterial pathogens

Conclusion

After 70 years use of antibiotics, concerns of reentering the “preantibiotics” era has become very real because of the rapid spread of antimicrobial resistance and little to no progress in the development of new antibiotics. Alternative approaches, based on natural or synthetic molecules able to modulate virulence and cell-to-cell communication, become one of the highest priorities of modern medicine and biotechnology. Current technological progress allowed the development of nanosized molecular particles, composed of different components which showed a great antimicrobial effect while at the same time safe for the human use.

WHO Global Action Plan on antimicrobial resistance, recommendations of professional organizations and scientific projects in progress emphasize priority needs of joint action to combat antibiotic resistance with greatest goal to control infections, improve health and save lives.

Key words: alternative, antimicrobials, nanoparticles, nanotechnology, resistance.

References:

- Azam A, Ahmed AS, Oves M, Khan SM, Habib SS, Memic A. Antimicrobial activity of metal oxide nanoparticles against Gram-positive and Gram-negative bacteria: a comparative study, International Journal of Nanomedicine, 2012:7 6003–6009.
- EASAC and FEAM, Joint Statement from the Presidents, July 2016.
- Holban AM, Grumezescu AM, Novel Molecular Approaches in Targeting Microbial Virulence for Handling Infections, De Gruyter Open Ltd, Warsaw/Berlin, GmbH, Berlin/Munich/Boston, 2015.
- Juan L, Zhimin Z, Anchun M et al. Deposition of silver nanoparticles on titanium surface for antibacterial affect. International Journal of Nanomedicine, 2010:5, 261-267.
- O’Neill J. Tackling drug-resistant infections globally: final report and recommendations. London: H M Government/Wellcome Trust, 2016.
- Santos CL, Albuquerque AJR, Sampaio FC, Keyson D. Nanomaterials with Antimicrobial Properties: Applications in Health Sciences. Microbial pathogens and strategies for combating them: science, technology and education © FORMATEX 2013.
- Troitzch D, Borutzky U, Junghannz U. Detection of antimicrobial efficacy in silver-coated medical devices. Hyg Med, 2009, 34 (3).
- WHO. Global action plan on antimicrobial resistance. Geneva: World Health Organization, 2015.
- Woolhouse M, Ward M, van Bunnik B, Farrar J. Antimicrobial resistance in humans, livestock and the wider environment. *Philos Trans R Soc Lond B Biol Sci* 2015; **370.**