Mogućnosti i izazovi alternativnih strategija i nanotehnologije u kontroli antimikrobnih rezistencija i infekcija

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Uvod

Infektivne bolesti uzrokovane bakterijama rezistentne na antibiotike (AMR) pretstavljaju najveći globalni problem i veliki izazov nauke i medicine. Preko 700 000 umrlih u svetu godišnje (33.000 u Evropi), uključući 214 000 smrti zbog neonatalne sepse, prouzrokovane su od AMR. AMR mogu ubiti 10 miliona ljudi od 2050, ako se ne preduzmu efikasne aktivnosti. Životi ljudi zavise od efikasnosti antibiotika.
Prioritetna lista WHO (SZO) patogenih bakterija uključuje: Kritični prioritet: *Acinetobacter baumannii*, carbapenem-rezistentan; *Pseudomonas aeruginosa*, carbapenem-rezistentan; *Enterobacteriaceae*, carbapenem-rezistentne, ESBL-produkujuće; Visoki prioritet: *Enterococcus faecium*, vancomycin- rezistentan; *Staphylococcus aureus*, methicillin-rezistentan, vancomycin-intermedijeran i rezistentan; *Helicobacter pylori*, clarithromycin-rezistentan; *Campylobacter* spp., fluoroquinolone-rezistentan; *Salmonellae*, fluoroquinolone-rezistentne; *Neisseria gonorrhoeae*, cephalosporin-rezistena, fluoroquinolone-rezistentna; Srednji prioritet: *Streptococcus pneumoniae*, penicillin-neoosetljiv; *Haemophilus influenzae*, ampicillin-rezistentan; *Shigella* spp., fluoroquinolone- rezistentna.

Cilj rada

Pretstaviti mogućnosti i ograničenja trenutne antimikrobne terapije i trenutnih, novih koncepata, pristupa i metoda koji obećavaju prevazilaženje ogromnog problema sa AMR.

Metodi i diskusija

Mogućnosti trenutnih koncepata antimikrobne terapija protiv rezistentnih Gram pozitivnih bakterija (vancomycin, daptomycin, ceftaroline i telavancin), i protiv *Multi-antibiotski rezistentne* / MDR, *Ekstenzivno antibiotski rezistentne* /XDR, *Pan-antibiotik rezistentne* /PDR Gram-negativne bakterije (colistin, polymyxin B, carbapenems, tigecycline, fosfomycin, aminoglycosides i rifampicin) su ograničene zbog mogućnosti potencijalne selekcije i brzog širenja rezistentnih vrsti, toksičnosti, redukcije normalne microbiote i visoka cena.
Zbog toga, jedan od najvećih izazova naučnicima i najveći prioritet moderne medicine i biotehnologije je razvoj novih alternativnih metoda. Pristup koji obećava čini se da je manipulacija mikroba upotrebom prirodnih ili sintetskih molekula za kontrolu mikrobnog ponašanja i virulencije. Trenutni pristupi uključuju:

- Biološke faktore (Bakteriofagi, Sintetska biologija);
- Fizičke faktore (Hladna plazma, na niskim temperaturama, Fotodinamička antimikrobna hemoterapija);
- Hemiske modulatore virulencije i Alternativne antimikrobne komponente:

    - Prirodne modulatore viruencije
    - Sintetske modulatore virulencije i modulatore “Quorum Sensing” signala
- Povećanje efikasnosti antimikrobnih komponenata upotrebom Nanotehnologije:
    - Upotreba nanostruktura za antiinfektivnu terapiju
        - Cink oksid nanočastice
        - Srebrne nanočastice
        - Magnetne nanočastice kao Fe3O4
    - Antimikrobni nano-častice
    - Antimikrobni nano-nosači
    - Modifikovane, nano-površine (anti adherenthe nano-površine)

Nanomaterijali metala (srebro, zlato, bakar, titanijum, cink, magnezijum, kadmijum i aluminijum) poseduju unikatne antimikrobne aktivnosti. Srebrni joni pokazuju najjači baktericidni efekat, nisu toksični za humane ćelije u niskim koncentracijama. Nano sistemi na bazi oksida metala ili intermetalnih oksidiranih komponenti (kao što su TiO2, ZrO2, SnO i SiO2) isto tako pokazuju antibakterijske i antivirusne aktivnostiu. Nanotehnologija uključuje instrumente ili materijale koji imaju najmanje jednu dimenziju, približno 1–100 nm dužine.
Sedam novih EU naučnih projekata o AMR, imaju cilj razvoja novih antibiotika, vakcina i alternativnih tretmana infekcija za rezistentnim mikrobima. Drugi projekti su dizajnirani da identifikuju bolje metode upotrebe trenutno dostupnih antibiotika ili studije antibiotske rezistencije u lancu ishrane. Tri projekata rade na razvoju novih nanotehnologija: PneumoNP (nano terapeutici za tretman infektivnih pneumonija); FORMAMP (nove nano formulacije antimikrobnih peptida) i NAREB (nano terapeutici za nove rezistentne bakterije).

Zaključak

Nakon 80-tak godina upotrebe antibiotika, brige zbog ponovnog ulsaka u “preantibiotsku” eru postale su realne zbog brzog širenja antimikrobne rezistencije i nedostatka razvoja novih antibiotika. Alternativni pristupi, postali su najveć prioriteti modern medicine i biotehnologije. Trenutni tehnološki progres omogućuje razvoj molekularnih častica sa nanoveličinama, koje pokazuju veliki antimikrobni efekat dok su istovremeno bezbedne za humanu upotrebu, sa glavnim ciljem kontolisati infekcije, poboljsati zdavlje i spasiti zivote.

Possibilities and challenges of alternative strategies and nanotechnology in control of antimicrobial resistance and infections

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Introduction

Infection diseases caused by antimicrobial resistant bacteria (AMR) present major global health concern and a great challenge for science and medicine. Over 700 000 deaths worldwide (33.000 in Europe), including 214 000 neonatal sepsis deaths, are caused by AMR each year. AMR may kill 10 million people per year, by 2050 unless successful action is taken. People's lives depends on effectiveness of antibiotics. WHO priority pathogens list includes: Critical priority: *Acinetobacter baumannii*, carbapenem-resistant; *Pseudomonas aeruginosa*, carbapenem-resistant; *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing; High priority: *Enterococcus faecium*, vancomycin-resistant; *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant; *Helicobacter pylori*, clarithromycin-resistant; *Campylobacter* spp., fluoroquinolone-resistant; *Salmonellae*, fluoroquinolone-resistant; *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant; Medium priority: *Streptococcus pneumoniae*, penicillin-non-susceptible; *Haemophilus influenzae*, ampicillin-resistant; *Shigella* spp., fluoroquinolone-resistant.

Aim

To present possibilities and limitations of current antimicrobial therapy and current, new concepts, approaches and methods promising to overcome tremendous problem with AMR.

Methods and Discussion

Current concepts in antimicrobial therapy against resistant Gram-positive bacteria (vancomycin, daptomycin, ceftaroline and telavancin), and against *Multidrug-resistant*/MDR, *Extensively drug-resistant*/XDR, *Pandrug-resistant/*PDR Gram-negative bacteria (colistin, polymyxin B, carbapenems, tigecycline, fosfomycin, aminoglycosides and rifampicin) are limited due to concerns of 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 to control microbial behavior and virulence. Current approaches includes:

- Biological Factors (Bacteriophages, Synthetic Biology);
- Physical Factors (Cold Plasmas at 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
    - Antimicrobial Nanoshuttles
    - Antimicrobial Nano-modified Surfaces (Anti-adherent Nano-surfaces)

Metal nanomaterials (silver, gold, copper, titanium, zinc, magnesium, cadmium, and alumina) possess unique antimicrobial activities. Silver ions showed strongest bactericidal effect, non-toxic to human cells in low concentrations. Nano systems based on metal oxides or intermetallic oxide compounds (such as TiO_2, ZrO_2, SnO and SiO_2) also shows antibacterial and antiviral activities. Nanotechnology includes devices or materials that have at least one dimension, approximately 1–100 nm in length.

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, are working to develop novel nanotechnology: PneumoNP (Nano therapeutics to treat pneumonia infections); FORMAMP (Innovative Nano formulation of antimicrobial peptides) and NAREB (Nano therapeutics for antibiotic resistant emerging bacterial pathogens).

Conclusion

After 80 years use of antibiotics, concerns of reentering the "preantibiotics" era has become very real because of the rapid spread of antimicrobial resistance and lack of development of new antibiotics. Alternative approaches, become one of the highest priorities of modern medicine and biotechnology. Current technological progress allowed the development of nanosized molecular particles, which showed a great antimicrobial effect while at the same time safe for the human use, with great goal to control infections, improve health and save lives.