

Conference report

Antibiotic resistance and antibiotic alternatives: looking towards the future

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The international interdisciplinary conference on “Antibiotic Resistance and Antibiotic Alternatives: Looking towards the Future” was held in London in November 2015. The issue of antibiotic resistance of microorganisms is among the most pertinent themes and major worldwide concerns for medical, veterinary and social communities. This is why the conference attracted the attention of researchers from all over the world. During the three days of intensive work, scientists and physicians from Europe, North and South America, Asia, Africa and Australia gave more than 20 lectures and exhibited about 60 poster presentations in three sessions: Antimicrobial Resistance (Chair: Dr Stephen Mortlock), Replacing Antibiotics (Chair: Dr Konstantinos Beis) and Infection Control and Industrial Applications (Chair: Dr Sanjib Bhakta). Each session was followed by free discussions, during which the participants exchanged ideas and suggested interesting approaches to solving the problem.

Most of the lectures and posters discussed the reasons and sources of antibiotic resistance, including excessive use and misuse of antibiotics as well as incomplete treatment for bacterial infections in humans and in veterinary medicine. Antibiotic circulation in the “soil–water–humans–animals–fish” chain plays an important role in the development of antibiotic resistance. Antibiotic-resistant species are found within the community as well as in hospital pathogens, and their ever increasing number leads to inefficient clinical treatment, prolonged hospitalisation and rising patient mortality. Antibiotic resistance poses a serious threat to mankind, is causing a worldwide increase in the number of patients infected by drug-resistant bacteria, difficulties in treatment of common infections and tens of thousands of deaths annually. The appearance of multidrug-resistant bacterial strains has seriously exacerbated the situation. The problem demands immediate globally coordinated solutions. Otherwise, mankind may enter a post-antibiotic era when people could die from the most common infections, as occurred in the pre-antibiotic era. This issue was discussed by Dr Prakash U. Tahiliani from the Prime Ever Ayurvedic Research Laboratories (Navsari, Gujarat, India), who spoke about this danger for mankind

and stressed the need to take urgent steps to cope with the problem of natural and acquired antibiotic resistance. Dr Stephen Mortlock from the University of Surrey (Guildford, UK) raised the issue of the prevalence of infections in the community which are caused by one of the major hospital-acquired pathogens, *S. aureus*, especially MRSA strains. This phenomenon is attributed to misuse of antibiotics in prior antimicrobial therapy or previous hospitalisation of patients, particularly in less developed countries. Fifteen years of surveillance in Ecuador revealed a significant diversity in antibiotic resistance rates between one specific hospital and the nationwide hospital net, as reported by Dr Jeannete Zurita (The Biomedical Research Unit, Zurita & Zurita Laboratorios, Quito, Ecuador). It was assumed that specific conditions, including the employment of highly qualified staff, adherence to hygiene protocols and control over antibiotic consumption, can lead to lower resistance rates.

Special attention was paid by lecturers to mechanisms of bacterial resistance to antibiotics, which include the action of drug efflux pumps in case of intrinsic as well as acquired resistance and proteolytic degradation of antibiotics. The latter can be carried out, for instance, by β -lactamases, New Delhi metallo- β -lactamase 1, carbapenemases or membrane-associated resistance proteins, when the genes coding for these enzymes are located in multidrug-resistance plasmids or in chromosomes. The increased resistance of microorganisms in biofilms compared to planktonic cells is related to poor penetration of antibiotics into a biofilm matrix, to the specific microenvironment in biofilms and to launching of adaptive mechanisms by microorganisms. A comprehensive review of basic drug-resistance mechanisms was presented by Dr Hendrik W. Van Veen from the University of Cambridge (Cambridge, UK), who emphasised the role of drug efflux pumps and multidrug transporters in bacterial resistance to antimicrobial agents.

The key topic of the Conference discussions was the quest for ways to combat antibiotic resistance and to find alternatives to antibiotic treatment. Professor Robert Allaker (Queen Mary University of London, London, UK) talked about nanoparticles based on the metals copper, zinc, tungsten, titanium and silver, as well as their oxides and combinations between the metals and oxides. These nanoparticles possess high biocidal and anti-adhesive properties and can therefore be used as antimicrobials for inhibition of planktonic bacterial cells and for prevention of biofilm formation of oral pathogens. Nanoparticles have high antimicrobial activity and reduced toxicity to eukaryotes and thus seem suitable for coating dental implants.

A potential alternative approach to inhibiting infections by the repurposing of existing drugs against new targets was proposed by Dr Sanjib Bhakta from the University of London and UCL (UK) in his plenary lecture. Non-steroidal anti-inflammatory drugs were found to exhibit selective bactericidal activity against replicating, non-replicating and multidrug-resistant clinical isolates of *M. tuberculosis*. Repurposing of drugs bears certain advantages over the development of novel medications, since it can save time of operation and

investment of material and human resources. The issue of the re-introduction of old antibiotics, such as penicillin, which for a long time have rarely been used against methicillin-sensitive and resistant strains of *S. aureus* for treatment of eye infections was discussed by Professor Regis P. Kowalski from the University of Pittsburgh (Pittsburgh, PA, USA). He reported that topical application of penicillin against bacterial samples isolated from the cornea induced a bactericidal effect, indicating a resurgence of penicillin-sensitive *S. aureus* strains and enabling the comeback of penicillin as an effective antibiotic for the treatment of keratitis. Professor Emilce de los A. Méndez (Universidad Nacional del Litoral, Santa Fe, Argentina) dedicated his lecture to one of the most common hospital pathogens, methicillin-resistant *S. aureus*. The results of a study of more than one hundred hospital isolates of MRSA showed bactericidal activity of vancomycin alone or combined with other drugs (ciprofloxacin, gentamicin, rifampin and imipenem). Antimicrobial combinations were highly effective due to a synergistic effect.

Professor Shunmugiah Karutha Pandian from the Alagappa University (Science Campus, India) spoke of the need to reduce uncontrolled and excessive antibiotic use in order to stop the evolution of multidrug-resistant bacterial strains. He suggested that microbial pathogenesis could be treated by targeting quorum sensing pathways and by preventing biofilm formation of pathogens with the help of natural compounds such as a cyclo(L-leucyl-L-prolyl) dipeptide and a cyclic terpene limonene. A similar idea of targeting virulence mechanisms and biofilm formation of pathogens was presented by Dr Domenico Schillaci from the University of Palermo (Palermo, Italy). Antivirulence factors such as curcumin and its derivatives were found to inhibit the enzyme sortase A, which is responsible for the anchoring of microbial surface components that recognise adhesive matrix molecules to the cell wall of Gram-positive bacteria (*S. aureus*, *E. faecalis*, *E. faecium* and *C. difficile*). This new therapeutic approach, involving the use of antivirulence drugs, is proposed for the treatment of bacterial infections and is supposed to become a part of the strategy for overcoming antibiotic resistance. Ways for limiting *S. aureus* and *S. pyogenes* infections were highlighted by Professor Susan McDowell from the Ball State University, Muncie (Indiana, USA), who proposed several alternatives to antibiotics: HMG-CoA reductase inhibitors such as simvastatin, CDC42 protein inhibitors, PI3K inhibitors and prenyl transferase inhibitors, which act on host cellular pathways exploited by bacteria.

Professor Annette Draeger (Universität Bern, Bern, Switzerland) dedicated her presentation to Gram-positive pathogens that attack host cells by secreting cytotoxic pore-forming toxins. She suggested that artificial liposomes capable of competing with host cells be applied for toxin binding. Liposomes composed of cholesterol and sphingomyelin were shown to protect monocytes from toxins secreted by *S. aureus*, *S. pneumoniae* and *S. pyogenes*. Liposomal treatment of mice infected with *S. aureus* and *S. pneumoniae* substantially increased mice viability. Since liposomes are not toxic for humans and are not bactericidal, they

do not cause resistance and can be used for neutralisation of bacterial toxins of antibiotic-sensitive and resistant bacteria.

Mr Jasmeet Singh Khara noted a decline in the development of antibiotics and proposed using synthetic antimicrobial peptides characterised by a broad spectrum of activity and rapid killing of pathogens, including resistant bacteria, exhibiting synergy with conventional antibiotics and not observed as developing resistance. Dr Konstantinos Beis (Imperial College London, London, UK) devoted his lecture to antimicrobial peptides – microcins, non-lytic antimicrobial peptides produced by Enterobacteriaceae. Microcins can become an alternative to current antibiotics or can be applied for their internalisation. An interesting way to combat resistant and/or persistent bacteria, such as *P. aeruginosa*, by means of artilysins was suggested by Dr Stefan Miller from Lisando GmbH (Regensburg, Germany). Artilysins are novel recombinant enzymes in which peptidoglycan-degrading endolysins are fused with targeting peptides that transfer the endolysins through the outer membrane of Gram-negative bacteria. Artilysins are fully biodegradable and show broad applicability for reducing infections caused by Gram-positive and Gram-negative bacteria.

An ecologically friendly way to arrest pathogens, including antibiotic-resistant bacteria, was proposed by Dr Iryna Sorokulova (Auburn University, Auburn, USA) who presented antibacterial properties of *Bacillus* bacteria, especially *Bacillus subtilis*. These probiotic bacteria eliminate pathogens by producing bacteriocins, biosurfactants, antibiotics and lytic enzymes, by immunomodulation and with the help of signalling effects. The activity of *Bacillus subtilis* was shown *in vitro*, in animal models and in clinical trials. A similar idea, of treatment by probiotics, was presented by Dr John Nichols (the University of Surrey, Guildford, UK) who reported on a pilot study in which patients suffering from recurrent diverticulitis took daily doses of probiotic *Lactobacillus casei Shirota* (Yakult). Replacement of antibiotics by probiotics was effective and resulted in a decrease in symptom frequency and even in recovery from the disease.

Ms Agota Simon from the University of Bucharest (Magurele, Romania) raised the issue of challenges of antimicrobial treatment during long-term space missions and suggested that photosensitive non-antibiotics excited by UV laser beams could solve the problem. In my lecture, I showed that photodynamic antimicrobial chemotherapy can become a good alternative or complement to antibiotic treatment against Gram-positive and Gram-negative bacteria. The photodynamic technique is based on the use of dyes called photosensitisers, which can be activated by visible external indoor or outdoor illumination or by chemiluminescent and sonoluminescent light. No bacterial resistance to photosensitisers has been reported to date. Photosensitisers can be applied alone or combined with antibiotics.

In my opinion, and I am sure that most of the participants will agree, one of the most interesting ideas was presented by Dr Hans Kollberg (Uppsala University, Sweden) who suggested fighting antibiotic resistance using avian

immune globulins. This idea is based on the fact that chickens are protected from infections by egg yolk immunoglobulin. Simple and inexpensive vaccination of hens with various pathogens can yield high concentrations of specific antibodies, which are effective against the pathogens but are not toxic for humans, without inducing resistance or disturbing the normal flora and not causing adverse effects. The proposed method was proven for several bacteria, including *P. aeruginosa*, in the treatment of cystic fibrosis patients.

Dr Jens Madsen (University of Southampton, Southampton, UK) announced an approach to fighting infections through the boosting of the immune system by fragments of innate immunity proteins – collagenous lectins with a high ability to bind sugar units of bacterial liposaccharides. Another strategy that can replace antibiotic treatment is homeopathy. Mrs Alison Fixsen (the University of Westminster, London, UK) reported positive results in homeopathic treatment of otitis media with effusion. Homeopathic treatment had fewer side effects and broader therapeutic opportunities than conventional treatment. This fact may have significant impact on high-risk individuals and communities and could lead to a reduction in antibiotic use among children.

In a free discussion, the participants of the Conference expressed the view that despite a dramatic increase in resistant bacterial strains, mankind is not in a post-antibiotic era, and total cessation of antibiotic therapy is not yet possible. In order to arrest the propagation of resistant bacteria, it is important to reduce antibiotic use and replace or complement antibiotic treatment by folk medicine, homeopathy, natural products, probiotics and non-antibiotic antimicrobials such as antimicrobial peptides and photosensitisers. The interdisciplinary approach and combination therapy should be elaborated for effectively combating antibiotic-resistant bacteria.



Speakers from the first day of the conference: from left to right: Jeannete Zurita, Emilce Mendes, Regis Kowalski, Stephen Mortlock, Hendrik Van Veen, Susan McDowell and Hans Kollberg