

MASTERING ANTI-INFECTIVE THERAPIES

▷ WHY DO WE NEED TO MASTER ANTI-INFECTIVE THERAPIES? AND WHY TO WE NEED NEW ONES?

Mastering anti-infective therapy is a worldwide challenge at a time where resistances emerge and expand globally in bacteria, viruses, parasites and fungi. Numerous epidemiological studies have demonstrated the link between the extended use of anti-infectives and occurrence of resistance. There is thus an urgent need to master anti-infective agents by qualified infectious diseases physicians both in the hospital setting and the community. Protocols and evaluation of strategies need to be performed to reduce the inappropriate consumption of these agents and improve the quality of their prescription during both curative or prophylactic approaches. Facing such microbial resistances would ideally require the availability of new anti-infectives and vaccines. However, several of them are currently lacking. Finally, it should be emphasized that new concepts for evaluating anti-infective agents in development are warranted.

Olivier Lortholary, *Hôpital Necker & Institut Pasteur, Paris, France*

▷ CONFLICTING EVIDENCE ABOUT THE RELATIONSHIP BETWEEN ANTIBIOTIC USE AND RESISTANCE

Once valid consumption data are available, it is tempting to start an analysis of the associations between consumption data and resistance data. An ecological relationship between outpatient antibiotic use and rates of resistance has been demonstrated in several studies. Although the ecological relationship between resistance and the use of antimicrobials clearly exists, it is multifactorial and often confounded by a number of variables (patient compliance, lag time, quality of data). Ecological studies have two major shortcomings. The first arises from the fact that they do not link the exposure in the individual to the outcome of that individual, which creates the so-called "ecological fallacy". The second difficulty is the lack of control of confounding. Significant correlations between consumption and resistance do not necessarily imply causal relationships. Despite these methodological limitations, there are several reasons for the widespread use of ecological studies: low cost and convenience, measurement limitations of the individual-level studies, design limitations of individual-level studies, interest in ecologic effects, simplicity of analysis and presentation.

Herman Goossens, *University of Antwerp, Belgium*

▷ DETERMINANTS OF ANTI-INFECTIVE PRESCRIBING: PATIENTS' AND CLINICIANS' PERSPECTIVES

Over 80% of all antimicrobials are prescribed in primary care and over 50% of these prescriptions are probably unnecessary. Changing this is a highly complex matter. Patients' ideas feeling and expectations, diagnostic uncertainty, the desire to practice evidence based medicine and to preserve relationships, the communication skills of clinicians, time constraints, reimbursements systems and medico legal climate are just some of the factors that influence prescribing behaviour. This talk will present conceptual issues and state of the art evidence regarding broader determinants of anti-infective prescribing. In addition, 'hot off the press' results of new studies will be presented.

Christopher C. Butler, *Cardiff University, United Kingdom*

▷ IMPACT OF HEALTH CARE SYSTEMS ON DRUG USE

It is estimated that about half of all medicines are used inappropriately worldwide. Such inappropriate use wastes resources and can cause poor patient outcomes, adverse drug reactions and increased antimicrobial resistance. Many different actors are involved in drug use and they are greatly influenced by the type of health care system in place. Health system factors associated with more appropriate drug use include:

- Implementation of essential drug lists and standard treatment guidelines,
- Separation of prescribing and dispensing functions,
- Adequate regulation including the licensing of drug outlets and prescribers, limiting prescription of medicines by level of prescriber and enforcing regulation of drug promotional activities,
- System of continuing medical education, supervision, audit and feedback and peer review,
- Charging patients per drug item rather than per drug prescription (covering all items) where user fees are in place.

Kathleen Holloway, *WHO, Geneva, Switzerland*

▷ ANTI-INFECTIVE USAGE IN ANIMALS – A RISK FOR HUMAN HEALTH?

The use of antibiotics in animal rearing has been controversial ever since this practice began. There is clear evidence that resistance genes can be, and are, transferred from animal to human bacteria. Food is considered to be the main vehicle for transfer. Conversely, infections with methicillin resistant staphylococci of human origin are increasingly reported in pets and horses. The relative impact on human health of resistance genes derived from animal production is difficult to assess. However, animals need anti-infectives too and resistance will reduce the efficacy of the available

drugs. It is time that the veterinary and medical profession join forces to develop and implement effective strategies to contain resistance to anti-infectives.

Christina Greko, *National Veterinary Institute, Uppsala, Sweden*

▷ IMPACT OF MICROBIAL RESISTANCE ON CLINICAL OUTCOME AND HEALTH EXPENSES

Antimicrobial resistance is a prevalent and important problem worldwide. These infections are more difficult to treat than infections with similar organisms which are susceptible to commonly used agents, and effective therapy is often delayed. Infections with resistant organisms lead to adverse clinical outcomes, increased morbidity and mortality and are costly to the healthcare system. The magnitude of the adverse outcomes relate to the virulence of the organisms, the patient underlying condition, the syndrome, and the delay of appropriate therapy. Infections with resistant gram-positive, and gram-negative will be discussed along differences between various healthcare systems. Measuring and quantifying these effects is important both for resource allocation, and for designing strategies to combat resistance and improve patients' outcomes.

Yehuda Carmeli, *Tel Aviv Medical Center, Israel*

▷ PHARMACEUTICAL PROMOTION AND PREVENTION OF ANTIBIOTIC RESISTANCE

A tension exists between pharmaceutical firms' need to rapidly expand sales of new drugs in order to recoup development costs, and the need for limited and judicious use of new antibiotics in order to limit the spread of resistance. In this presentation, several case studies of promotion of anti-infective drugs will be discussed. What messages do they convey about the decision to treat and treatment choice? Are these messages consistent with public health goals to limit the development of resistance? A discussion of current regulatory frameworks governing drug promotion, and the experience with direct-to-consumer advertising and physician-oriented promotion will be included.

Barbara Mintzes, *University of Sussex, Brighton, United Kingdom*

▷ EDUCATION AND DECISION MAKING

Education is a key component of national and international strategies to control antibiotic use and resistance by encouraging prudent prescribing. The educational challenge involves a range of key stakeholders that not only include prescribing professionals, pharmacists and, increasingly nurse practitioners, but also includes a public focus. Undergraduate and postgraduate medical education has increasingly emphasised the importance of acquiring appropriate knowledge, skills and attitudes which are central to life-long learning and professional development. This requires a dynamic approach when managing infection since antibiotic resistance constantly erodes the efficacy of existing therapies. Examples of new initiatives directed at undergraduate and public education will be presented that illustrate the diversity of approaches.

Roger Finch, *University of Nottingham, United Kingdom*

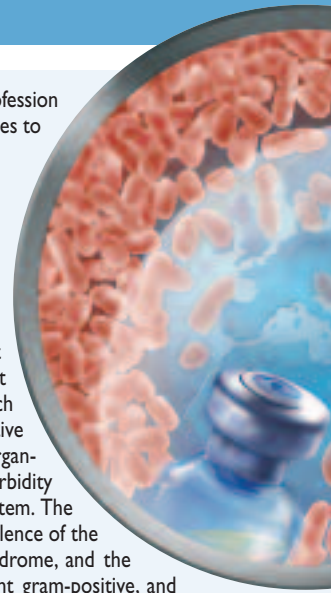
▷ BRINGING NEW ANTI-INFECTIVES TO THE PATIENTS - ROLE OF THE INDUSTRY

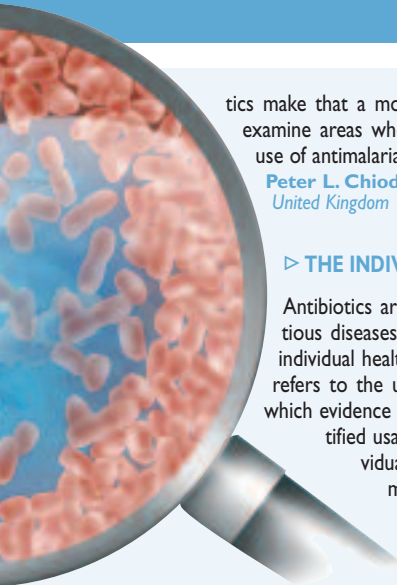
The pharmaceutical industry has traditionally been heavily engaged in R&D for new anti-infectives. However, changing use of antibiotics have resulted in many major pharma companies switching out of antibiotics in favour of either antivirals or focus on more chronic diseases. In its place, an increasing number of small biotech companies are filling this void. More harmonisation of regulations, better reimbursements, including acceptance of significant price premium for innovative medicines and faster (but still appropriate) adoption of newer and better antibiotics would further encourage more R&D investment.

Goran A. Ando, *Novexel SA, Romainville, France*

▷ OPTIMISING ANTIMALARIAL CHEMOPROPHYLAXIS

Effective malaria prevention depends upon matching the choice of antimalarial agent to: the species present in a given area; the likely drug-sensitivity of the local strains; patient tolerance; patient choice, including the influence of their peers and the media; and likely patient compliance. All these factors influence the actual performance of an antimalarial drug in practice. Compared to bacteria, malaria parasites are difficult to test for drug sensitivity on a large scale, but new developments in molecular diagnos-





tics make that a more realistic possibility. This presentation will examine areas where new methodology can help optimise the use of antimicrobial chemoprophylactic agents.

Peter L. Chiodini, *Hospital for Tropical Diseases, London, United Kingdom*

▷ THE INDIVIDUAL IMPACT OF ANTIBIOTIC USAGE

Antibiotics are effective agents to treat and prevent infectious diseases, and therefore have a positive impact of the individual health. The term "inappropriate use of antibiotics" refers to the usage of these drugs out of the situations in which evidence of its efficacy has been presented. Such unjustified usage might have deleterious effects for the individual (i.e., accumulation of resistant strains in the microbiota, that might be involved in future resistant infections, effects of the immune system, or in the bacterial metabolism of oestrogen or phytochemicals in the gut), but also beneficial effects (i.e., prevention of infections and/or host-to-host transmission of under-diagnosed pathogens, or reduction in para-microbial diseases). The risk/benefit ratio of these effects for the individual has not been calculated, and deserves of a specific programme of research.

Fernando Baquero, *Ramón y Cajal University Hospital, Madrid, Spain*

▷ SURVEILLANCE OF THE ANTIBIOTIC USAGE

Antibiotic use is the principal driving force for the emergence and spread of bacterial resistance. Thus, mastering antibiotic usage in conjunction with the control of cross transmission of resistant bacteria is now a national public health priority. In the community, the challenge for public education on antibiotic use is to achieve a meaningful reduction in unnecessary antibiotic use without adversely affecting the management of bacterial infections. In hospitals, to decrease antibiotic use might be more difficult than in the community. This presentation will review (i) how to survey antibiotic use in hospital and in the community and (ii) whether better antibiotic prescribing can turn the tide of bacterial resistance.

Didier Guillemot, *Institut Pasteur, Paris, France*

▷ SURVEILLANCES OF ANTIBIOTIC RESISTANCE: CAN THE RESULTS BE MISLEADING?

Surveillances of antibiotic resistance are important in that they are used for recommendations about empiric treatment. High levels of resistance are likely to result in recommendations to use antibiotics with broader spectrum and/or higher price. With few exceptions, e.g. the EARSS project on frequencies of resistance in blood or cerebrospinal isolates, surveillance systems are sponsored by pharmaceutical companies. Their goal is obviously to show that resistance is not an obstacle to use of their products. Common weaknesses of surveillance systems are (i) lack of denominators, (ii) non-representative selection of samples/strains and (iii) non-representative selection of laboratories from which strains are obtained. For example, it is of limited interest for a physician treating an elderly patient with pneumococcal pneumonia that the frequency of penicillin resistant in that species is high if the information was obtained from samples from day-care children. It is equally misleading to report frequencies of resistance in a country based on information from one or two private hospital laboratories, especially if the majority of the population receives health care at government sponsored facilities. It is also important to realise that bacteriological cultures are today normally taken only when something is abnormal in the course of the infections, e.g. failure of antibiotic therapy or early recurrence of an infection. This is likely to result in falsely high frequencies of resistance. Ideally, surveillances should be performed on all patients (age an type of care to be defined) with a given type of infection during a defined time period.

S. Ragnar Norrby, *Swedish Institute for Infectious Disease Control, Solna, Sweden*

▷ STRATEGIES TO IMPROVE THE USE OF MEDICINES: WHAT MAKES THEM EFFECTIVE AND SUSTAINABLE?

Inappropriate use of medicines is a prominent constraint in ensuring the accessibility of the community to essential medicines. Worldwide more than 50% of all medicines are prescribed, dispensed, or sold inappropriately, while 50% of patients fail to take them correctly. Efforts have been paid in the last 2 decades to improve the use of medicines, ranging from training health professionals, developing clinical guidelines, establishment of drugs and therapeutics committee in hospitals, monitoring and evaluation of prescribing, etc. Effective strategies have been identified and promoted. However, the improvements are not always maintained; as the medicine use often returns to the previous

baseline after a period of time and makes the energy, time, and money spent on activities wasteful. This presentation will discuss key factors of long-impact strategies; an array of well-proven examples will be displayed.

Sri Suryawati, *Gadjah Mada University, Yogyakarta, Indonesia*

▷ INDIRECT EFFECTS OF CONJUGATE VACCINES

Haemophilus, pneumococcal and meningococcal conjugate vaccines have proven hugely successful in paediatric practice. They are able to protect against several invasive infections - like bacteremia and meningitis - and are also efficacious in preventing non-invasive disease like otitis media and pneumonia. Besides these direct effects, conjugates seem also to have indirect effects. Among those are interference with the responses of other vaccines, changes in the nasopharyngeal flora and in the etiology of subsequent infections, and consequently even changed antimicrobial usage patterns among paediatricians and primary care physicians.

Juhani Eskola, *National Public Health Institute, Helsinki, Finland*

▷ REVOLUTIONIZING THE DIAGNOSTIC OF INFECTIOUS DISEASES WITH SMART CD_s THAT "READ" DNA IN A FEW MINUTES

Today, as in the time of Pasteur, it still takes at least two days to identify microbes responsible for infections. This lack of rapid tests results in imprecise diagnosis, inappropriate therapy, over-use of antibiotics, development of drug resistance, high health care costs, and difficulty in controlling epidemics. By merging genomics, nanotechnologies, microfluidics, biosensor technologies and microarrays, we are now developing low cost point-of-care SMART CD_s that can detect DNA in a few minutes. These new affordable devices should revolutionize clinical practice and give public health authorities the tools of the future to better control infectious diseases throughout the world.

Michel G. Bergeron, *Laval University, Sainte-Foy, Canada*

▷ EVALUATION OF THE SELECTIVE POTENTIAL FOR RESISTANCE TO ANTIBACTERIAL AGENTS

Since the selection of resistant bacteria is the most important culprit of antibiotic treatments, it is of utmost importance to quantify and evaluate it. Indeed, the evolution of bacterial resistance to antibiotics is currently so worrisome that any advantages that a new antibiotic would have in that matter in comparison with its competitors and/or predecessors would be of primary importance for its development and acceptability.

Antoine Andreumont, *Groupe Hospitalier Bichat-Claude Bernard, Paris, France*

▷ IS THERE A CRITICAL NEED FOR CONTINUED DISCOVERY AND DEVELOPMENT OF ANTI-INFECTIVES? A PHARMACEUTICAL COMPANY PERSPECTIVE

Anti-infective agents and vaccines have made a huge impact on humankind in the face of relentless attack from microbial adversaries and testify to the importance of investment both in pharmaceutical and academic research and development. However, such investment is declining rapidly across the industry as a consequence of increasing commercial and technical barriers, inexorably leading to an impending public healthcare crisis and the spectre of large-scale anti-microbial resistance in the absence of new agents. Against this backdrop, steps require to be made on a broad range of fronts. These span from political initiatives to provide incentives for continued research and development through to harnessing new technologies to drive down costs and increase the chances of technical success in anti-infective discovery and development.

Christopher A. Hitchcock, *Pfizer Global Research R & D, Sandwich, United Kingdom*

▷ PRESERVING THE POWER OF ANTIMICROBIALS: THE U.S. GOVERNMENT RESPONSE

The federal and state governments of the United States have engaged in a concerted effort to improve surveillance, prevention and control, research and product development to combat antimicrobial resistance. Activities include a multi-agency, interdisciplinary task force, surveillance for many different drug-resistant infections as well as antimicrobial usage, campaigns to improve antimicrobial use in the community and to improve infection control in healthcare settings, providing grants to researchers to study microbiologic and epidemiologic factors associated with the spread of antimicrobial resistance, and discussions with pharmaceutical companies to encourage antimicrobial development. Further work is planned in these areas to reduce the risk of antimicrobial resistance in the community, in healthcare settings, and in agriculture.

J. Todd Weber, *National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, USA*

▷ THE EDC VIEWS TOWARDS AN EUROPEAN STRATEGY

To be determined.