

# Antibiotics Chemotherapy



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## Publications of the ISC

Some years ago, the International Society of Chemotherapy (ISC) started a major project on publications. Two types of publication were planned – a newsletter and a journal.

The ISC has produced newsletters sporadically over its 40 years of existence. They were not very exciting, produced in small numbers and showed marked changes from one issue to another. Four years ago, the present newsletter – *Antibiotics Chemotherapy* – developed from discussions between the chairmen of European societies and Cambridge Medical Publications (CMP) on the production of a newsletter for the European Societies. CMP wisely advised we had an international newsletter for all societies and, with the help and enthusiasm of the ISC Executive, the ISC as a whole now produces the news. This year is the fourth full year of *Antibiotics Chemotherapy*. We have had some interesting items to read in the office during this time and we hope that we have made the correct selection for your entertainment.

The Society Journal stems from the efforts of Ragnar Norrby (President of ISC 1993 – 1997) to find a vehicle for the many papers provided by our worldwide membership. It proved difficult to find a journal that encompassed all aspects of both cancer and infection.

Efforts from 1996 onwards have been made to have two



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Hong Kong – venue for the 7th Western Pacific Congress on Chemotherapy and Infection.

separate journals, one for infection and one for cancer chemotherapy. So far, we only have one – the *International Journal of Antimicrobial Agents (IJAA)*. The detailed negotiations with Elsevier Science and with the distinguished Editors of the then existing *IJAA* went on for several months led by Ragnar Norrby (as President) and by Tom Bergan thereafter. These were successfully concluded in an agreement to have joint ownership of the Journal between Elsevier Science and the ISC. The editorial team of the ISC became responsible for Volume 10 and the first issue came out in April 1998. The Journal issues were running a little behind the proposed date when the ISC took over, and it has been necessary to publish several extra issues each year to bring the issues up to date. By the end of 2000 we will have completed Volume 16 so now we are right on time. Volumes 17 and 18 will appear in 2001.

Both ISC publications have got off to a flying start and now is the time to take stock. This was considered in depth by the Executive Committee of the ISC in June 2000.

The major changes for 2001 will be the Newsletter. This does not mean a change in style, but a change of Editors. We will now have three Editors in three geographically distinct areas of the world. Victor Lim from Malaysia, Kurt Naber from Germany and Robert Sidwell from USA will take over from the present Editors in 2001. We wish them all success and pleasure in producing the Newsletter. Production will remain with CMP but new editorial voices will be heard. Faridah Moosdeen will continue to collate the Newsletter as Managing Editor in the ISC office. Send your contributions to any of the editors or directly to the office. The involvement of the societies in the Newsletter is of great importance and we hope to hear of any meetings

*continued on page 3*

# Antibiotics Chemotherapy

## EDITORS



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Tom Bergan



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### Member Societies of the International Society of Chemotherapy

**Affiliated Societies:** Arab Society of Chemotherapy, Microbiology and Infectious Diseases; Argentine Society of Cancerology; Argentine Society of Infectious Diseases; Association pour l'Organisation de Réunions Interdisciplinaires de Chimiothérapie Anti-Infectieuse (AORIC); Austrian Society of Chemotherapy; British Society for Antimicrobial Chemotherapy; Bulgarian Society of Chemotherapy; Canadian Infectious Disease Society; Chemotherapists' Association of Ukraine; Chinese Pharmacology Society, Section of Pharmacology; Croatian Society of Chemotherapy; Cyprus Society of Chemotherapy and Infections; Czech Society of Chemotherapy; Czech Society for Infectious Diseases; Deutsche Gesellschaft für Infektiologie; Deutsche Vereinigung zur Bekämpfung der Viruskrankheiten eV; Dutch Society of Medical Microbiology; European Society for Paediatric Infectious Diseases; European Societies for Chemotherapy and for Infectious Diseases Affiliated to ISC; Georgian Society of Paediatric Chemotherapy; Hellenic Society for Chemotherapy; Hellenic Society for Infectious Diseases; Hellenic Society for Microbiology; Hong Kong Society for Microbiology and Infection; Hungarian Society for Chemotherapy; Indian Society for Antimicrobial Chemotherapy; Indonesian Society for Antimicrobial Chemotherapy; Infectionists' Scientific Society of Republic Belarus; Infectious Diseases Society of the Netherlands and Flanders; Infectious Diseases Society of South Africa; Inter-American Society for Chemotherapy (IASC); Inter-regional Association for Clinical Microbiology and Antimicrobial Chemotherapy (Russia); Israel Society for Infectious Diseases; Japan Society of Chemotherapy; Korean Society of Chemotherapy (Seoul); Lebanese Society for Infectious Diseases; Malaysian Society of Infectious Diseases and Chemotherapy; Mediterranean Society of Chemotherapy; Moroccan Society of Chemotherapy; National Society of Chemotherapy of the Russian Federation; Paul-Ehrlich-Gesellschaft für Chemotherapie; Philippine Society for Microbiology and Infectious Diseases; Polish Medical Association (Section of Chemotherapy); Portuguese Cancer Society; Portuguese Society of Infectious Diseases; Scandinavian Society for Antimicrobial Chemotherapy; Scottish Microbiology Association; Slovak Society of Chemotherapy; Slovak Society of Infectious Diseases; Slovenian Society of Chemotherapy; Società Italiana di Chemioterapia; Society of Chemotherapists in Bulgaria; Society of Infectious Disease (Singapore); Spanish Society of Chemotherapy; Swiss Society of Infectiology; Taipei Society of Infectious Diseases; Turkish Society of Antimicrobial Chemotherapy (ANKEM); Turkish Society of Chemotherapy; Western Pacific Society of Chemotherapy.

**Associate Member:** International Society of Antimicrobial Activity of Non-Antibiotics. ■

## Publishing Information

### MANUSCRIPTS

The Editors are happy to receive unsolicited manuscripts or photographs for consideration, but cannot accept responsibility for any loss or damage to such material. Manuscripts should be submitted in English, typed on white paper using double spacing with margins of at least 3 cm. Authors should submit material on computer disk (Word or ASCII format) or by e-mail wherever possible. Tables and figures should be separated from the text and should clearly indicate the author's name. Colour photographs and illustrations are encouraged.

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## From the ISC Secretariat

### 12th MCC and 7th WPCCID

The last two meetings this year are the 12th Mediterranean Congress of Chemotherapy, held in Marrakesh, Morocco, 11–14 November, and the 7th Western Pacific Congress of Chemotherapy and Infectious Diseases to be held in Hong Kong from 11–14 December. There is also a pre-Congress meeting in Guangzhou and a post-Congress meeting in Beijing, China, in conjunction with the Western Pacific Congress. Up-to-date programmes of each meeting were published in issue 4.2 of the Newsletter. Most of the topics address problems in chemotherapy within the respective regions. Every region has quite specific peculiarities in their approaches to infection and therapy. It would be very useful to have different ideas and considerations in these meetings with international participation. The Executive of the ISC anticipates that a local Society to serve North African colleagues will have been formed at the Marrakesh meeting.

### Global Resistance Day at ICAAC

A programme on 'Global Resistance Day' was held the day before the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy in Toronto, Canada, in September. This



Victor Lim.

was a programme put together by Ethan Rubinstein and involved eight international organizations/societies, including the ISC. The issues discussed were on global antimicrobial resistance, use of antibiotics in animals and humans, methodology and therapy and how resistance can be reduced. This issue of the Newsletter publishes extracts of two lectures, one by William Craig of the USA (page 4) and one by Henrik Wegener of Denmark (page 12). If you would like reprints of the handout, please contact Department of Meetings and Expositions, American Society for Microbiology, 1752 N Street, NW, Washington, DC 20036-2804, USA.

### Participation of Member-Societies in the ISC

What is the role of ISC with Member-Societies? ISC would really like more involvement and active participation of all Member-Societies in its activities. We understand that our colleagues are very busy with their own daily tasks, but it would be very nice to get feedback now and then so that



Kurt Naber.

the ISC can serve its members better. Member-Societies can share their activities with other members through the Newsletter; those who have recently held meetings can publish them (and photos) for all to share.

### Venue for the 25th ICC, 2007

The Council Meeting of the ISC will be held at the 22nd International Congress of Chemotherapy (ICC) in Amsterdam, The Netherlands, next year. At this meeting, the venue for the 25th ICC in 2007 will be decided. This is an important meeting as it will be a quarter of a century of ICCs held. The ICCs in 2003 and 2005 will be held in South Africa and The Philippines, respectively. It would be appropriate if the 25th ICC could be held in another geographical area. Member-Societies will have received a letter of invitation to become hosts of the ICC. If you are interested in becoming the host and putting in a lot of hard work, please contact the Secretariat with your intentions. Member-Societies should also think about their



Robert Sidwell.

nominations for three vacancies on the Executive Committee from July 2001.

### Hamao Umezawa Memorial Award

As mentioned in the last Newsletter, we welcome nominations for the Hamao Umezawa Memorial Award, to be presented at the ICC next year. This is the highest Prize given by the ISC in recognition of services to science in chemotherapy. There is a medal as well as a sum of money for the award.

### New Board of Editors of Antibiotics Chemotherapy

The present Editors of the Newsletter have served a term of 4 years and three new Editors have been appointed: Victor Lim, Kurt Naber and Robert Sidwell (see photos). The Secretariat will remain the collective office for any articles you may wish to submit. To the outgoing Editors, the ISC would like to say a hearty thank you for their contributions and effort; to the incoming Editors, the ISC extends its best wishes in their new undertaking. ■

*continued from page 1*

(and reports) you have and receive photographs of special events in your society. We have always in the past tried to put a face to the name.

The Journal has been successful in receiving many papers for consideration for publication and is publishing a lot of pages in 2000. Next year the Journal will have six issues

per volume, with two volumes to be published. From now on the Journal will be monthly. Like the Newsletter, it is time to start changes in personnel at the Journal. David Williams' term of office as Editor-in-Chief has been agreed to be for 5 years from 1998 and will end in 2002. All future Editors/Editorial Board members will have a fixed-term of office and

the complex arrangements for introducing this are now being taken. By the time of the next issue of the Journal, there will be one new item to include: each Member-Society of the ISC will have one Editorial Board member and societies are currently sending their proposal for this person. Why not subscribe to the Journal in 2001 at the special

low price? (see subscription form on page 14). You will see the changes in each volume. Meanwhile, keep sending in the manuscripts. The success of the Journal depends on the quality of the information it is able to present. ■

**David Williams  
Tom Bergan  
Faridah Moosdeen**

# Pharmacodynamics and treatment strategies against bacteria

~ Presented at the 'Global Resistance Day' Symposium in conjunction with the 40th

ICAAC, Toronto, Canada in September 2000

WA Craig



UNIVERSITY OF WISCONSIN,  
MADISON, WISCONSIN, USA

Dr William A Craig is currently Professor of Medicine and Head of the Clinical Pharmacology Section at the University of Wisconsin in Madison, Wisconsin, USA. He was Chief of Infectious Diseases at the William S Middleton Memorial Veterans Hospital. He retired from the Veterans Administration in 1998. Dr Craig has published over 200 articles dealing primarily with the pharmacokinetics and pharmacodynamics of antibacterials. He is an Editor of *Antimicrobial Agents and Chemotherapy* and serves on the Editorial Board of four other journals. He is currently completing his last year as Chair of the Program Committee of the Interscience Conference on Antimicrobial Agents and Chemotherapy. He is also a member of the Executive Council of the International Society of Chemotherapy. He serves as a member of the Antimicrobial Susceptibility Subcommittee of the National Committee for Clinical Laboratory Standards (NCCLS). He recently completed a 4-year term as Chair of the Anti-Infective Advisory Committee of the US Food and Drug

Administration (FDA). He is also a member of the Alpha Omega Medical Honor Society.

## Background

The primary goal of antimicrobial therapy over the years has been on enhancing clinical cure. That is the major outcome used by the FDA and other regulatory agencies for approval of new antimicrobials. However, in this era of increasing drug resistance, treatment strategies should also focus on maximizing bacteriological efficacy and preventing the development, emergence and spread of resistant organisms. Eradication of the infection pathogen at the site of infection is becoming an important goal of antimicrobial therapy. For one reason – dead organisms cannot become resistant. Eradication of pathogens from sites of spread, such as the nasopharynx for *Streptococcus pneumoniae*, can also be important in reducing transmission of pathogens from one individual to another. Knowledge of the pharmacodynamic characteristics of antimicrobials has enhanced our ability to identify drugs and dosage regimens that enhance bacterial eradication and can also prevent the emergence of resistant organisms.

## Pharmacokinetic and pharmacodynamic parameters

Specific pharmacokinetic/pharmacodynamic (PK/PD) parameters, such as time above MIC, peak/MIC ratio and AUC/MIC ratio, have been correlated with bacteriological and clinical efficacy. Beta-lactam and macrolide antibiotics that provide serum

concentrations that exceed the MIC for at least 40–50% of the dosing interval produce a high rate of bacterial eradication in acute otitis media and maxillary sinusitis due to *Haemophilus influenzae* and *S. pneumoniae*, including strains with decreased susceptibility to penicillin. Even higher times above MIC (80–100% of the dosing interval) are associated with eradication of *S. pneumoniae* from the nasopharynx. High peak/MIC ratios of 8–10 or higher with aminoglycosides are associated with decreased mortality in Gram-negative bacteraemia and a rapid clinical response in Gram-negative nosocomial pneumonia. A 24-hour AUC/MIC ratio of 100–125 or higher with fluoroquinolones significantly increases the probability of bacteriological and clinical cures in infections due primarily to Gram-negative bacilli. Lower 24-hour AUC/MIC ratios in the range of 25–35 are necessary for fluoroquinolones to produce a high rate of efficacy in pneumococcal infections.

Pharmacokinetic/pharmacodynamic parameters have also been correlated with the drug's ability to prevent the emergence of resistant organisms. Peak/MIC values of 8–10 or higher and 24-hour AUC/MIC ratios of 100 or greater have significantly reduced the risk for the emergence of resistant organisms during treatment with fluoroquinolones of patients that are infected with Gram-negative bacilli, primarily strains of *Pseudomonas aeruginosa*. Similar high peak/MIC and 24-hour AUC/MIC ratios have reduced the emergence of resistant organisms *in vitro* and in

animal models following exposure of Gram-negative bacilli to both aminoglycosides and fluoroquinolones. Lower ratios may be able to prevent the emergence of resistance with *S. pneumoniae* during exposure to fluoroquinolones. Much less information is available on other drug-organism combinations. High 24-hour AUC/MIC ratios do not reduce the development of resistance with Gram-negative bacilli producing type-1 beta-lactamase, such as *Enterobacter* species, following monotherapy with cephalosporins. Much more data are needed on the pharmacodynamic characteristics and parameters of antimicrobials and their dosage regimens that facilitate or prevent the development and emergence of resistant organisms.

## Drug combinations, rotation and short-course therapy

Other therapeutic strategies to reduce resistance include drug combinations, antimicrobial rotation and shorter duration of treatment. Drug combinations have been very helpful in preventing the emergence of resistant organisms in tuberculosis and other mycobacterial infections. Drug combinations have been less effective in preventing resistance in *P. aeruginosa*. Antimicrobial rotation in intensive-care units has yielded mixed results so far. Studies designed to document bacteriological cure over time have demonstrated repeatedly that bacteria are eradicated many days before the usual duration of therapy. Trials with shorter durations of therapy in respiratory infections have been encouraging, but more data on the optimal duration of therapy in a large variety of infections are clearly needed. ■

# Xenotransplantation and the risk of zoonoses ~

Presented at the 3rd ECC, Madrid, Spain in May 2000

J Stoye



NATIONAL INSTITUTE FOR MEDICAL RESEARCH, MEDICAL RESEARCH COUNCIL, LONDON, UK

**Dr Jonathan Stoye is a research scientist at the UK Medical Research Council's National Institute for Medical Research. He received his first degree from Cambridge University, UK, his doctoral degree from the University of Basel, Switzerland, and was then a research associate at Tufts University in Boston, USA. His research interests include retrovirology, xenotransplantation and genomics.**

## The rationale and risks of xenotransplantation

Xenotransplantation may well provide a solution to the existing shortage of organs for transplantation. It also offers exciting new possibilities for

cell or tissue therapy for a number of conditions including Parkinson's disease and diabetes. For this potential to become reality, three major problems must be overcome: rejection by the recipient's immune system; possible species-specific physiological incompatibilities between source and recipient; and infectious disease risks.

Unsurprisingly, allotransplantation provides numerous examples of infection. Some of these arise from environmental sources or from the recipient's natural flora, but a significant fraction is donor associated. These considerations have raised the spectre of transmission of novel pathogens from animal blood products, cells, tissues and organs into human recipients during the course of xenotransplantation. Such an agent might then spread to the general population. This is currently a topic of considerable concern.

## Pigs as the donor animal of choice

The pig appears to offer the best option as a xenotransplant source animal. Transgenic pigs have been bred which can provide organs that are not susceptible to hyperacute rejection; pig organs and

humans have similar physiology; pigs have large litters and grow rapidly. Further, there has been considerable demand for high health status pigs over the past few years and this had led to the development of a variety of procedures, beginning with hysterotomy under aseptic conditions, for producing pigs free of most pathogens. Common pathogens known to cause disease in both humans and swine can be excluded in this fashion.

## Congenitally acquired and germ-line transmitted pathogens

Unfortunately, the techniques used to generate specific pathogen-free herds cannot exclude pathogens that infect foetuses congenitally, such as cytomegalovirus, porcine parvovirus and circovirus, or that are passed in the germ line. None of these are known to infect humans; whether adaptation to allow growth on human cells could occur is unknown. It also seems improbable that we have identified all porcine viruses capable of transplacental infection and further research in this area is warranted. Although the congenitally acquired pathogen may ultimately prove more important, it is the germ line-transmitted viruses, called endogenous retroviruses, that are currently attracting the most attention. All vertebrates are thought to carry tens of thousands of these elements that have made their home in the genome following infection of germ cells. They are inherited as Mendelian genes, and can therefore only be eliminated by selective breeding. The vast majority are defective but some can give rise to infectious retroviruses, a tiny number of which are

associated with spontaneous neoplasms in their host species. Little is known about the pathogenic potential of endogenous retroviruses following transfer from one species to another.

## Porcine endogenous retroviruses

A few years ago, several groups suggested that porcine endogenous retroviruses (PERVs) with potential to grow in human cells might exist and, if so, they might represent a potential hazard of xenotransplantation. To pose a problem such PERVs must:

- Exist;
- Be inherited in herds to be used as cell/organ sources;
- Be expressed in the cells/organs to be transplanted;
- Infect recipients;
- Grow to high titres and cause pathology.

A variety of studies have since shown that multiple copies of at least two classes of PERVs (PERV-A, PERV-B), with the capacity to grow on human cells, can be found in the genomes of all pigs. These viruses are expressed in some, but apparently not all, pig tissues. However, they do not appear to be very infectious for humans *in vivo*. Studies of around 200 people exposed to a variety of live porcine material show no signs of infection with PERVs. Although care must be taken not to over-interpret these negative data (since both the level of exposure and degree of immunosuppression in the study group was variable and poorly controlled), it does appear that the risk posed by PERVs is not as great as originally feared. Although these elements must still be considered a potential hazard, the potential benefits of xenotransplantation would appear to justify the continuation of limited and closely monitored clinical trials. ■



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*Pigs are the preferred source animal.*

# Contaminating DNA in antibiotics provides drug-resistance R genes to sensitive bacteria

## Spread of drug resistance

Drug resistance has developed soon after the introduction of each antibiotic for clinical application today. This now seems to be widespread and universal and is attributed to several causes, such as gene mutations in the bacterial chromosomes, resulting in the selection of drug-resistant cells. This type of resistance, however, develops slowly with only a limited potentiality for dissemination to and among other bacteria. The spectacular emergence of drug resistance appears to be mostly due to the acquisition of R plasmids by the sensitive bacteria. The question of what may be the source or origin of these R genes and their mode(s) of dissemination among bacteria arises. Early experimental studies showed that some streptomycete genes can be replicated and maintained in *Escherichia coli* hosts, suggesting the existence of compatible DNA sequences between them.<sup>1</sup> This signified that possibly other streptomycete R genes may also be similarly, but naturally, 'cloned'<sup>2</sup> and replicated among commensal/pathogenic bacteria, present in human/animal tissues and on body surfaces.<sup>3</sup> The antibiotics themselves could probably serve as a source for dispersion or dissemination of such genes due to their presence as contaminating R-gene DNA in various antibiotic preparations.<sup>4</sup>

## DNA in antibiotics

Based on this hypothesis, the first observation was made when a concentrated solution of streptomycin, on being electrophoresed through an agarose gel column and stained with ethidium bromide, showed a barely visible band of DNA.<sup>4</sup> This became distinctly visible after it was separated from the antibiotic and concentrated. Following this, a systematic search for DNA and deoxyribose sugars was carried

out in streptomycin, kanamycin, polymyxin, penicillin G, ampicillin, methicillin, cloxacillin and mitomycin C, as well as on chloramphenicol and erythromycin. This was performed by an exhaustive removal of the antibiotic by dialysis and determination of the nucleic acids by chemical and physical means. DNA and RNA sugars were detected in all the antibiotics tested which varied from trace to nano- or micrograms per gram amounts, except for erythromycin and chloramphenicol.

These 'DNA' materials proved to be DNase sensitive, RNase and pronase resistant. They consisted of fragments of about 6 Mdal. When isolated and purified, these could repeatedly be transferred to several *Sm*<sup>s</sup> recipient enterobacteria, vibrios, *E. coli* 600 and *Salmonella typhi* 57.

After transformation, the *S. typhi* revealed similar plasmid DNA bands in them (originally absent in wild-types), the G+C%mol of these plasmid DNA showed close similarity to that of *Streptomyces griseus* chromosome DNA.<sup>4</sup>

In a similar study, DNA was reported to be present in several antibiotic preparations, suggesting these to be the source of drug-resistance genes.<sup>5</sup> These workers used other physical and molecular biological techniques to characterize the DNA detected, e.g. by fluorescence measurements and polymerase chain reaction (PCR) amplification of the streptomycete 16S ribosomal DNA sequences. This showed that a number of antibiotic preparations employed for human and animal uses were contaminated with chromosomal DNA of the antibiotic-producing organism(s). The DNA showed identifiable antibiotic-resistance gene sequences. It seemed plausible that the uptake of

such DNA by bacteria, and its functional incorporation into the bacterial plasmid or chromosome could happen and may lead to replication of R genes making the organisms resistant. These workers<sup>4</sup> were also of the opinion that the presence of DNA (R genes) encoding drug-resistance in antibiotic preparations was a factor in the rapid development of multiple antibiotic resistance in bacteria.<sup>5</sup>

A similar report was presented on the detection of DNA in several antibiotic preparations with subsequent experimental evidence for the dissemination of several types of antibiotic resistance genes – including those for oxytetracycline and streptomycin.<sup>6</sup> The DNA was extracted, purified and characterized by molecular, biological and biophysical techniques, including PCR amplification. Ribosomal producer strain-specific DNA could be detected in all the antibiotic preparations tested. Some could be amplified and showed a homology with *S. griseus* DNA.<sup>4,5</sup>

## Uptake of R-gene DNA

The evidence suggests that R genes, as DNA in antibiotics, are available to sensitive bacteria colonizing various body surfaces and to those which are pathogenic. The most likely means of uptake of such R-DNA seems to be by genetic transformation. There are several instances of uptake of such DNA experimentally by the natural transformation process.<sup>4,7,8</sup> Such transformation is assumed to take place only infrequently and is usually considered to be of lesser significance as regards total transfer of resistance genes. In a clinical setting,<sup>3</sup> however, under strong selection pressure exerted by the antibiotics used, even just a few initial transformant cells could outgrow the entire population

and interfere with antimicrobial therapy. Feed additives in animal husbandry may also favour uptake of free DNA, and promote gene transfer.<sup>6</sup>

These findings suggest that R-gene DNA from antibiotic-producing bacteria and fungi could account for acquisition of drug resistance in bacteria. ■

**AN Chakrabarty**

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# 4th Symposium on the Control of Surgical Infections

Florence, Italy,  
19–21 April,  
2001



## PRELIMINARY SCIENTIFIC PROGRAMME

### PLENARY LECTURE

Guidelines on antimicrobial chemotherapy for prevention and treatment of infections in the intensive care unit.

### SYMPOSIA

- **Guidelines for prevention of surgical site infection**  
Risk factors; the immune system; infection after laparoscopic surgery; choice of antimicrobial agents for surgical prophylaxis; the use of cephalosporins; guidelines for prevention.
- **Changing patterns of microbial epidemiology and new chemotherapeutic strategies for the control of septic complications in clean surgery**  
Microbial epidemiology patterns; septic complications in clean surgery; MRSA in orthopaedic implant surgery; glycopeptides in the treatment of septic complications after cardiac surgery; new strategies in infection prevention using biomaterials and tissue engineering products in plastic and reconstructive surgery.
- **Guidelines for prevention and treatment of infection in orthopaedic prosthetic surgery**  
Risk assessment for surgical-site infections in orthopaedics; antibiotic prophylaxis; two-stage exchange hip arthroplasty for deep infection; one-stage exchange knee arthroplasty for deep infection; gentamicin PMMA beads and other local antibiotic carriers in two-stage revision of total knee.
- **Antibiotic prophylaxis in clean surgery**  
Breast surgery and hernia repair; neurosurgery; vascular surgery; endoscopic and minimally invasive surgery; clean non-implant wounds.
- **Control of catheter-related infections**  
Diagnosis and intravascular



## 22nd International Congress of Chemotherapy

30 June–4 July 2001  
Amsterdam,  
The Netherlands



## 4th European Congress of Chemotherapy and Infection

5–8 May 2002  
Paris, France



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treatment; prevention and treatment of central venous catheter-related sepsis; infectious complications and safety of central venous catheters in AIDS patients; strategies in prevention in oncologic patients.

- **Current incidence, prevention and treatment of ventilator-associated pneumonia**  
Epidemiology; risk factors and mortality; empirical antimicrobial de-escalating chemotherapy and preventive measures; treatment options.
- **Strategies for prevention and treatment of sepsis in post-surgical intensive care**  
Toward a new definition of sepsis;

Gram-negative versus Gram-positive bacteria in sepsis; antibiotic-induced endotoxin release and clinical sepsis; treatment of documented and suspected neutropenia-associated invasive fungal infections; pathogenesis of septic shock: implications for prevention and treatment. ■

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## Erratum

### **Antibiotics Chemotherapy 2000, Vol 4 No 2**

**GJ Scampardonis. The Hellenic army's campaign against malaria, Thessaly, Greece, 1936–1940. Page 5.**

Dr Emman Detorakis should have been named as co-author of the article. The correct citation should be:

**GJ Scampardonis, E Detorakis. The Hellenic army's campaign against malaria, Thessaly, Greece, 1936–1940. *Antibiotics Chemotherapy* 2000; 4 (2): 5. ■**

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## Fighting antibiotic resistance successfully – an ISC/ETM collaboration

The ISC collaborated with the EuroTransMed Foundation (ETM) for continuing medical education in producing a special symposium on antibiotic resistance that was broadcast via satellite television to over 200 hospitals across Europe in October 2000. The meeting, organized by the ISC Secretary-General, Jean-Claude Pechère, was also webcast live on the internet.

Professor Pechère moderated the meeting, broadcast from the London Television Centre. The topics and speakers were:

- **Professor Dominique L Monnet**, the Statens Serum Institute, Copenhagen, Denmark  
– *The positive experience in Nordic countries of antibiotic resistance*
- **Professor Didier Pittet**, University of Geneva Hospitals, Switzerland  
– *Effective infection control in hospitals*
- **Professor Christina Vandenbrouke-Grauls**, Free University, Amsterdam, The Netherlands  
– *The positive experience against MRSA in Amsterdam*
- **Dr Rosamund Williams**, World Health Organization, Geneva, Switzerland  
– *Global strategies for overcoming resistance.*

The programme is available on video and CD-ROM from the ETM website where you can also find, free of charge, a text summary of the programme and a real-audio version. Hospitals can also acquire a real-video version for their servers through the ETM website available at: [www.etm.nl](http://www.etm.nl).

The ETM is an international doctors' organization founded in The Netherlands, which broadcasts symposia on a range of topics to its own network in Europe. The ETM programmes are produced to high standards and the ISC has taken the opportunity to encourage more worldwide strategies against antibiotic resistance. ■

## ISAAR 2001, 12–13 April 2001, Seoul, Korea

### Drug resistance in the 21st Century: a new beginning

Emergence and spread of antimicrobial resistance are among the most threatening health problems despite remarkable advances in modern medicine. During the past decade, there has been a decline in the power of antimicrobial agents and an increasing danger of infectious diseases. Increasing prevalence of current antimicrobial resistance and newly emerging resistance are anticipated in the 21st Century. The International Symposium

on Antimicrobial Agents and Resistance (ISAAR) contributes to the pivotal exchange of state-of-the-art information and data on infectious diseases and antimicrobial agents.

Epidemiology, mechanisms of resistance, pathogenesis, clinical impact of infectious diseases, development of antimicrobial agents and vaccines, and guidelines for treatment and prevention are the major issues of the international symposium.

The 3rd ISAAR will broaden the scope of the challenges of drug resistance. The meeting will cover more than 45 current topics by

internationally renowned scientists from all over the world. The meeting is organized by the Asian-Pacific Research Foundation for Infectious Diseases under the auspices of the ISC, the Western Pacific Society of Chemotherapy, the International Vaccine Institute, the Korean Society for Chemotherapy, the Korean Society of Infectious Diseases, the Korean Society for Nosocomial Infection Control and the Samsung Medical Center, Seoul, Korea. ■

**Jae-Hoon Song**  
Chair, Organizing Committee,  
Samsung Medical Center, Seoul,  
Korea

# International Congress of Chemotherapy – 25 years ago

The 9th ICC was held in 1975 in London, UK, and you can see how the scene has changed. Some things remain the same. The opening ceremony varies in the entertainment but the speeches and the ISC plaque are still going strong. There were projectors in 1975 but many talented performers liked to use the blackboard. On the social scene, men liked talking in groups (and smoking was still permitted). Women as ever liked dancing (a bit more decorous in those days and holding the partner was common). Hair was longer and men's ties were wider than today's fashions.



© 9th ICC

*The opening lecture by the late Sir Ernest Chain.*



© 9th ICC

*Presentation of the ICC plaque at the opening ceremony. Walter Marget (Germany) and the late Sir Charles Stuart Harris.*



© 9th ICC

*George Daikos (Greece; a former president of ISC) could always be found on the front row. Behind him another constant attendee from Greece, Seraphim Kastenakis, with Walter Siegenthaler (Switzerland; President of 10th ICC).*



© 9th ICC

*Lining up for the photograph has not changed David Williams (UK), Sir Robert Williams (UK), George G Jackson (USA), the late Sir Charles Stuart Harris (UK), Edward Lowbury (UK) and Gerry Collee (UK).*



© 9th ICC

*Session 395 chaired by Richard Wise (UK). Pre-combinatorial chemistry.*



© 9th ICC

*Some presenters preferred to use the blackboard. Plenty of chalk available. The late H Kuemmerle of Germany (then Secretary-General of ISC) chairing a talk by Calvin Kunin (USA).*



© 9th ICC

*Social activity at the 9th ICC.*

# Antimicrobial action – more than just killing micro-organisms

## Introduction

Since the widespread use of antibiotics began more than 50 years ago, most doctors have barely paused to think about how best to use them, even though they receive lots of advice. Most physicians regard antibiotics as essential adjuncts in solving many clinical problems. The gradual development of antibacterial resistance has limited the choice of therapeutic options, but is usually solved by a new batch of antibiotics. Patients have also had to comply with treatment, and endure symptoms and side-effects for longer periods than is necessary.

## Optimal dose and duration of therapy

Pharmacodynamic studies have shed light on how to dose antibiotics to obtain maximum antimicrobial effect. With regard to resistance, it is also necessary to reconsider duration of treatment. The Ehrlichian approach of *frappe fort, frappe vite* (hit hard and hit fast), aims to:

- Eradicate pathogens more quickly and thoroughly;
- Reduce excessive stimulation of the body's defences, thereby limiting symptoms and enabling the patient to feel better sooner;
- Minimize opportunities for the selection of resistant strains.

The greater scrutiny placed on antibiotic use stemming from resistance problems has also brought into question the rationale behind traditional antibiotic regimens. When antibiotics were new, courses were similar to those of other drugs, i.e.

given at regular intervals depending on, for example, half-life. Now that pharmacokinetics and pharmacodynamics are taken more into account, and because efficacy is taken for granted, patient compliance, convenience and cost are being given higher priority.

## Minimizing excessive immunological responses

Rapid eradication by cidal agents can be seen with classical kill-curve studies, but the rapid lysis of bacteria caused by agents such as beta-lactams can lead to the massive release of cell wall and cellular components. This can stimulate cytokine responses leading to increased symptoms and signs of endotoxemia. Some antibiotic classes including quinolones do not yield such a massive release of endotoxin, lipopolysaccharide or teichoic acid (Table 1).<sup>1</sup> Macrolides are known to suppress the release of several bacterial enzymes and exotoxins including the Shiga-like toxins of *Escherichia coli* O157:H7.<sup>2</sup>

Proinflammatory cytokines are switched off sooner by more 'gentle' killing. Some antibiotics, such as quinolones and macrolides, also directly reduce cytokine, phagocyte and other inflammatory cell activities.<sup>3</sup> Production of mucus is suppressed and local secretion of immunoglobulins is reduced. The immunomodulatory effect of macrolides explains their usefulness in the treatment of diffuse panbronchiolitis in Japan.

Studies in acute exacerbations of

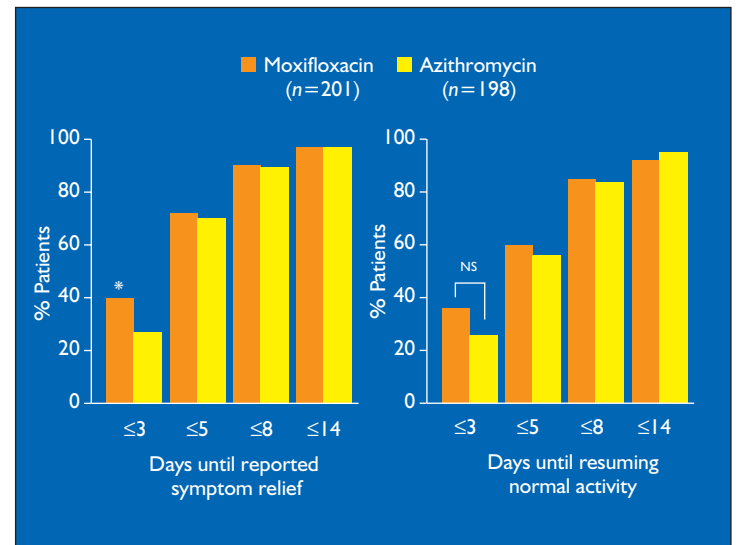


Figure 1. Patient views on therapy outcomes at follow-up. Patients were surveyed at 14–21 days after the start of treatment to indicate on which day they perceived an improvement in their condition (left panel) and the day they were able to resume normal daily activities (right panel). Data are expressed as the cumulative percentage of all patients' responses for each time interval. \*P=0.012 via Fisher's exact test (two-tailed); NS, P=0.07 (two-tailed); n=399.

chronic bronchitis with the quinolone moxifloxacin have shown a more rapid elimination of pathogens and a faster relief from symptoms compared to the macrolide azithromycin (Figure 1).<sup>4,5</sup>

## Conclusion

Some antibiotics have non-microbiological immunomodulatory effects in man.<sup>6</sup> Interactions between antibiotics and the immune system could contribute to therapeutic efficacy in many infections, giving rise to future prospects in the treatment of chronic infections caused by moderately resistant organisms. ■

Glenn Tillotson, Bayer Corporation, and Paul Iannini, Yale University School of Medicine, Connecticut, USA

## References

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6. Iannini P, Tillotson G. From bench to bedside: inter-relationships among pathogens, patients, and antimicrobial therapy. *Consultant* 2000, in press.

Table 1: Lipoteichoic acid (LTA) and teichoic acid release from *S. pneumoniae* due to antibacterial action of moxifloxacin versus ceftriaxone

Time after dosing (hours)	Moxifloxacin (ng/ml)	Ceftriaxone (ng/ml)	P-value
1	281	1734	P<0.01
3	685	3248	P<0.01
12	2512	3827	NS

NS, not significant. From Schmidt H, Dalhoff A, Stuert K et al. Moxifloxacin in the therapy of experimental pneumococcal meningitis. *Antimicrob Agents Chemother* 1998; **42**: 1397–1407.

## 22nd ICC – Scientific Programme



### 22nd International Congress of Chemotherapy 30 June – 4 July 2001, Amsterdam, The Netherlands

[www.eurocongres.com/icc](http://www.eurocongres.com/icc)

#### COMPASSION AND SCIENCE

##### From the President

The 22nd ICC is the first of the new Millennium. We look to the future as the logo shows. A future that will bring many changes: old

ways to treat infections will vanish; completely new tailor-made drugs will be designed; the resistance problem will grow, but new strategies to combat resistant micro-organisms will be developed.

The way we practice medicine may change but the way we care for the patient will remain the same. Issues on compassion and

science will be incorporated in the programme. Audiences in the developing countries will have the opportunity to participate in the programme through internet communication. Newer techniques, such as interactive sessions and electronic posters, will be available.

We hope to combine cutting-edge science for the basic scientists

with new information, important for the practising physician, and a forum where the drug industry can discuss their new compounds in an informal atmosphere.

We look forward to welcoming you in Amsterdam. ■

**Jan Verhoef**

President, Executive Organizing Committee

#### PLENARY LECTURES

- WHO reaction to the HIV epidemic
- Infection as a cause of cancer
- Gene therapy
- Epidemiological modelling of effects of intervention
- Symptoms and suffering at the end of life
- Molecular approaches to the development of new antimicrobials
- Angiogenesis: past, present and future
- Pathogenesis of infections in the post-genome era
- DNA vaccines in haematological malignancies

#### CONGRESS SYMPOSIA

- Probiotics:** Mechanisms; immunological effects in upper respiratory infections; *H. pylori*; diarrhoea
- Tropical diseases:** Development of resistance in malaria; tafenoquine; *Strongyloides stercoralis*; resistance in leishmaniasis
- Travel medicine:** Travel-associated parasitic infections; new zoonotic paramyxoviruses; schistosomiasis and new treatment; encephalitis syndromes; dengue vaccines
- Cancer – angiogenesis:** Anti-VEGF strategies; angiogenesis and the immune response, inhibitors and chemotherapy; endostatin/angiostatin
- Cancer – immunotherapy:** Tumour/dendritic cell fusion vaccines; allogeneic mini stem cell transplantation; peptide vaccines; phage-generated antibody targeting
- Cancer – designer drugs:** EGF receptor tyrosine kinase inhibitors; farnesyl transferase inhibitors; ADEPT and GDEPT; selective oestrogen receptor antagonists
- Cancer in developing countries:** The problem; WHO essential drug programme and oncology; clinical trials; anticancer agents from non-western cultures
- AIDS/HIV:** HIV vaccines; co-receptor usage; prevention – vertical transmission; therapeutic options for developing countries; gene therapy; antiretroviral therapy; antiretroviral drug resistance; metabolic complications; fusion inhibitors; IL-2; evolution of HIV; paediatric HIV; HIV and hepatitis; HIV and tuberculosis;

procreation in HIV patients

**Clinical trials:** The weak point; the regulations; drug development guidelines – western world, Japan

**Pathogenesis of infection:** Toll-like receptors; apoptosis in infectious diseases; viral immune escape mechanisms; macrophage migratory inhibitory factor

**Development of new antibiotics:** Bioinformatics; enhancing discovery; bacterial genomic information; the quorum system; RNA technology; novel classes

**Urinary tract infections:** Pathogenicity islands of *E. coli*; host response; pathogenesis in women with diabetes mellitus; how PK/PD apply to UTI; bacterial resistance for outcome

**Influenza – options for treatment:** Zanamivir; oseltamivir; RWJ-270201; current drug resistance profiles; amantadine and rimantadine

**Viruses:** Parainfluenza; modalities for RSV; adenoviruses; HHV-6; enterovirus and pleconaril  
**Resistance in viruses:** shingles therapy; cytomegaloviruses; influenza viruses; hepatitis B virus

**Micro-organisms and chronic diseases:** Atherosclerosis; sarcoidosis and asthma; Guillain-Barré and *Campylobacter jejuni*; *Tropheryma whippelii*

**New vaccines in clinical practice:** Bacterial meningitis; otitis media; community-acquired pneumonia; vaccination against UTI; Lyme borreliosis

**Drug resistance – pumps:** Quinolone resistance in Gram-positive cocci; efflux in eukaryotic cells; pumps in *Pseudomonas aeruginosa*; efflux pumps in *Candida*

**Strategies in the hospital to prevent and combat resistance:** Modelling; infection control; antibiotic policies; therapeutic strategies; MRSA, VISA, GISA and VRE

**Antimicrobial resistance:** Surveillance in Russia; Southern Europe; Japan; Northern Europe; the environment

**The compromised patient:** New aspects of infections in neutropenics; growth factors; quinolones and azoles; intravascular

catheter-related infections; risk factors for fungal infections in neutropenia

**Pharmacokinetics and pharmacodynamics:** Drug discovery; dose selection; the new born; new antifungal agents; artemisin and quinine

**Difficult to treat meningitis:** Prevention of sequelae; meningococcal vaccines; antimicrobial resistance; dexamethasone; activated protein C

**Understanding and treatment of chronic hepatitis:** Origin and evolution; new targets for hepatitis C; hepatitis B therapy; hepatitis C therapy; hepatocellular carcinoma

**Clinical syndromes:** Cystic fibrosis; prosthesis related infections; ehrlichiosis; bartonellosis; diffuse panbronchiolitis

**Food and waterborne diseases:** Legionella in tropical countries; BSE in Europe; eradication of *Campylobacter*; water safety initiatives

**Pneumonia during the last decade:** Aetiology, risk stratification; ventilator-associated pneumonia; pneumococcal bacteraemia

**Tuberculosis, the agent and the disease:** Virulence, why is TB out of control? Drug-resistant organisms; DOTS implementation; vaccine development

**Emerging infections and problems:** Bioterrorism; non-human usage of antibiotics; new rickettsial diseases; West Nile viruses; Hanta virus pulmonary syndrome

**Revolutionary technologies in microbiology:** Genomic-based diagnosis; FISH; rapid detection of group B streptococci

#### Free IJAA issues with your registration!!

Participants at the 22nd ICC will receive Volume 18 (six issues) of the *International Journal of Antimicrobial Agents (IJAA)* included in their registration.

Participants are invited to submit articles presented at the 22nd ICC, for publication in the *IJAA*.

# Use of antimicrobials as animal growth promoters – impact on resistance

Presented at the 'Global Resistance Day' Symposium in conjunction with the 40th ICAAC, Toronto, Canada in September 2000

HC Wegener



DANISH ZOOZOSIS CENTRE,  
COPENHAGEN, DENMARK

**Dr Henrik Caspar Wegener received his degrees from the Royal Veterinary and Agricultural University in Denmark. He worked at the Danish Veterinary Laboratory (DVL), where he was responsible for bacterial diagnosis and epidemiology with special emphasis on zoonotic infections, as well as the development and application of molecular, immunological and biochemical methods for detection, identification and characterization of zoonotic micro-organisms. He established an epidemiological research and surveillance unit (The Danish Zoonosis Centre) aimed at detecting and responding to new and emerging animal and food-related public-health risks in Denmark, where he is the Head of Research. Dr Wegener is also currently part of the Animal and Food-related Public Health Risks Team of the World Health Organization, whose activities involve strengthening laboratory capacities globally to assess, monitor and respond to public-health threats stemming from the use of antimicrobials in food-producing animals.**

Antimicrobials are used in livestock for the treatment and prevention of diseases and the promotion of growth. Antimicrobial growth promoters (AGPs) are added to feed usually in the dose range of 20–60 mg/kg of feed. AGPs have been used for nearly all types of livestock and for all age groups. The mechanism whereby AGPs promote growth is not precisely known and may differ for different classes of antimicrobials. It is generally recognized, however, that a main effect of AGPs is inhibition of intestinal microbes.

## Antibiotic classes

Almost all classes of antimicrobials used in humans are also used in livestock. Differences exist, however, between different regions and countries in which classes of antimicrobials are approved for growth promotion. In the USA, many antimicrobials for human therapy (e.g. tetracycline and penicillin) are also used as AGPs. In the European Union, regulations have attempted to avoid overlap between classes of antimicrobials used for human therapy and AGPs; until recently these attempts have not always been successful.

Classes of antimicrobials commonly used as AGPs include: glycopeptides, streptogramins, everninomycins, macrolides, tetracyclines, penicillins, quinoxalines, ionophores, bacitracin and flavofosfolipol (bambermycin). These classes of antimicrobials include ones primarily active against Gram-negative and Gram-positive bacteria.

According to the animal drug industry, global AGP sales totalled US\$2.2 billion in 1999. This represents approximately 10 million kilograms of antimicrobials used worldwide as AGPs.

## Development of resistance

Because AGPs are used in doses lower than those used for treatment (sub-therapeutic doses), they have been said to exert only a minimal selective pressure on the enteric bacteria. Recent studies, however, have shown that the AGPs exert a strong selective pressure, and lead to a high prevalence of resistance in some bacterial species in livestock.

The use of AGPs, in particular macrolides, has been associated with the development of resistance in several animal pathogens: *Serpulina hyodysenteria*, *Staphylococcus hyicus*, *Streptococcus suis* and *Mycoplasma hyosynoviae*. The current animal health impact of this resistance is minor because other therapeutic alternatives exist, but AGP use may have contributed to increased costs of treatment.

Scientific evidence indicates that AGP use has resulted in resistance in human pathogenic bacteria in food-animals, including *Salmonella* (tetracycline resistance), *Campylobacter* (macrolide resistance), *Enterococcus faecium* (resistance to glycopeptides, streptogramins, macrolides and everninomycins) and *Enterococcus faecalis* (macrolide resistance).

## Spread of resistant strains

Scientific evidence also indicates that these bacteria can spread easily from food-animals to humans either by direct contact or, more frequently, via food. This link between animals and humans is widely accepted for *Salmonella* and *Campylobacter*. Enterococci have been indicated to spread freely between animals and humans. AGP use has resulted in resistance in *E. faecium* in animals which has spread to humans through food. Intestinal carriage of

vancomycin-resistant *E. faecium* is a risk factor for this infection in humans.

Many AGPs are not absorbed from the gut by the animals. Consequently, unmetabolized AGPs, along with resistant enteric bacteria, are released into the environment in relatively large amounts. The environmental impact of this contamination has not been fully assessed. However, identical genes conferring resistance to AGPs have been detected in enteric bacteria and in other bacterial genera in soil, indicating that communication exists between these ecosystems.

## The economics of AGP

The use of antimicrobials for growth promotion is claimed to be economically beneficial to animal producers. Recent studies, however, question the economic importance of AGPs. Poultry producers in the UK, Sweden and Denmark have stopped using growth promoters without reductions in growth rates. Detailed studies by the poultry industry in Denmark suggest that, since there are cost savings from not purchasing growth promoters, and discontinuing AGP has not influenced growth rates, discontinuing the use of AGPs was economically beneficial. Similarly, swine producers in Denmark and Sweden have discontinued use of AGPs, substituting their use with safer non-antimicrobial alternatives, such as organic acids, with no adverse effect.

## Impact on public health

It is not possible to measure precisely the magnitude of the public-health impact of the use of AGPs in agriculture. The current scientific evidence, however, supports the following conclusions:

- The use of AGPs has created a major reservoir of

# The use of viral enzymes in tumour gene therapy ~

Presented at the 3rd ECC, Madrid, Spain in May 2000

## V Vonka



DEPARTMENT OF EXPERIMENTAL VIROLOGY, INSTITUTE OF HEMATOLOGY AND BLOOD TRANSFUSION, PRAGUE, CZECH REPUBLIC

**Vladimir Vonka is Professor of Microbiology at Charles University and is Head of the Department of Experimental Virology, Institute of Haematology and Blood Transfusion, Prague, Czech Republic. His current scientific interests lie in oncogenic viruses, gene therapy and anticancer vaccines.**

As originally understood, the term 'gene therapy' (GT) meant gene transfer into a patient's cells in order to provide them with an important missing function. With malignant tumours becoming the dominant objects of GT intervention, the concept and content has changed. Contemporary tumour GT strategies include antisense

sequences or ribozymes, which inhibit transcription or translation of genes whose products are significant in tumour pathogenesis and maintenance of phenotype. Another strategy is the introduction into tumour cells of fully functional tumour suppressor genes, e.g. p53, which are involved in more than 50% of human malignant tumours. A further strategy is based on the insertion of suicide genes (SG), whose products render the tumour cells highly susceptible to otherwise harmless substances. One can insert into tumours genes of immunostimulatory factors that can elicit an effective immune response to tumour-specific antigens without developing toxicity, as frequently happens upon systemic administration. Procedures that do not directly affect tumour cells but genetically modify therapeutically relevant nontumour cells are today classified under tumour GT, e.g. the transfer of genes into bone-marrow cells, which then become more resistant to cytostatic drugs. Tumour GT in its broadest sense includes the insertion of suicide genes into donor cells in allogenic transplantation; the products of these genes can make prompt and effective control over graft-versus-host disease

possible. The latest hit in GT is the utilization for tumour treatment of cytolytic viruses so modified that they preferentially reproduce in replicating but not in nonreplicating cells, or only reproduce in cells containing a p53-gene nonfunctional product. Some mutants of herpes simplex virus (HSV) and of adenoviruses produce the former and the latter type of action, respectively.

A variety of suicide genes have been proposed as SG for GT of malignant tumours; the majority of recent studies have been done with the thymidine kinase (TK) gene of HSV. Unlike cellular kinases, HSV TK phosphorylates nucleoside analogues such as aciclovir (ACV) or ganciclovir (GCV) which are widely used in treatment of herpesvirus infections. Cellular kinases phosphorylate newly produced ACV- or GCV-monophosphate to triphosphate, GCV- or ACV-triphosphate acts as a terminator of DNA-strand growth and interferes with DNA synthesis in replicating cells. The effects of SG products are not limited to the genetically modified cells. The nearby, genetically unmodified tumour cells are affected and killed. This phenomenon, called the bystander effect (BE), is not fully understood. However, it seems that, for example, with

HSV TK, the toxic metabolites penetrate into neighbouring cells via gap junctions. In the case of products of some other suicide genes (e.g. *E. coli* cytosine-deaminase, which converts the non-toxic 5-fluorocytosine to the toxic 5-fluorouracil) the toxicity may spread to the surrounding cells paracrinely. Evidence has been accruing that immune activities are also involved in BE. These are apparently conditioned by release of tumour antigens from dying cells, but also by cytokine activation in these cells, followed by necrosis and inflammation within the tumour area. Thus, SG-based therapy is capable of destroying the whole tumour mass and at the same time of inducing systemic antitumour reactions. The latter reactivity can be monitored by the development of concomitant tumour immunity and resistance to subsequent challenge by homologous tumour cells. These observations imply that GT and immunotherapy of tumours strongly overlap. The recent findings lend strong support to the concept of simultaneous use of SG and genes for immunostimulatory factors in GT. It represents one of the most promising strategies in the development of therapeutic tumour vaccines and might prove particularly useful in tumours resistant to standard therapy. ■

resistant bacteria in food-animals, some of these bacteria are pathogenic to animals and/or humans;

- Human pathogenic bacteria that are resistant to AGPs can spread from animals to humans;
- Treatment of human

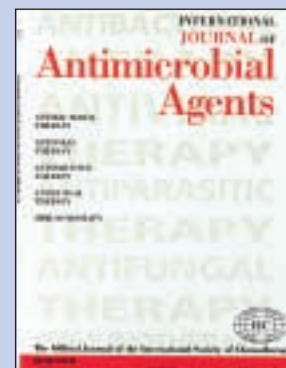
infections with antimicrobials belonging to classes also used as growth promoters has been compromised by resistance in bacteria that can spread from animals to humans, most notably glycopeptide- and streptogramin-resistant *E. faecium*.

### Conclusions

In the face of rapidly increasing levels of resistance in human pathogenic bacteria and a shortage of antimicrobial alternatives, there is a need for enhanced prudence in the use of antimicrobials in all areas. Studies demonstrate that use of AGPs constitutes a

public-health risk and AGPs are not necessary for profitability in modern animal production systems. The use of AGPs belonging to classes of antimicrobials used in human medicine should be terminated. Other AGPs should be phased out within the next 5 years. ■

# INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS



The number of papers received for publication in 2000 was 30% more than the papers received in 1999. Papers are received from all around the world and some issues this year will be very thick. In 2001 the Journal will be publishing a monthly issue with two volumes (Volumes 17 and 18) of six issues each.

The changes in 2001 will involve a rotation of Editors and an increase in the International Editorial Board. Each ISC Member-Society will nominate their representative to the Editorial Board. These changes will be made in Volume 17, issue 1.

## PLEASE KEEP SENDING YOUR PAPERS TO THE JOURNAL.

For a preview of the contents, please visit [www.ischemo.org](http://www.ischemo.org) where there is a link to the publishers.

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If you are registered for the ISC in Amsterdam, you will receive Volume 18 of the Journal sent directly to your home. This cost is included in the registration fee for the Congress. If you are being registered for the Congress by an agent or as an industry delegate, you will have to ensure the correct address is registered.

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# Opinion ~ outpatient parenteral antimicrobial therapy

Intravenous (IV) antibiotic therapy has been a mainstay of treatment for serious infections since the 1940s. While for many years it was considered a procedure that required hospitalization, it was more than 25 years ago that outpatient IV antibiotic therapy in children with cystic fibrosis and recurrent respiratory infections was first described in the English literature. Since that time, outpatient parenteral antibiotic therapy (OPAT) has grown rapidly in many countries. There has been a proliferation of infusion therapy providers in the USA such that nearly one in a

thousand Americans receives OPAT each year. China has had hospital-based infusion therapy clinics for many years. Many European countries have been slow to accept OPAT, with the exception of Italy, where intramuscular administration is the dominant form of therapy. The growth of OPAT in South America and developing countries varies with the funding available.

In some countries, OPAT has evolved from hastening hospital discharges to avoiding admissions altogether if there is ready access to a clinic or home-care nurses. In some infectious disease practices, the number of patients

being treated with OPAT may outnumber those being cared for with IV antibiotic therapy in the hospital. The ability to put together an effective infusion therapy team makes the infectious disease specialist even more valuable and cost-efficient.

There are a number of reasons OPAT has been so successful and should continue to grow and develop. These include:

### Patient benefits

Patients treated in an outpatient facility or at home avoid problems inherent in the hospital system. With OPAT, patients can recover in the comfort of their own homes, and many can return to work or school. Avoiding or leaving the hospital setting may also facilitate the transition from the role of the 'sick patient' back to the familiar, functioning self – thus speeding both adaptation and recovery.

### Cost containment

A number of studies have documented the cost savings of OPAT with antimicrobial agents. A hospital bed often costs more than US\$1000 a day in the USA, with fixed overhead costs of maintaining the physical plant, equipment, provision of meals, nursing and administrative staff. In a model of OPAT home infusion, if patients or family members are willing and able to administer IV medications, overhead and staff costs are virtually eliminated and the cost of IV antibiotic therapy can be reduced to approximately US\$200 per day.

The comparative economics of hospital and outpatient antimicrobial therapy should also take into account the rather different objectives associated with the two therapeutic settings. In the hospital, efforts are directed towards curing patients and discharging them. Cure is also an objective of OPAT, but the goal goes beyond that. The patient's quality of life during and after IV therapy is also a significant concern that must be factored, with outcome, into the cost-benefit analysis.



Alan D Tice.

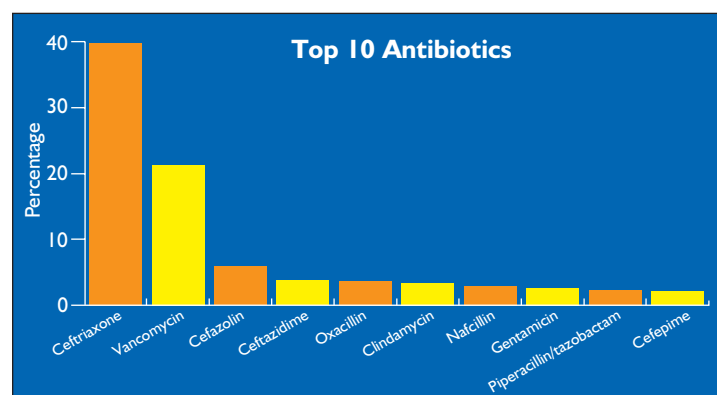
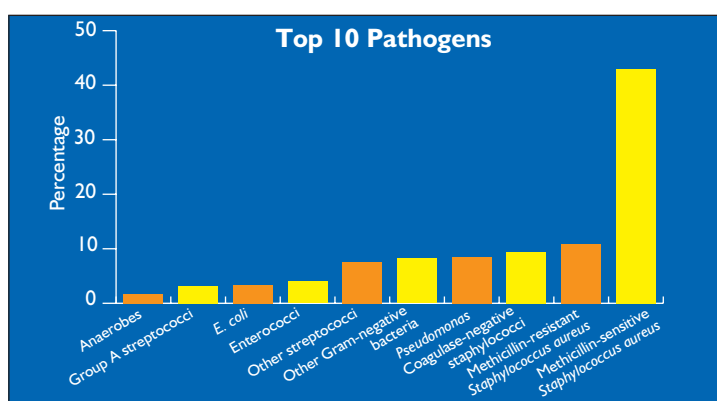
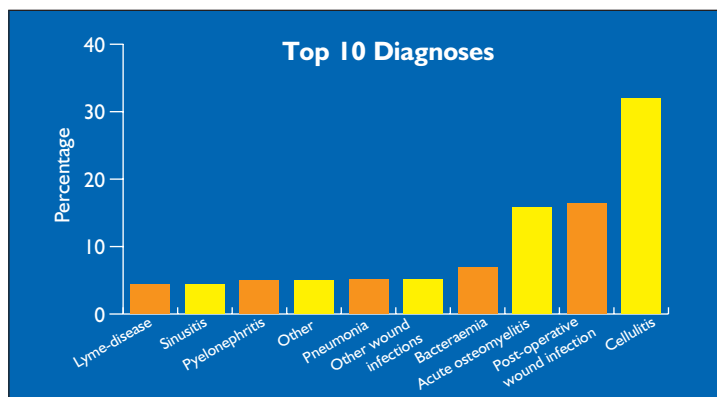
### Nosocomial infections

Hospital-related infections are estimated to affect over 5% of hospitalized patients, with an average 4-day extension of hospitalization and a direct loss of more than 20 000 lives annually in the USA. Additional healthcare costs have increased as a result of nosocomial infections. There is also an increased prevalence of organisms that are highly resistant to antimicrobials in hospitals due to the heavy use of antibiotics there. Examples of these are the drug-resistant enterococci, staphylococci and Gram-negative bacteria.

There are also special considerations in relation to OPAT. Patient selection for OPAT becomes a new concept for many physicians. The home and family situation needs to be assessed to assure compliance and safety as well as ready availability of emergency services. Plans to implement therapy with the evolving technology of vascular access and infusion devices must be made. Patients and their families must be more informed about the disease and the treatments received. Treatment needs to be adjusted to each patient's lifestyle. Children not requiring skilled nursing observation or interventions can probably benefit the most from avoiding hospital.

Although the success of OPAT has been remarkable in terms of efficacy, cost savings and patient satisfaction, its limits are

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uncertain and safety is of concern. The problems associated with outpatient therapy are different from those found in the hospital, where emergency staff and equipment are readily available. There is much less

medical supervision and control of the patient's environment at home, particularly with the reduced number of physician's visits. Outpatient therapy also puts patients at greater risk should severe reactions to medication or rapid deterioration of a disease state happen at

home. Because of possible emergencies, many OPAT programmes will not accept patients who do not have a telephone and ready access to transportation or ambulance services.

Fortunately, there is an evolving literature on OPAT and practice guidelines have been written by the Infectious Diseases Society of America (IDSA) and organizations in Canada, the UK, and Australia. OPAT Outcomes Registries have also been established with about 20 sites inside and another 20 outside the USA. These registries are now accumulating a critical mass of patients to determine the effectiveness and safety factors involved in OPAT. They are also shedding light on clinical outcomes of serious infection and will be increasingly able to tell us the most effective antibiotic to use for specific infections and the likelihood of serious adverse effects. Membership in the International OPAT Outcomes Registry is free of charge.

Additional information can be obtained by reviewing the web pages available at: [www.OPAT.com](http://www.OPAT.com) or [www.IDLinks.com](http://www.IDLinks.com)

#### Further reading

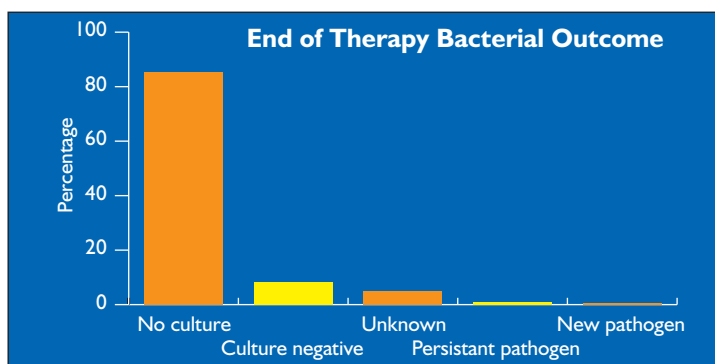
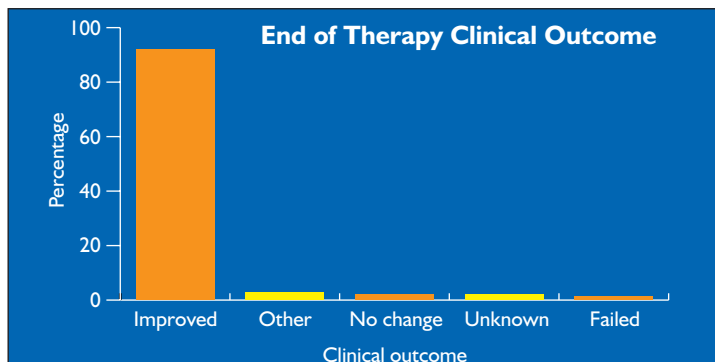
1. Tice, AD. *Handbook of Outpatient Parenteral Therapy for Infectious Diseases*. Scientific American Inc. New York, USA, 1997.
2. Williams DN, Rehm SJ, Tice AD *et al*. Practice guidelines for community-based parenteral anti-infective therapy. *Clin Infect Dis* 1997; **25**: 787-801.
3. Tice AD, Hoaglund PA, Schleis TG, Kunkel MJ. Measuring outcomes with Outpatient Parenteral Antimicrobial Therapy (OPAT) (poster). Presented at 4th Decennial International Conference and Healthcare-Associated Infections, Atlanta, GA, March 5-9, 2000.
4. Martinelli LP, Tice AD, Hoaglund PA. OPAT Outcomes Registry. Outpatient parenteral antimicrobial therapy (OPAT): bone and joint infections, an outcomes analysis (poster). Presented at IDSA 2000, New Orleans, LA.
5. Martinelli LP, Tice AD, Hoaglund PA. OPAT Outcomes Registry. Outpatient parenteral antimicrobial therapy (OPAT): safety, efficacy, and outcomes (poster). Presented at IDSA 2000, New Orleans, LA.
6. Tice AD, Hoaglund PA. Outpatient parenteral antimicrobial therapy (OPAT) for acute and recurrent lung infections (poster). Presented at ICAAC, September, 2000, Toronto, Ontario, Canada.

**Alan D Tice**

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## Diary Dates

### ISC Meetings

#### 30 June-4 July 2001, Amsterdam, The Netherlands

22nd International Congress of Chemotherapy  
CONTACT: Congress Secretariat, EuroCongress Conference Management, Jan van Goyenkade 11, 1075 HP Amsterdam, The Netherlands.  
Tel: +31 20 679 3411  
Fax: +31 20 673 7306  
E-mail: [icc@eurocongres.com](mailto:icc@eurocongres.com)

#### 5-8 May 2002, Paris, France

4th European Congress of Chemotherapy and Infection (ECC)  
CONTACT: Congrex Sweden AB, PO Box 5619, Linnegatan, 89A, SE-114 86 Stockholm, Sweden.  
Tel: +46 8 459 6600  
Fax: +46 8 661 9125  
E-mail: [congrex@congrex.se](mailto:congrex@congrex.se)  
[www.congrex.se/ecc-4](http://www.congrex.se/ecc-4)

### Other Meetings

#### 11-14 March 2001, Edinburgh, UK

1st European Conference on Cancer Strategies and Outcomes  
CONTACT: c/o Conference Associates, 50 Vineyard Path, London SW14 8ET, UK.  
Tel: +44 0208 939 6390  
Fax: +44 0208 876 1051  
E-mail: [boa@icmgb.com](mailto:boa@icmgb.com)  
[www.euro-cancer.org](http://www.euro-cancer.org)

#### 12-13 April 2001, Seoul, Korea

3rd International Symposium on Antimicrobial Agents and Resistance  
CONTACT: Susan Chung, Secretariat ISAAR 2001, Samsung Medical Center, 50 IL won-dong, Kangnam-ku, Seoul 135-710, Korea.  
Tel: +82 2 3410 0327  
Fax: +82 2 3410 0060  
E-mail: [susan@smc.samsung.co.kr](mailto:susan@smc.samsung.co.kr)  
[www.ansorp.org/meeting/2001](http://www.ansorp.org/meeting/2001)

#### 19-21 April 2001, Florence, Italy

4th Symposium on the Control of Surgical Infections  
CONTACT: EIFT srl, Via XX Settembre 102, 50129 Florence, Italy.  
Tel: +39 055 486 147  
Fax: +39 055 474 426  
E-mail: [info@jchemother.it](mailto:info@jchemother.it)

#### 30-31 May 2001, Yokohama, Japan

49th General Meeting of the Japanese Society of Chemotherapy  
CONTACT: Dr Hiroshi Takemura, Conference Secretariat, St Marianna University School of Medicine, Department of Microbiology, 2-16-1 Sugao, Miyamae-ku, Kawasaki-shi 216-8511, Japan.  
Tel: +81 44 977 8111 (ext 3539)  
Fax: +81 44 977 7818  
E-mail: [takeh@marianna-u.ac.jp](mailto:takeh@marianna-u.ac.jp)

#### 24-27 June 2001, Berlin, Germany

ISSTD/ISTTI International Congress on Sexually Transmitted Infections

CONTACT: Congress Partner, Krausenstr 63, 10117 Berlin, Germany.  
Tel: +49 30 2045 0041  
Fax: +49 30 2045 0042  
E-mail: [berlin@cpb.de](mailto:berlin@cpb.de)

#### 14-17 October 2001, Cannes, France

Resistance to Antimicrobial Agents  
CONTACT: Omega Studio srl, Via Cenisio, 87 - 20154 Milan, Italy.  
Tel: +39 02 34 94 935  
Fax: +39 02 33 15 959  
E-mail: [omega@omegastudio.com](mailto:omega@omegastudio.com)  
[www.omegastudio.com](http://www.omegastudio.com)

#### 21-24 October 2001, Portofino, Italy

2nd International Meeting on Antimicrobial Chemotherapy in Clinical Practice  
CONTACT: Dante Bassetti, University of Genoa, Largo G. Gaslini 5, I-16147 Genoa, Italy.  
Tel: +39 010 555 26 68  
Fax: +39 010 555 26 14  
E-mail: [mattba@tin.it](mailto:mattba@tin.it)