

Antibiotics Chemotherapy



APRIL 2002
VOLUME 6
NUMBER 1

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Scientific communications: virtual or reality?

Information technology and telecommunications have progressed rapidly in the past few years. How can we in the scientific world harness this technology for our benefit? The International Society of Chemotherapy (ISC) was established to further communication regarding infection and its therapy, but how far can it go to improve communication with its members?

Being able to find information on the Internet augurs well for people with limited access to resources, for those in small institutions or in economically disadvantaged countries. Websites of societies such as ours should contain useful information, provide expert discussion groups, publish consensus statements on current issues and provide a forum for debate.

Access to journals

Subscription to scientific journals is often included in the organization's membership fee. There are many journals one would like to have but to be a member of a number of different societies would incur substantial fees. Much discussion is taking place to increase access to journals on-line. Some publishers have decided only to allow issues published 6 months previously to be made available free of charge. This seems inadequate as new information evolves rapidly and becomes outdated quickly. There is a move by the World Health Organization and some publishers to allow specific institutions in countries with a low gross



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Paris, France – venue for the 4th ECC (4–7 May 2002).

domestic product to have free access to journals.

Many scientific meetings are held each year – some would say too many. One of their aims is to disseminate information to those in training. However, it is becoming increasingly difficult to attract large numbers of participants, as the cost of attendance can be prohibitive. Perhaps IT could be used to hold 'virtual' meetings with on-line interaction between participants. However, such solutions may be costly and, of course, lack the 'human' factor. Social interaction at meetings is invaluable in forming links between scientists, leading to collaborative research.

Rapid communications

Speed of connection and data transmission has made communication much easier. Data can now be sourced at the patient's bedside, so that one is no longer weighed down by hefty reference books. Prescribers' enquiries can be looked up and answered immediately. Most websites

with such information update their data constantly.

In addition, almost every medical practitioner has access to e-mail technology. This forms a useful medium for interaction with colleagues thousands of miles away, and for obtaining rapid answers. Patients can also be very well informed about their disease. This raises questions about whether or not practitioners are as well informed as their patients, and therefore highlights the importance of not being complacent about one's knowledge.

There are many ways in which IT can be useful in the communication of science. The issue, however, remains that of cost. There are hardware and transmission costs even if we have voluntary help with content.

How much longer will it be before 'virtual' communication becomes total reality to us all? ■

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Antibiotics Chemotherapy

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Antibiotics Chemotherapy is the official newsletter of the International Society of Chemotherapy. Distribution is made possible by educational grants and this issue has received generous support from:



This is gratefully acknowledged by the International Society of Chemotherapy and Cambridge Medical Publications.

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Further details from: Robert Kasproicz, Publisher,
Cambridge Medical Publications, Wicker House, Worthing,
West Sussex BN11 1DJ, UK.
Tel: +44 (0) 1903 288117; Fax: +44 (0) 1903 234862;
E-mail: rkasproicz@hbase.com

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Station Lane, Witney, Oxfordshire OX8 6YF, UK.
Fax: +44 1993 774676



Antibiotics Chemotherapy, ISSN 1469-199X, is produced on behalf of the ISC by Cambridge Medical Publications, a division of PAREXEL MMS Europe Ltd, Wicker House, High Street, Worthing, West Sussex BN11 1DJ, UK.
Tel: +44 1903 205884; Fax: +44 1903 234862;
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Vice-President

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Secretary-General

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Honorary Treasurer

Erdal Akalin was Professor of Medicine at the Hacettepe University Medical School, Ankara, Turkey. He founded the Infectious Disease

Section in the Medical School and was its Director. Since September 1994 he has been a director and medical advisor at Pfizer-Turkey, Istanbul, and a team member in various international functions of the Pfizer Pharmaceuticals Group. Erdal Akalin's research interests are in antibiotic use and bacterial resistance, healthcare systems, quality in healthcare and disease management.



Immediate Past-Vice-President

Ron Feld is a Professor of Medicine at the University of Toronto, Canada. He is also Director for

Continuing Education in Oncology. His major interests cover all aspects of cancer chemotherapy, particularly gastrointestinal and lung cancer.



Member as ICC President

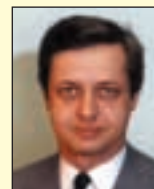
Wim Sturm is Professor and Head of the Department of Medical Microbiology, Nelson R Mandela School of Medicine in Durban, South Africa, and President of the 23rd International Congress of Chemotherapy to be held in Durban. He is Director of the MRC Genital Ulcer Disease Unit and Chair of the STD and HIV Treatment, Prevention and Epidemiology Research Group of the African Centre for Health and Population Studies. He is also the President of the South African STD Society.



Ordinary Member

William A Craig is Professor of Medicine at the University of Wisconsin. He was Chief of Infectious Diseases at the Williams S Middleton

Memorial Veterans' Hospital for 25 years and remains as a consultant. His research interests focus on the pharmacodynamics of antimicrobials. He was Chair of the Program Committee for ICAAC from 1998 to 2000 and is Chair of the Program Committee for the current 2002 IDSA Annual Meeting.



Ordinary Member

Wolfgang Graninger is Professor of Medicine and Head of the Department of Infectious Diseases at the University of Vienna, Austria. He

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Ordinary Member

Keith Klugman is Professor of Infectious Diseases in the Department of International Health at Emory University in Atlanta, Georgia,

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Ordinary Member

Victor KE Lim is Director of the Infectious Diseases Research Centre at the Institute for Medical Research in Malaysia, having been seconded to the Ministry of Health from the National University of Malaysia where he has been Professor of Microbiology in the Faculty of Medicine since 1989. He is presently the Secretary-General of the Western Pacific Society of Chemotherapy and President of the Malaysian Society of Infectious Diseases and Chemotherapy. His fields of interest include antimicrobial chemotherapy and infectious diseases, in particular hospital-acquired infection.



Ordinary Member

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Ordinary Member

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Co-opted Member

Hakima Himmich is Professor of Internal Medicine at the School of Medicine in Casablanca, Morocco. She is also Head of the Infectious Diseases Unit at the University Hospital Centre in Casablanca and is currently President of the Moroccan Association of Fight

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Co-opted Member

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Liaison Member

Morimasa Yagisawa is the Managing Editor of the *Journal of Antibiotics*, an international journal devoted to research on bioactive microbial products. He is also the Executive Director of the Japanese Antibiotics Research Association, to which more than 60

Japanese pharmaceutical companies are affiliated. He has major interests in the research and development of novel antimicrobial agents and is a member of the American Society for Microbiology (ASM) Program Committee for ICAAC.

A voyage of discovery in viral chemotherapy ~

Hamao Umezawa Memorial Lecture, presented at the 22nd ICC, Amsterdam, The Netherlands, July 2001

Erik De Clercq



REGA INSTITUTE FOR MEDICAL RESEARCH, KU LEUVEN, MINDERBROEDERSSTRAAT 10, B-3000 LEUVEN, BELGIUM

Many viral infections particularly require the use of chemotherapy. Among the DNA virus infections there are the herpesviruses: herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus type 6 (HHV-6), type 7 (HHV-7) and type 8 (HHV-8), papillomaviruses (human papilloma virus [HPV]) and polyomaviruses, hepadnaviruses (hepatitis B virus [HBV]), adenoviruses and poxviruses (i.e. smallpox, monkeypox and molluscum contagiosum). Among the RNA virus infections there are: retroviruses (human immunodeficiency virus [HIV]), orthomyxoviruses (influenza), paramyxoviruses (parainfluenza, respiratory syncytial virus [RSV]), hepaciviruses (hepatitis C virus [HCV]), picornaviruses (entero- and rhinoviruses) and haemorrhagic fever viruses (flavi [dengue fever, West Nile], arena [Lassa fever], bunya [Hantaan] and filo [Ebola]).

In the search for 'magic bullets' against these virus infections, a variety of approaches have been

explored. As a result, the following compounds have been developed:

- Interferon and interferon inducers;
- Suramin and other polyanionic substances;
- DHPA [(S)-9-(2,3-dihydroxypropyl)adenine] and S-adenosylhomocysteine (SAH) hydrolase inhibitors;
- Ribavirin and IMP (inosine 5'-monophosphate dehydrogenase inhibitors);
- BVDU [brivudin, (E)-5-(2-bromovinyl)-2'-deoxyuridine];
- Acyclovir (esters) and other acyclic guanosine analogues;
- 2',3'-dideoxynucleoside analogues (nucleoside reverse-transcriptase inhibitors [NRTIs]);
- Non-nucleoside reverse-transcriptase inhibitors (NNRTIs);
- Bicyclams;
- Acyclic nucleoside phosphonates.

Interferon and interferon inducers

Since its discovery in 1957 by Isaacs and Lindenman, interferon was quickly recognized as a broad antivirally active principle that may have far-reaching applications in the treatment of various virus infections. Polyacrylic acid and polymethacrylic acid were among the first synthetic inducers of interferon: they showed antiviral effects both *in vitro* and *in vivo* which could be ascribed to induction of interferon on the one hand, and inhibition of virus adsorption (by the polyanions themselves) on the other hand.

Efficacy was demonstrated against vesicular stomatitis virus (VSV) and vaccinia virus. Polyacrylic acid was found to provide long-term prophylactic protection against vaccinia virus infection and could be implemented, for example, in the case of an outbreak or attack with poxviruses such as monkeypox or smallpox.

Various double-stranded RNA molecules have also been recognized as inducers of interferon, among which is poly(I).poly(C).

The principal indications for the clinical use of human α - and β -interferon are multiple sclerosis, hepatitis B, hepatitis C (pegylated interferon in combination with ribavirin) and some malignant diseases such as multiple myeloma and kidney carcinoma.

Suramin and other polyanions

Suramin was identified in 1979 as a powerful inhibitor of the reverse transcriptase of several (animal) RNA tumour viruses. It was the first compound to be found active *in vitro* against the infectivity and cytopathicity of HIV, and was also the first compound to enter the clinic for the treatment of HIV infections.

The principal, as yet projected, indications for the clinical use of polyanions are in the form of vaginal microbicides for the prevention of genital transmission of HIV and HSV infections and other sexually transmitted microorganisms.

DHPA and SAH hydrolase inhibitors

DHPA [(S)-9-(2,3-dihydroxypropyl)adenine] is a broad-spectrum antiviral agent with a distinct, albeit relatively weak, potency against both DNA and RNA viruses. It was the first acyclic nucleoside analogue accredited with broad-spectrum antiviral activity. Later it was shown to exert its antiviral action through inhibition of S-adenosylhomocysteine (SAH) hydrolase and, subsequently, various other adenosine analogues were also described as broad-spectrum antiviral agents targeted at SAH hydrolase.

The SAH hydrolase inhibitors possess a characteristic antiviral activity spectrum,

encompassing, in particular, poxviruses (i.e. vaccinia), (\pm) RNA viruses (reo) and ($-$) RNA viruses (bunya-, arena-, rhabdo-, filo-, ortho- and paramyxoviruses). This also includes a number of haemorrhagic fever viruses, such as Ebola virus, against which SAH hydrolase inhibitors have proved effective in a lethal mouse model.

The principal, as yet projected, indication for the clinical use of S-adenosylhomocysteine hydrolase inhibitors is currently the treatment of haemorrhagic fever ($-$) RNA virus infections (i.e. Ebola virus infections).

Ribavirin and IMP dehydrogenase inhibitors

Ribavirin (1- β -ribofuranosyl-1-2,4-triazole-3-carboxamide) was the first nucleoside analogue shown (in 1972) to be active against a broad spectrum of DNA and RNA viruses, including picorna-, toga-, flavi-, bunya-, arena-, reo-, rhabdo-, ortho- and paramyxoviruses. Shortly after the discovery of ribavirin as an antiviral agent, IMP dehydrogenase was identified as a principal target for its mode of action. As ribavirin is a relatively weak inhibitor of virus replication, attempts made to increase its potency have led to the discovery of EICAR (5-ethynyl-1- β -D-ribofuranosylimidazole-4-carboxamide), which showed a 10- to 100-fold greater potency and an activity spectrum similar to that of ribavirin. EICAR may be a promising lead compound for the treatment of various RNA viruses (i.e. flavi-, bunya-, arena-, reo-, rhabdo- and paramyxovirus), infections that are presently not amenable to antiviral therapy.

The principal projected indications for the clinical use of IMP dehydrogenase inhibitors are RSV infections (ribavirin); hepatitis C (ribavirin, in combination with [pegylated] interferon) and

herpesvirus infections (in combination with acyclic guanosine analogues) in immunosuppressed patients (mycophenolic acid).

Brivudin (BVDU)

Brivudin [(*E*)-5-(2-bromovinyl)-2'-deoxyuridine] was described in 1979 as a potent and selective inhibitor of herpes simplex virus (HSV). Unlike acyclovir, BVDU proved significantly less active against HSV-2 than HSV-1. In comparison with acyclovir, BVDU turned out to be much more effective against VZV, apparently because of its exquisite affinity for the VZV thymidine kinase (TK).

The principal indications for the clinical use of BVDU are HSV-1 infections, both primary and recurrent, herpetic keratitis and herpes labialis, and VZV infections – varicella (chickenpox) and zoster (shingles).

Recently, we have discovered a new class of bicyclic furanopyrimidine analogues that are extremely potent and selective inhibitors of VZV, but are not active against HSV-1, HSV-2 or any herpesviruses other than VZV.

Acyclovir (esters) and other acyclic guanosine analogues

The advent of acyclovir [9-(2-hydroxyethoxymethyl)guanine] in 1977 heralded a new era in antiviral chemotherapy, that of specificity, based on a specific interaction with a virus-encoded enzyme, namely TK. The compound was found to selectively inhibit HSV-1 and HSV-2 replication as the consequence of a selective recognition by the virus-induced TK.

Valaciclovir, the valyl ester of acyclovir has, because of its better oral bioavailability profile, superseded acyclovir itself in the peroral treatment of herpesvirus infections.

Several other acyclic guanoside analogues (i.e. ganciclovir, penciclovir and H2G) have been developed.

The principal (and projected) indications for the clinical use of acyclic guanosine analogues

are HSV-1, HSV-2, VZV and CMV infections (therapy and/or prevention) and other human herpesvirus infections (EBV, HHV-6, HHV-7 and HHV-8). Whereas ganciclovir has remained the drug of choice for the treatment of CMV infections in immunocompromised patients, acyclovir (valaciclovir) and famciclovir are primarily used in the treatment of HSV-1, HSV-2 and VZV infections, in both immunocompetent and immunocompromised patients.

Dideoxynucleoside analogues

The activity of azidothymidine (zidovudine, AZT) against HIV was first revealed in 1985 when it was found to inhibit the infectivity and cytopathicity of HIV in cell culture assays.

It was the first of a whole series of 2',3'-dideoxynucleoside analogues that include didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC) and abacavir (ABC) and that would, subsequently to AZT, join the current armamentarium for the treatment of HIV infections.

The principal indications for the clinical use of 2',3'-dideoxynucleoside analogues, also referred to as NRTIs, are HIV infections, where they are used in multiple, triple or quadruple drug combinations with NNRTIs and protease inhibitors (PIs).

Non-nucleoside reverse-transcriptase inhibitors

The NNRTIs made their appearance on the anti-HIV drug scene around 1989–1990 with the discovery of two seemingly unrelated classes of compounds: HEPT [1-(2-hydroxyethoxymethyl)-6-(phenylthio)thymine] and TIBO [tetrahydroimidazo(4,5,1-*jk*)(1,4)benzodiazepin-2(1*H*)-one and -thione]. Both HEPT and TIBO were recognized as 'unique' compounds in that they demonstrated high specificity against HIV-1, relative to HIV-2 or other retroviruses. No other compounds had ever been reported before to act in such a way.

There are now more than

40 NNRTIs. Three of these compounds, nevirapine, delavirdine and efavirenz, have already reached the market stage. Others may undoubtedly follow as the 'newer' NNRTIs show activity against those HIV-1 strains that have acquired resistance to the 'older' NNRTIs.

The emergence of NNRTI-resistant HIV strains can be prevented if the NNRTIs are combined with NRTIs and used from the beginning at sufficiently high concentrations.

The principal indications for the clinical use of NNRTIs (nevirapine, delavirdine and efavirenz) are HIV-1 infections, where they are used in multiple, (triple, quadruple) combinations with NRTIs (AZT, ddI, ddC, d4T, 3TC, ABC) and PIs (saquinavir, ritonavir, indinavir, nelfinavir, amprenavir and lopinavir).

Bicyclams

The bicyclams were discovered in 1992 as potent and selective inhibitors of HIV replication, interacting with an early event in the viral replicative cycle.

The exact target for the mode of action of the bicyclams was revealed in 1997 when the compound AMD3100 was found to interact highly specifically with CXCR4, the receptor for the CXC-chemokine SDF-1 (stromal cell-derived factor) and the co-receptor for the X4 or T-lymphotropic HIV strains.

The principal, as yet projected, indications for the clinical use of bicyclam derivatives are HIV infections as well as other pathological processes mediated by CXCR4 and/or its natural ligand (stromal cell-derived factor [SDF-1]).

Acyclic nucleoside phosphonates

In 1986 we described (*S*)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine (HPMPA) as a novel selective broad-spectrum anti-DNA virus agent with activity against virtually all DNA viruses (polyoma, papilloma, adeno, herpes and pox). This compound could be designated as an acyclic nucleotide analogue. The cytosine counterpart of HPMPA, HPMPA, HPMPA (cidofovir),

first described in 1987, was developed as an antiviral drug.

The antiviral activity spectrum of cidofovir is truly remarkable in that it encompasses herpesviruses, polyomaviruses, papillomaviruses, adenoviruses and poxviruses.

The compound has been approved for the treatment of CMV retinitis in AIDS patients, and offers great promise and potential for the treatment of progressive multifocal leukoencephalopathy (PML), HPV-associated lesions, TK-deficient HSV and VZV infections, EBV, HHV-6, HHV-7 and HHV-8 infections, poxvirus infections (variola, vaccinia, cowpox, monkeypox, orf and molluscum contagiosum) and adenovirus infections.

In addition to cidofovir, two other acyclic nucleoside phosphonates, PMEA [9-(2-phosphonylmethoxyethyl)adenine, adefovir] and PMPA [(*R*)-9-(2-phosphonylmethoxypropyl)adenine, tenofovir] have been pursued for clinical development.

Conclusion

While for many years virus infections were considered intractable to chemotherapeutic approaches, we have witnessed within the past 2 decennia, and particularly the last 5 years, the advent of a large variety of now formally approved antiviral drugs, i.e. for the treatment of HSV, VZV, CMV, HIV, HBV and HCV infections, and also for the treatment and prevention of influenza A and B virus infections.

Many of the compounds mentioned above have not yet acquired a market position and are still in the developmental stage.

It remains to be seen if any of these compounds will ever qualify as 'magic bullets' but, even if they do not, they will have contributed to progress in the antiviral chemotherapy field and the conquest of the ever increasing number of virus infections. ■

Use of antimicrobials outside human medicine and resultant antimicrobial resistance in humans*

Antimicrobial resistance

The widespread use of antimicrobials outside human medicine is of serious concern, given the alarming emergence in humans of bacteria that have acquired resistance to antimicrobials through this use. Some of the newly emerging resistant bacteria in animals are transmitted to humans, mainly via meat and other food of animal origin, or through direct contact with farm animals. Examples include the food-borne pathogenic bacteria, such as *Salmonella* and *Campylobacter*, as well as *Enterococcus*. Resistance of these bacteria to classic treatment in humans is often a consequence of the use of certain antimicrobials in agriculture.

Further study is required to investigate other possible ways of transmission of antimicrobial-resistant bacteria to humans. The impact on human health of the widespread distribution of non-metabolized antimicrobials through manure and other effluent from farm animals into the environment is still unknown.

Antimicrobial use in food animals

Antimicrobials are used for mass prophylaxis against infectious diseases, or continuously in feed at very low doses (parts per million) for growth promotion, particularly in pig and poultry production. Use of antimicrobials for these purposes has become an important part of intensive animal husbandry.

The amount of antimicrobials used in food animals is not known precisely. National statistics on the amount and pattern of use of antimicrobials in human medicine or elsewhere exist in only a few countries. It is estimated that about half of the total amount of antimicrobials produced globally is used in food animals.

A recent review in Europe has shown that an average of 100 mg of antimicrobials are used in animals for the production of 1 kg of meat for human consumption.

To some extent, pharmaceutical industry marketing of antimicrobials influences the prescribing behaviour of veterinarians and patterns of use among farmers. Unlike the situation in human medicine, there are currently few countries with industry codes or rules that oversee advertising practices for antimicrobials for non-human use.

Improper prescribing and dispensing, lack of licensing and enforcement, poor drug quality, inadequate veterinary education and food safety are some of the factors present in countries of economic transition where there is intensive animal production.

With the emergence of vancomycin-resistant enterococci in many hospitals, the question arises whether the use of vancomycin in agriculture could have compounded the problem. Vancomycin-resistant strains have been isolated in animals, food and non-treated people in countries where vancomycin is also used as a growth promoter in animals. Denmark banned the use of vancomycin in animal growth promoters in 1995, and all European countries followed suit in 1997. The prevalence of resistant enterococci in animals and food, particularly in poultry, fell sharply.

Antimicrobial use in aquaculture

Various antimicrobials are licensed and used in fish and shrimp production, particularly in Asia. Little information is available on the type and amount of antimicrobials used in aquaculture, making assessment of emerging public health risks difficult. Some countries have been looking for

non-antimicrobial alternatives, and Norway, for example, has reduced the use of antimicrobials by more than 90%, after changing its production practices and increasing the use of vaccines. There is definitely an urgent need to review the current usage patterns of antimicrobials.

Containment of antimicrobial resistance

The World Health Organization (WHO) is developing a Global Strategy for the containment of antimicrobial resistance. This strategy targets all areas where antimicrobials are used in the community, hospitals and agriculture.

The WHO has joined other organizations such as the United Nations Food and Agriculture Organization (FAO) and the Office International des Epizooties (OIE) in developing global principles and recommendations for antimicrobial use in agriculture. The global principles may be seen at the following web address: www.who.int/emc/diseases/zoo/who_global_principles.html

Through a concerted effort with partners from national agencies and research institutions, the WHO is enhancing food-borne disease surveillance and antimicrobial resistance testing of food-borne bacteria. The laboratory strengthening focuses on salmonellosis and antimicrobial resistance surveillance in food-borne *Salmonella*, and includes the following activities:

- Development of the Global Salm-Surv (www.who.int/salmsurv), a web-based databank on national and regional laboratories;
- Establishment of an electronically linked network of national and regional reference laboratories;
- Conducting external quality assurance programmes. By the end of 2000, as many as 80 national reference

laboratories had completed evaluation of *Salmonella* typing and antimicrobial testing;

- Establishment of international centres of excellence for surveillance and containment of antimicrobial resistance resulting from antimicrobial use in agriculture.

Containment of antimicrobial resistance will require national and local efforts to reduce the use of antimicrobials, and some countries have brought in legislation to help them take steps in this direction.

For example, since 1986 Sweden has banned the use of all animal growth promoters, including those not used in human medicine.

Denmark suspended the use of animal growth promoters in 1999 and Switzerland followed suit in 2000. Studies in Denmark have shown no significant economic impact or negative change in animal health status or food safety as a result of reduced antimicrobial usage in animals.

The WHO encourages countries to use all opportunities to reduce the use of antimicrobials outside human medicine. The overall aim is to ensure that infectious diseases in humans can be controlled more efficiently. ■



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*Based on WHO Fact Sheet 267, January 2002.

Prince Mahidol Award 2001

Three scientists whose work has benefited people in developing countries share the Prince Mahidol Award for 2001.

■ Sir David Weatherall, of the UK, received the award in the field of medicine.

■ Professor Barry Marshall, of Australia, and Professor Lam Sai Kit, of Malaysia, shared the award in the field of public health.

Sir David, a retired regius professor of medicine at Oxford University, UK, was chosen for his pioneering research on thalassaemias in molecular genetics, haematology, pathology and clinical medicine. His discovery demonstrated how molecular genetics could be applied to design practical strategies for disease prevention, control and alleviation of symptoms.

Professor Marshall, clinical professor of medicine at the University of Western Australia, together with his colleague, Robin Warren, first reported in 1983 the identification and culture of a novel organism – now identified as *Helicobacter pylori*. His breakthrough analysis transformed therapy for peptic ulcer from consumption of antacids and H₂ receptor antagonists or radical gastric surgery to a short, highly effective course of antibiotics.

Professor Lam Sai Kit is a virologist at the University of Malaya. His research in dengue was recognized worldwide. In recent years, his involvement in emerging disease had led to the critically acclaimed discovery of Nipah virus, which caused an outbreak in Malaysian pig farms and was later transmitted to people in Malaysia and Singapore.

The three award winners were selected from a list of 47 nominees from 25 countries.

The 10th anniversary award, consisting of a medal, a certificate and US\$50 000, was conferred by His Majesty King Bhumibol Adulyadej of Thailand on 31 January, 2002. ■



8th Western Pacific Congress on Chemotherapy and Infectious Diseases

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Developing countries given greater access to leading biomedical journals

The World Health Organization (WHO) and six large medical journal publishers have launched an initiative to enable some 100 developing countries to gain access to information in about 1000 leading medical and scientific journals. Starting in 2002, this arrangement is available through the Internet to medical schools and research institutions free of charge or at very reduced rates.

The medical journal publishers are Blackwell Science, Elsevier Science*, the Harcourt Worldwide

STM Group, Lippincott Williams & Wilkins, Springer-Verlag and John Wiley.

This initiative will be for an initial period of 3 years, during which time the institutions will be identified and the process put into place. The WHO has established a project called Health InterNetwork that aims to strengthen public health services by providing public health workers, researchers and policy makers access to high-quality and relevant information through an Internet

portal. It also aims to improve communication and networking.

The group of countries selected in the first phase are those that have a gross domestic product of US\$1000 or less. Materials will be provided free of charge. In the second phase, the publishers will consider extending the facility to another group of countries.

The publishers' statement of intent is at: www.who.int/library/reference/temp/statement_of_intent.pdf ■

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vaccine production and increase stocks of vaccine for use in the event of an outbreak.

The World Health Organization (WHO) confirms that the best method of stopping a smallpox outbreak, should it occur, remains the same – search and containment. That means identifying persons with smallpox, identifying those persons who have been in contact with them, and vaccinating them. People who have been vaccinated in the past are unlikely to develop the most serious effects of smallpox.

Advice and background information on smallpox is available through the WHO website. The WHO also provides 'Frequently Asked Questions and Answers' about smallpox and a smallpox 'Fact Sheet' with an electronic slide set of training materials. Other information that can be provided to Health Ministries on request includes a list of vaccine manufacturers that have the potential to produce smallpox vaccine and the names of laboratories that can diagnose smallpox. The WHO has also re-established a team of technical experts in smallpox who are available to assist countries in the investigation of, and response to, outbreaks.

Should an outbreak of smallpox be detected in any country, this should be treated as an international emergency. The WHO will help countries to pool available resources in order to contain the disease as rapidly and effectively as possible. ■

News

Smallpox vaccination – WHO guidance

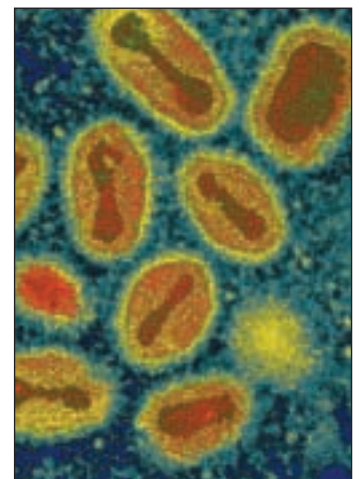
Existing smallpox vaccines have proven efficacy but they also have a high incidence of adverse events. The risk of adverse events is sufficiently high that mass vaccination is not warranted if there is little or no real risk of exposure. Individual countries that have reason to believe that their people face an increased risk of smallpox because of deliberate use of the virus are considering

options for increasing their access to vaccines. The vaccines would be given to people who are at risk of exposure to smallpox, including health and civil workers, and would be used in a search-and-containment exercise should an outbreak occur.

Vaccination of entire populations is not recommended. There is a risk of severe reactions to the vaccine, including death; in

any event, vaccination can prevent smallpox even after exposure to the virus.

Presently, anyone planning to work with this virus or at risk of exposure to the virus should be vaccinated. That view has not changed, but what has changed is the increasing attention being given to the extent and quality of existing vaccine stocks, and to the possible need both to stimulate



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Smallpox virus: vaccination is effective but the risk of adverse events means it is not warranted in the absence of risk of exposure.

Topics in Food Safety

Salmonella infection from birds

Salmonella species can infect birds as well as humans. In the case of such infection in chickens, the consequences to man are well known, but a recent report from the New Zealand Health Ministry demonstrates the potential importance of infection in wild birds.

In New Zealand before 1998, *Salmonella typhimurium* type 160 had been found only in birds, mainly sparrows. It was the cause of outbreaks of fatal disease in sparrows using bird tables and bird feeders in gardens.

Similar outbreaks in sparrows and finches are caused by *S. typhimurium* phage type 40 and *Escherichia coli* 086, and have occurred in the UK and North America. Although most of the dead birds have been found at wild bird feeding sites, food is not thought to be the primary source of the bacteria. A more likely explanation is that, when large numbers of birds congregate in a small area, if one or more is naturally infected and contaminates the feed and site, infection is readily transmitted.

In New Zealand the first human case of *S. typhimurium* type 160 occurred in 1998 and there was another in 1999. In 2000, there was a sharp increase: 1802 cases were reported and there was one death. In 2001, by 14 December there were 2275 cases.

In November 2001, *S. typhimurium* type 160 was said to have accounted for '47% of all gastroenteritis' (*New Zealand Herald*, 9 February 2002). Whether this was 47% of *Salmonella* infections or 47% of gastroenteritis infections of all types is not clear, but the number was plainly substantial and, in New Zealand, which has a total population of some 3.6 million people, the organism has become established as a

significant cause of gastroenteritis in humans in just 2 years.

How do humans become infected?

The results of a study carried out by the New Zealand Health Ministry indicate that the victims of *Salmonella* infection are 30 times more likely to have touched wild birds in the 3 days preceding the onset of their illness than uninfected people around them. They are also four times more likely to have had contact in the preceding month with someone suffering from diarrhoea or vomiting. In one very small study of hens' eggs (918 bought from Auckland supermarkets used by victims) the organism was not found, but the Medical Officer of Health in Canterbury, New Zealand, said that, in 2001, at least 11 *Salmonella* cases had been linked to the handling or eating of raw eggs and that nine had been caused by *S. typhimurium* type 160.

Nevertheless, it is apparent that the disease may be transmitted to man other than by food, and *Salmonella* infection previously believed to occur in man almost exclusively as a consequence of food poisoning may not be an indication of food poisoning at all.

In the past year, other diseases, previously thought to be almost entirely food-borne, have been shown to be transmitted in other ways.

In June 2001, a Scottish *E. coli* Task Force concluded that most sporadic *E. coli* O157 cases were derived from the environment and not from food. There are about 1000 reports of *E. coli* O157 infection in the UK each year.

In the autumn of 2001, the UK's Advisory Committee on the Microbiological Safety of Food was told that as many as half of the campylobacter infections could be derived



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A study by the New Zealand Health Ministry indicated that victims of Salmonella infection are 30 times more likely than uninfected people to have had recent contact with wild birds.

from the environment. There are currently about 54 000 reported campylobacter infections in England and Wales each year and most of these had been assumed to be food-borne. It has been calculated that, for every reported case, there are nearly seven others which are not reported, bringing the total to well over 400 000 a year. *Campylobacter* species are, therefore, thought to be the largest single bacterial cause of food poisoning in the UK.

The events in New Zealand suggest that it may be appropriate to look again at *Salmonellas*, arguably the organisms most closely identified with food poisoning. Over the past 3 years the number of reported infections in England and Wales has fallen from 32 000 per annum to 14 800 or less. However, it has been calculated that, for every reported case, there are two others, making about 44 000 in

all. Can we be certain that none of these were derived from an environmental source? The sparrow *Salmonellas* were identified only because they are of a distinctive phage type. If they had been of a type already spread by food, the significance of sparrows might have gone unnoticed. ■



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Selecting an advanced-generation fluoroquinolone: antimicrobial activity and prescribing convenience

As life expectancy increases and patients with chronic organic disorders live longer, physicians are faced with an increasingly complex patient population. It is a constant challenge to balance the benefits of antibiotics with the potential risks of using these drugs in patients who have multiple chronic medical problems such as renal insufficiency or diabetes mellitus. For treatment of bacterial infections, this means physicians must seek antimicrobial agents that not only demonstrate high rates of clinical and bacteriological efficacy, but that also allow for convenient empiric prescribing with a low risk of toxicity. Thus, there is a need for antibiotics that not only have good pharmacokinetic/ pharmacodynamic and drug-interaction profiles, but that also can be prescribed to a broad range of patients without inconvenient dosage adjustments and monitoring.

Since the first systemic fluoroquinolone – ciprofloxacin – was launched in the late 1980s, several newer generation fluoroquinolones (moxifloxacin, gatifloxacin and levofloxacin) have become available. These are frequently prescribed for the treatment of common community-acquired respiratory tract infections because they are efficacious against common respiratory pathogens, have favourable pharmacokinetic profiles that allow for once-daily dosing and are well tolerated with a low incidence of side-effects. Despite their similarities, these new fluoroquinolones are different in important ways. It is important to know these differences as they may significantly impact the convenience and cost of antibiotic therapy, especially in patients with comorbidities.

Antimicrobial activity

The recently introduced fluoroquinolones, moxifloxacin

and gatifloxacin, have potent activity against *Streptococcus pneumoniae*. Moxifloxacin, in particular, demonstrates enhanced *in vitro* potency (MIC₉₀ ranging from 0.06 mg/l to 0.25 mg/l) against *S. pneumoniae* and is generally two- to four-fold more active than gatifloxacin and four- to 16-fold more active than levofloxacin against penicillin-susceptible, -intermediate and -resistant strains of *S. pneumoniae*.¹ When compared to the earlier generation quinolones, these advanced-generation fluoroquinolones also provide an expanded spectrum of activity against Gram-positive cocci, intracellular bacteria and atypical organisms (e.g. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*).¹ In addition, moxifloxacin has significant *in vitro* activity against many anaerobic bacteria including the *Bacteroides fragilis* group.

Pharmacokinetic features

The pharmacokinetic profiles of intravenous (IV) formulations of moxifloxacin, gatifloxacin and levofloxacin are similar to their respective oral formulations, thereby facilitating IV-to-oral switching without the need for dose adjustments.²⁻⁴ All three fluoroquinolones are well absorbed after oral administration, with bioavailability of approximately 90% for moxifloxacin, 96% for gatifloxacin and 99% for levofloxacin. The drugs are widely distributed into body tissues and fluids, including respiratory tissues, with concentrations approximately equal to or exceeding plasma concentrations.²⁻⁴ Volume of distribution ranges from 1.7 l/kg to 2.7 l/kg for moxifloxacin, from 1.5 l/kg to 2.0 l/kg at steady-state for gatifloxacin, and from 1.1 l/kg to 1.6 l/kg (volume standardized to a 70 kg person) after single or multiple 500 mg or 750 mg

doses of levofloxacin.²⁻⁴

There are significant differences between the excretion pathways of moxifloxacin and the other two advanced-generation quinolones. The elimination of moxifloxacin is primarily non-renal, with approximately 20% excreted unchanged in the urine. As a result, dosage adjustment is not necessary in patients with renal impairment, including elderly patients with reduced creatinine clearance (Table 1).² In contrast, both gatifloxacin and levofloxacin are excreted largely in the urine, with more than 70% of an administered gatifloxacin dose recovered as unchanged drug within 48 hours following oral or IV administration. Dosage adjustments to avoid accumulation are therefore required with gatifloxacin for patients with creatinine clearance <40 ml/min and with levofloxacin for patients with creatinine clearance of <50 ml/min. Dosage adjustments are also required in patients receiving haemodialysis or continuous ambulatory peritoneal dialysis (Table 1).^{3,4}

Drug interactions and precautions

The absorption of all fluoroquinolones is decreased following the administration of products containing multivalent cations such as magnesium and aluminium antacids, iron products and sucralfate.²⁻⁴ Drug interactions and precautions are listed in Table 1.

A potentially clinically significant drug interaction has been reported following co-administration of gatifloxacin and digoxin. In healthy volunteers receiving both gatifloxacin and digoxin, increases in digoxin peak serum concentrations of up to 58% were observed.³ While no adverse cardiac events were associated with this increase,

patients co-administered gatifloxacin and digoxin should be monitored for signs of digoxin toxicity. No clinically significant interaction with digoxin has been reported for moxifloxacin or levofloxacin.

While a pharmacokinetic drug reaction has not been reported with the co-administration of warfarin and levofloxacin, there have been post-marketing reports that levofloxacin enhances the effects of warfarin. Elevations of prothrombin time with concurrent warfarin and levofloxacin use have been associated with episodes of bleeding. As a result, prothrombin time, or other suitable anticoagulation tests, should be closely monitored in patients receiving both warfarin and levofloxacin.⁴ Patients should also be monitored for evidence of bleeding.⁴ An interaction with warfarin has not been observed with moxifloxacin or gatifloxacin.

Both gatifloxacin and levofloxacin should be used with caution in diabetic patients who are receiving oral hypoglycaemics and/or insulin (Table 1). Disturbances in blood glucose, including symptomatic hyper- and hypoglycaemia, have been reported in diabetic patients taking gatifloxacin or levofloxacin. In these patients, careful monitoring of blood glucose is recommended.^{3,4} A similar interaction has not been reported for moxifloxacin, and additional glucose monitoring precautions are not required.²

Safety and tolerability

Fluoroquinolones are usually well tolerated, with gastrointestinal (e.g. nausea, vomiting and diarrhoea) and central nervous system (e.g. headache, dizziness and insomnia) side-effects being the most common. These side-effects are usually mild and do not result in discontinuation of the drug.

Table 1: Key features differentiating the advanced-generation fluoroquinolones

	Moxifloxacin IV/PO	Gatifloxacin IV/PO		Levofloxacin IV/PO	
Clinically important drug interactions					
Digoxin	No	Yes		No	
Probenecid	No	Yes		Yes	
Warfarin	No	No		Yes	
Antidiabetics	No	Yes		Yes	
Dosage adjustment for renal insufficiency^a					
		Initial dose	Subsequent dose	Initial dose	Subsequent dose
CAPD	No	400 mg	200 mg/24 h	500 mg	250 mg/48 h
Haemodialysis	No	400 mg	200 mg/24 h	500 mg	250 mg/48 h
If CL _{CR} 10–19 ml/min	No	400 mg	200 mg/24 h	500 mg	250 mg/48 h
If CL _{CR} 20–40 ml/min	No	400 mg	200 mg/24 h	500 mg	250 mg/24 h
If CL _{CR} 41–49 ml/min	No	None		500 mg	250 mg/24 h
If CL _{CR} 50–80 ml/min	No	None		None	

^aDose adjustments apply to acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, acute maxillary sinusitis or uncomplicated skin and skin structure infection.

CAPD, continuous ambulatory peritoneal dialysis; IV, intravenous; PO, oral.

Moxifloxacin, gatifloxacin and levofloxacin have the potential to prolong the QTc interval.^{2–4} Although cases of QTc interval prolongation have been reported for all three antibiotics, the actual prolongation is usually asymptomatic and not clinically significant. Cases of arrhythmia related to QTc interval are uncommon with only a few confirmed cases of torsades de pointes (TdP) reported for moxifloxacin, gatifloxacin or levofloxacin.

During a 5-year US-based study, voluntary reports to the FDA of fluoroquinolone-associated TdP revealed a total of 25 TdP cases: 13 cases were associated with levofloxacin prescriptions (out of 24 million levofloxacin prescriptions) and eight cases were associated with gatifloxacin prescriptions (out of three million gatifloxacin prescriptions).⁵ More recently, three cases of TdP associated with moxifloxacin therapy (out of 8.6 million moxifloxacin prescriptions worldwide) have been reported.⁶

It is important to note that TdP rates for all three of the newer quinolones are exceedingly low, and perhaps with the exception of gatifloxacin, do not exceed background rates of TdP in the general population. However, it

is still prudent to avoid the use of the newer quinolones in patients with uncorrected hypokalaemia and in patients receiving drugs that are known to prolong the QTc interval such as Class IA or Class III antiarrhythmic agents.^{2–4}

Efficacy

Moxifloxacin, gatifloxacin and levofloxacin are effective in the treatment of acute bacterial exacerbations of chronic bronchitis (ABECB), acute bacterial sinusitis (ABS) and community-acquired pneumonia. There is some evidence to suggest that patients who are treated with moxifloxacin may have faster symptom relief when compared to those treated with levofloxacin. Analysis of data from a comparative trial of moxifloxacin and levofloxacin in the treatment of ABECB found that patients taking moxifloxacin reported higher work-productivity than those taking levofloxacin. This translated into an indirect cost saving of US\$726 per patient per year.⁷ In another prospective study, the rate of symptom relief and the need for second prescriptions was assessed in patients with ABS treated with moxifloxacin, levofloxacin or amoxicillin/clavulanate.⁸ While there was

no statistically significant difference between treatment groups, there was a consistent trend towards moxifloxacin-treated patients reporting faster symptom relief and requiring fewer second prescriptions than comparator-treated patients.

Summary

Moxifloxacin, gatifloxacin and levofloxacin are clinically and bacteriologically effective in the treatment of ABECB, ABS and community-acquired pneumonia. Although they have comparable antimicrobial activity, pharmacokinetic and drug interaction profiles, there are several important differences between the three antibiotics. While all three drugs have potent activity against *S. pneumoniae*, *in vitro* studies suggest moxifloxacin to be two- to four-fold more active than gatifloxacin and four- to 16-fold more active than levofloxacin. The clinical significance of this remains to be determined.

Additional serum glucose monitoring is recommended when gatifloxacin or levofloxacin is prescribed to patients with diabetes. In contrast, moxifloxacin does not require any special precautions in diabetic patients. Dose adjustment for renal insufficiency is required for gatifloxacin and

levofloxacin because both of these antibiotics are cleared predominantly by the kidneys. Moxifloxacin, which has balanced hepatic and renal elimination, does not require dose reduction in renal or mild-to-moderate hepatic insufficiency. The potential interactions of gatifloxacin with digoxin and levofloxacin with warfarin should also be considered when prescribing these antibiotics. ■

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References

- Balfour JAB, Lamb HM. Moxifloxacin: a review of its clinical potential in the management of community-acquired respiratory tract infections. *Drugs* 2000; 59: 115–139.
- Avelox (moxifloxacin hydrochloride), Avelox I.V. (moxifloxacin hydrochloride in sodium chloride injection). Summary of product characteristics. Bayer Corporation, West Haven, CT, 2001.
- Tequin (Gatifloxacin) Tablets, Tequin (Gatifloxacin) Injection. Summary of product characteristics. Bristol-Myers Squibb Company, Princeton, NJ, 2001.
- Levaquin (R) Tablets/Injection (levofloxacin tablets/injection). Summary of product characteristics. Ortho-McNeil Pharmaceutical, Raritan, NJ, 2001.
- Frothingham R. Rates of Torsades de Pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin and moxifloxacin pharmacotherapy. *Pharmacotherapy* 2001; 21: 1468–1472.
- Grossman R, Kubin R, Reiter C. *Safety Update of Moxifloxacin: a Review of Clinical Trials and Worldwide Post-marketing Surveillance* (abstract). Presented at the International Congress on Infectious Diseases, Singapore, 11–14 March 2002.
- Li-McLeod J, Perfetto EM. Workplace costs associated with acute exacerbation of chronic bronchitis: a comparison of moxifloxacin and levofloxacin. *Manag Care Interface* 2001; 14: 52–59.
- Corcoran G, Roselli A, Haverstock D, Pause C, Faruqi M, Church D. Efficacy of moxifloxacin compared to levofloxacin and amoxicillin clavulanate in reducing 'practice time use' in the treatment of acute bacterial sinusitis. *Pharmacotherapy* 2001; 21: 382S.

Music and infectious diseases ~ Presented at the 3rd ECC, Madrid,

Spain in May 2000

M Gomis



HOSPITAL DE ALRE, MADRID, SPAIN

Since this article was accepted for publication, we have been saddened to learn of the death of Professor M Gomis, who was Professor of Infectious Diseases at the Hospital de Alre in Madrid, Spain, and a member of the Spanish Society of Chemotherapy.

Infectious diseases have been with us since human beings have been on the planet. Currently we have excellent diagnostic, clinical, microbiological and therapeutic procedures, mainly developed in the past few decades. Before this time, circumstances were

very different, with enormous hygiene and health problems, inadequate medical care or hospitals and the continuous threat of terrible diseases such as plague, malaria, syphilis, cholera or tuberculosis. The great masters of music, like the rest of humanity, have been affected by infections and, on many occasions, these put an end to their lives or limited and marred their artistic creations.

Plague devastated Europe over a period of several centuries. Figures such as Agricola, Obrecht and Guerrero probably died of plague. It is possible that Monteverdi died of malaria. Streptococcal infections fatally affected Mahler, Bizet, Supervía and, probably, Mozart. Lully, Scriabin, Rossini and Berg died of gangrene or other soft-tissue infection. Could Beethoven's deafness have been due to an infectious disease? It is a fact that, at the end of his life, a liver disease caused ascites and made it necessary to perform several paracenteses that resulted in peritonitis. Schubert had syphilis from the age of 25, dying of typhus when he was only 31. Many cases of dementia could also have had an infectious origin (syphilis?), such

as those suffered by Schumann, Donizetti, Wolf, Salieri, Joplin, etc. Syphilis shortened the life of Delius. It is possible that Paganini had both syphilis and tuberculosis, and did Chopin suffer from tuberculosis or had he merely bronchiectasis or some other type of pneumopathy? Szymanowski and Stravinsky both suffered from tuberculosis. Weber died at the age of 39 due to a tuberculous disease while in London attending the first performance of *Oberon*. Other famous people have also been afflicted by various infectious ailments, such as Rossini, who was tormented by the sequelae of a chronic gonococcal disease. In his last days, rectal cancer surgery was complicated by erysipelas or fasciitis, leading to his death.

AIDS has caused the deaths of various performers, such as Rudolf Nureyev, Scott Ross and Freddie Mercury.

On other occasions in history, infection has been so rife that it has appeared in various productions. Who doubts that the main character of Verdi's *La Traviata* was tuberculous? In the First Act Violetta was healthy and then becomes ill and, in the Final Act of this

opera, she dies from phthisis. Tuberculosis was synonymous with melancholia and a paradigm of wanted – or longed-for – love, although it became a fearsome disease to be kept secret. In both Puccini's and Leoncavallo's *La Bohème*, tuberculosis is again vital to the artistic creation. In Rossini's *El Barbero de Sevilla*, scarlet fever is clearly mentioned and its significance would have been understood by the audience at that time.

We could carry on mentioning a long list of musicians, artists or performers who have suffered from infections, died from them, and whose creations have been undoubtedly affected; however, it is also necessary to highlight that the universality of these diseases has been such that they have become part of artistic creation itself. ■

The work described here was undertaken in conjunction with the author's colleague, Dr B Sánchez Universidad Complutense, Hospital de Alre, Arturo Soria 82, E – 28027 Madrid, Spain.

Virulence and antifungal resistance in non-*albicans* *Candida* species

V Krcméry, Jr



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Vladimir C Krcméry, Jr, is Professor of Pharmacology at the University of Trnava and is Dean of the School of Public Health. He publishes widely and has more than 150 publications and more than 1100 citations to his name. He also gives invited lectures internationally.

Non-albicans Candida (NAC) species cause 35–65% of all candidemias in the general patient population. They occur more frequently in cancer patients, mainly in those with haematological malignancies and in bone marrow transplant

recipients (40–70%), but are less common among intensive therapy unit (ITU) and surgical patients (35–55%), children (1–35%) and HIV-positive patients (0–33%).

The proportion of NAC infections is increasing. Between 1970 and 1990 NAC caused between 10% and 40% of all candidaemias, in contrast to the period 1991–1998, when they caused 35–65%.

The commonest NAC species are *C. parapsilosis* (20–40% of infections), *C. tropicalis* (10–30%), *C. krusei* (10–35%) and *C. glabrata* (5–40%). At

least two other species are emerging: *C. lusitanae*, currently causing 2–8% of infections and *C. guilliermondii*, which causes 1–5%. Other NAC species, such as *C. rugosa*, *C. kefyr*, *C. stellatoidea*, *C. norvogensis* and *C. famata*, are rare, accounting for less than 1% of fungaemias in man. In terms of virulence and pathogenicity, some NAC species appear to be of lower virulence in animal models, yet display virulence in man greater than or equal to that of *C. albicans*.

continued on page 13

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Mortality due to NAC species is similar to that arising from *C. albicans* infection, ranging from 15% to 35%; however, differences exist between NAC species in both overall and attributable (fungaemia-associated) mortality: the lowest mortality is associated with *C. parapsilosis* and the highest with *C. tropicalis* and *C. glabrata* (40–70%). Overall mortality from other NAC species, including *C. krusei*, is similar to that arising from *C. albicans*.

In terms of mortality and patient type, mortality from NAC species appears to be highest in ITU and surgical

patients, and lowest in cancer patients, children and HIV-positive patients. There are no differences between overall and attributable mortality from NAC species among different patients, with the exception of *C. glabrata* that tends to infect immunocompromised individuals. In this species overall mortality is lower than *C. albicans*, whereas attributable mortality is higher.

There are several specific risk factors for particular NAC species: *C. parapsilosis* is related to foreign-body insertion, neonates and hyperalimentation; *C. krusei* and *C. glabrata* to azole prophylaxis; *C. tropicalis* and *C. krusei* to neutropenia and bone marrow transplantation;

C. glabrata to azole prophylaxis, surgery and urinary or vascular catheters; *C. lusitaniae* and *C. guilliermondii* to previous polyenes therapy (amphotericin B or nystatin); and *C. rugosa* to burns.

Antifungal susceptibility of NAC species varies significantly, in contrast to *C. albicans*, with some species being inherently or secondarily resistant to fluconazole, as follows: 75% of *C. krusei* isolates, 35% of *C. glabrata*, 10–25% of *C. tropicalis* and *C. lusitaniae*. Amphotericin B resistance is also seen in a small proportion: 5–20% of *C. lusitaniae* and *C. rugosa*, 10–15% of *C. krusei* and 5–10% of *C. guilliermondii*.

Other NAC species are akin to *C. albicans* – susceptible to both azoles and polyenes (*C. parapsilosis*, the majority of *C. guilliermondii* strains and *C. tropicalis*). Therefore, special directed therapy should be administered for fungaemia depending on the species identified – amphotericin B for *C. krusei* and *C. glabrata*, and fluconazole for other species, including polyene-resistant or -tolerant *Candida* species (*C. lusitaniae*, *C. guilliermondii*). *In vitro* susceptibility testing should be performed for most species of NAC, in addition to foreign-body removal, in order to optimize management. ■

Meeting Report

Emerging infections in Southeast Asia

Tuberculosis and dengue fever continue to be major public health problems in Southeast Asia. This was revealed at a meeting of Southeast Asian countries in Tokyo recently. The meeting on emerging and re-emerging infections was organized by the Southeast Asian Medical Information Centre (SEAMIC) and the International Medical Foundation of Japan, and attended by delegates from Indonesia, Malaysia, Thailand, the Philippines, Singapore and Vietnam.

In Indonesia, an estimated 450 000 new tuberculosis cases occur annually, but, due to inadequate diagnostic and treatment facilities, only 47 000 patients received standard treatment in 1999. In Malaysia, the number of new cases of tuberculosis diagnosed annually continues to rise, and there were 15 057 new cases in 2000 with 942 deaths. In view of this, Malaysia has formulated a plan to achieve a 100% DOTS (Directly Observed Treatment, Short-course) strategy by 2006.

Most countries also noted an increase in the incidence of dengue fever in 2001 compared with the corresponding period in

2000, although the increase is unlikely to be as high as that experienced in 1998 during the peak of the El Niño phenomenon. In many regions of Thailand the rate of dengue and dengue haemorrhagic fever exceeded 50 per 100 000 population. In Malaysia, the increase in incidence corresponded with a change in the virus serotype. In Vietnam, the problem is particularly acute in the central region, where the rate was reported to be 638 per 100 000 in 1998. Vietnam has experienced considerable success in the control of the mosquito vector using larvicidal crustaceans, namely *Mesocyclops* and *Copepods*.

Infection with HIV is another major health problem faced by all Southeast Asian nations. In Thailand, the number of HIV-infected persons has reached nearly 1 000 000. In Malaysia, the number of newly diagnosed HIV infections continues to increase, with 5107 cases in 2000 compared with 4692 in 1999; 75% of the cases were associated with intravenous drug use. In Indonesia it is estimated that there are now 80 000–120 000 people with HIV infection.

Outbreaks of hand, foot and mouth disease were reported in

Malaysia and Singapore in 2000. In Malaysia, increased numbers of cases were noted in the March–April and September–October periods of 2000. The 2000 outbreak in Singapore reached its peak in October and necessitated the closure of all pre-schools for a period of 2 weeks.

Leptospirosis is re-emerging in Thailand and there were over 13 000 cases in 2000 with 365 deaths. Over 80% of cases occurred in the northeast of the country. The Philippines has reported 546 cases of leptospirosis this year. Thailand also reported 56 cases of anthrax and 60 cases of meningococcal disease in 2000. No new cases of Nipah virus infection have been reported from Malaysia and Singapore since the 1999 outbreak.

All countries are making efforts for improved surveillance of infectious diseases. In the Philippines a National Epidemic Sentinel Surveillance System has been set up. Sentinel sites are hospitals with at least a 250-bed capacity and good laboratory facilities. Thailand has established a laboratory-based surveillance network for emerging and

re-emerging infections. Malaysia has established an Infectious Diseases Research Centre and plans to have an on-line system for infectious diseases surveillance. Singapore is embarking on a syndromic surveillance system and is building a public health laboratory at the Ministry of the Environment. With these activities it is hoped that more effective detection and control of emerging and re-emerging diseases will be possible in Southeast Asia. ■



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Meetings

8th Western Pacific Congress on Chemotherapy and Infectious Diseases, Perth, Australia, 1–5 December 2002

The programme of the 8th WPCCID promises to be at the forefront of knowledge, to challenge long-held concepts and to present the latest information on a wide range of topics relevant internationally and to the region. The organizing committee invites you to participate by submitting an abstract to share your latest research results with peers and to form new collaborative relationships and renew past acquaintances.

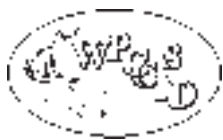
The main sessions are listed below.

Plenary sessions

- Why are bacteria becoming resistant? – *Patrice Courvalin*
- Microbial consequences of environmental and social change – *Tony McMichael*
- Advances in the understanding of the Helicobacters – *Barry Marshall*

Congress symposia

- Clinical relevance of resistance in *Streptococcus pneumoniae*
- Conjugate pneumococcal vaccines: Impact on invasive disease, on antibiotic resistance and use; herd immunity
- Antibiotic resistance: Making sense of macrolide resistance;



touchy topoisomerases; the ABC of efflux pumps; pump inhibitors – a viable option?

- Resistance management programmes: How to measure use and resistance; evidence that intervention works; consumer education
- Antibiotic use in animals – implications for human health
- MRSA: Local or worldwide epidemics; community strains; what the genome tells us
- VRE – local aspects of a global problem
- Group A streptococcus: Pathogenesis; molecular epidemiology; clinical aspects – toxic shock; immunotherapy; vaccine development
- Role of clinical laboratory in infection control; genetic techniques in infectious diseases
- Information technology and infectious diseases
- Antimicrobial pharmacodynamics – the science of dosing
- Infections in pregnancy – preventing vertical transmission



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Perth, Australia, venue for the 8th WPCCID.

- Implants and associated infections
- Melioidosis
- Malaria
- *Salmonella* – forgotten but not gone
- Immunotherapy for chronic viral infections
- HIV: Opportunistic infections and co-infections in HIV patients; complications of antiretroviral therapy
- TSE and vCJD
- Influenza virus infections
- New antiviral agents
- Ethics and immunization
- New and resurrected vaccines
- Antifungal therapy: Are yeasts honorary bacteria? Reality of treating cryptococcosis;

cryptococcus in the era of HAART; do the new antifungal agents fit into current management strategies? Antifungal combination therapy; drug interactions and adverse reactions. ■

John Turnidge
Chairman 8th WPCCID

For further information

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Southbank VIC 3006
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E-mail: wpccid@icms.com.au
www.icms.com.au/wpccid

1st ISC International Conference on New Cancer Therapeutics: Molecular Targets, Pharmacology and Clinical Applications Florence, Italy, 8–11 October 2003

The International Society of Chemotherapy (ISC), which was established in 1961, had its beginning in the fields of both cancer and antimicrobial chemotherapy. Now, 40 years on, the existing congresses of the ISC tend to have a slightly greater emphasis on antimicrobials. However, the area of cancer chemotherapy has also seen great advances over this 40-year period. As a result there is a definite need for the ISC to hold an annual congress that

specifically addresses cancer chemotherapy. This congress will be aimed at all scientists, physicians and researchers working on the pharmacological treatment of cancer, whether involved in the laboratory, or in pure or clinical research.

The congresses will initially be held in Europe, with the first in Florence, Italy, on 8–11 October 2003. The co-organizer will be the Italian Society of Chemotherapy, with Teresita Mazzei as the President.

The main topics will be:

- New anticancer drug discovery, screening and clinical development issues
- Signal transduction modulators
- Cell cycle inhibitors
- Apoptosis modulators
- Anti-invasion, antimetastatic and antivascular agents
- Chemopreventive agents
- Gene therapy and antisense approaches
- Immunoactive agents (vaccines, biologicals, antibodies)

- New conventional anticancer drugs
- Clinical pharmacology issues (pharmacogenetics, pharmacogenomics). ■

For further information

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New naming system for *S. pneumoniae* clones and the Pneumococcal Molecular Epidemiology Network (PMEN)

The pneumococci that we know of from undergraduate days have 90 different serotypes. Whether a particular strain is truly new or is a clone of one that has been identified somewhere else in the world is very difficult to determine. Hence, it would be useful to know the genetic background of the strain, especially if it has multiple antibiotic resistance.

An international group of experts has proposed a nomenclature in an attempt to tackle this problem.¹ It is an effort to standardize naming procedures and also to facilitate the surveillance of antibiotic-resistant organisms. The group established the Pneumococcal Molecular Epidemiology Network (PMEN) in 1997 under the auspices of the International Union of Microbiological Societies (IUMS). The PMEN is run by the Medical Research Council Pneumococcal Diseases Research Unit of the University of the Witwatersrand, South Africa, in conjunction with the Nosocomial Pathogens Laboratory Branch of the Centers for Disease Control and Prevention, in Atlanta, USA, and the research laboratory of Dr Brian Spratt at Imperial College, London, UK.

The PMEN has organized a

reference set of antibiotic-resistant pneumococcal clones that the American Type Culture Collection (ATCC) maintains. This will help scientists and clinicians to determine the origin of strains and whether a particular strain is the same or different in cases of relapses. The Network also helps in tracking resistance traits within and among strains, and in addressing other questions relating to the clonality of pneumococci.

Members of PMEN trace citations to published papers (in peer-reviewed journals) on each clone and then request these isolates and other information from the authors. The Network aims to get a sample of a strain as quickly as possible.

The identity of the clones is established using pulsed-field gel electrophoresis, BOX-PCR and multilocus sequence typing. Certain criteria for the clones and nomenclature have to be satisfied, and these can be found on the website: www.pneumo.com. An example of the naming of clones is as follows:

- Country^{first identified serotype} - sequential numbering in network - subsequent described serotype, e.g. Spain^{23F}-1, where:
- Spain (country in which the clone is first identified, based



Lesley McGee.

- on publication);
- ^{23F} (serotype of the clone first identified);
- 1 (clone number 1).

Members of a single clone may express different capsular polysaccharides. In the case of capsular switch, the nomenclature might be as follows: Spain^{23F}-1-19F, where: 19F - serotype 19F variant of Spain^{23F}-1 clone.

There are currently 16 distinct antibiotic-resistant pneumococcal clones that have been identified. It is, therefore, important that clones which authors might refer to as clone A or clone B can be identified immediately as belonging to one particular international clone. Hence, scientists who describe new pneumococcal clones are encouraged to contact the PMEN. ■



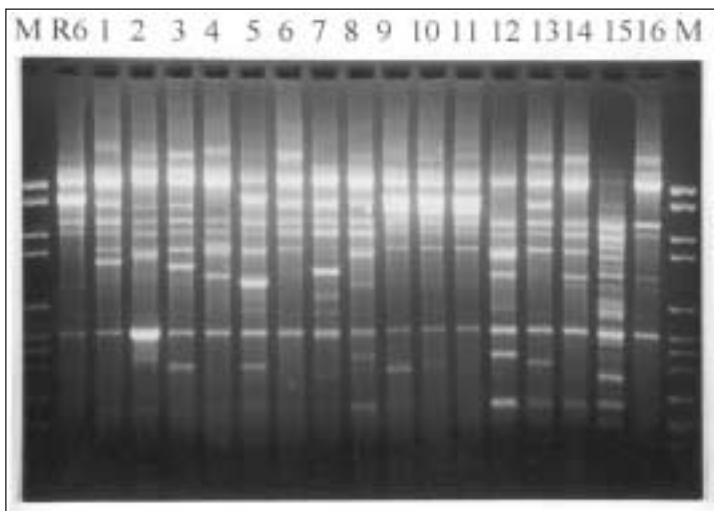
Keith P Klugman.

Lesley McGee
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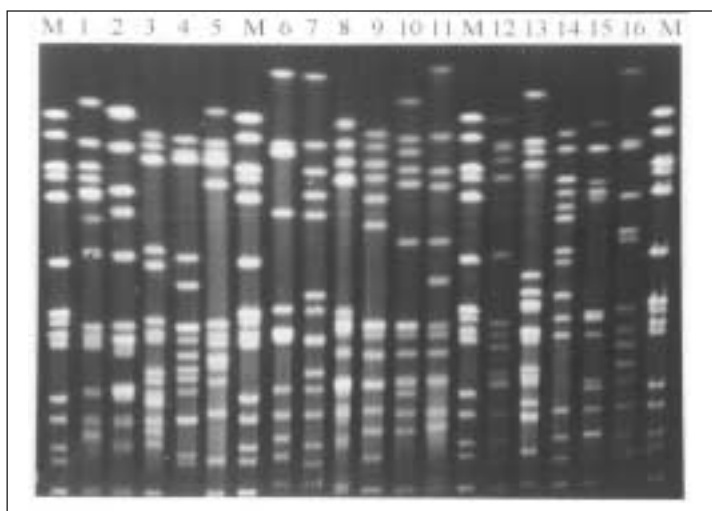
Keith P Klugman
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Reference

1. McGee L, McDougal L, Zhou J, Spratt BG, Tenover FC, George R *et al*. Nomenclature of major antimicrobial-resistant clones of *Streptococcus pneumoniae* defined by the Pneumococcal Molecular Epidemiology Network. *J Clin Microbiol* 2001; **39**: 2565-2571.



BOX-PCR fingerprint patterns of representative isolates.



PFGE fingerprint patterns of *Sma*I restriction digests of representative isolates.

Diary Dates

ISC Meetings

1-5 December 2002, Perth, Australia

8th Western Pacific Congress on Chemotherapy and Infectious Diseases

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Tel: +61 3 9682 0244
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www.icms.com.au/wpccid

24-26 January 2003, Budapest, Hungary

Hot Topics in Urinary Tract Infections, 1st Symposium of the ISC Disease Management Series

CONTACTS: For scientific information: Endre Ludwig, Hungarian Society for Chemotherapy
Tel/Fax: +361 455 8147
E-mail: ludwig@matavnet.hu
Organizing Secretariat: Convention Budapest Ltd, PO Box 11, H-1461 Budapest.

Tel: +361 216 1121/361 216 3421
Fax: +361 456 0888
E-mail: convention.budapest@mail.datanet.hu
www.convention.hu

7-10 June 2003, Durban, South Africa

23rd International Congress of Chemotherapy
CONTACT: 23rd ICC Secretariat, Congrex Holland BV, AJ Ernstraat 595K, 1082 LD, Amsterdam The Netherlands.
Tel: +31 20 50 40 200
Fax: +31 20 50 40 225
E-mail: icc2003@congrex.nl
www.congrex.nl/icc2003

8-11 October 2003, Florence, Italy

1st International Conference on New Cancer Therapeutics
CONTACT: Teresita Mazzei, Department of Pre-clinical and Clinical Pharmacology, Università degli Studi, Viale Pieraccini 6, 50139 Florence, Italy.
Tel/Fax: +39 55 427 1265
E-mail: isc2003@pharm.unifi.it

17-21 October 2003, Rhodes, Greece

5th European Congress of Chemotherapy and Infection (ECC-5)
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

Other Meetings

26-30 May 2002, Antalya, Turkey

17th ANKEM (Antibiotics and Chemotherapy) Congress
CONTACT: ANKEM Dernegi Rumeli Cad. Ipek Apt. No. 70 K 7 Osmanbey, 80220 Istanbul, Turkey.
Tel: +90 212 219 9339
Fax: +90 212 219 9341

4-6 June 2002, Moscow, Russia

5th International IACMAC Conference on Antimicrobial Therapy
CONTACT: IACMAC, PO Box 5, 214019 Smolensk, Russia.
Tel: +7 812 611 301
Fax: +7 812 611 294
E-mail: conference@antibiotic.ru
www.antibiotic.ru

18-22 October 2002, Nice, France

27th ESMO Congress (European Society for Medical Oncology)
CONTACT: ESMO Congress Secretariat, Via La Santa 7, CH-6962 Viganello-Lugano, Switzerland.
Tel: +41 91 973 1919
Fax: +41 91 973 1918
E-mail: chatrina@esmo.org

23-26 October 2002, Florence, Italy

4th International Meeting on the Therapy of Infections
CONTACT: American Express Services Europe Ltd, via Dante Alighieri, 22r, 50122 Florence, Italy.
E-mail: info@imti.it
www.imti.it/

16-19 October 2003, Santa Margherita, Portofino, Italy

3rd International Meeting on Antimicrobial Chemotherapy in Clinical Practice
CONTACT: Matteo Bassetti, Largo r.Benzi 10, 16132 Genoa, Italy.
Tel: +39 10 5552668
Fax: +39 10 3537680
E-mail: mattba@tin.it



23rd ICC

7-10 June 2003

join us at a unique venue

The challenge of the 23rd ICC is to link advanced scientific approaches to chemotherapy to basic and practical issues such as the accessibility and affordability of chemotherapeutic drugs in today's world.

This Congress aims to break the dichotomy between science and practice by bringing together an array of investigators and practitioners who deal with these concerns.

Durban, on the eastern coast of South Africa, is a unique venue. Its sophisticated technology research facilities complement the study of major health issues which affect a large percentage of the world's population.

The city offers optimal conference facilities in an enviable winter climate of warm sunny days. Most of the beachfront hotels are within walking distance of the International Conference Centre and, for the more adventurous, the surrounding countryside boasts game parks and lush scenery.

We invite you to an enticing Congress in an attractive place and we look forward to meeting you in Durban.

Host organizing committee:

Willem Sturm – *President*
Prashini Moodley – *Secretary*
Shaheen Mehtar – *Treasurer*
Gary Maartens – *Chair, Scientific Committee*

Members:

Lucille Blumberg
Estrelita Janse van Rensburg
Keith Klugman
Yesho Mahabeer

DURBAN

A preview of the 23rd ICC scientific programme:

- Global impact of community antibiotic resistance
- Drug development for tropical diseases
- Limited options: management of infections with highly resistant organisms
- Difficult decisions: febrile neutropenias, prosthetic devices
- Traditional medicines in the management of infection
- Viruses and malignancies
- Optimal management of cancer in areas of limited resources
- Oncology: anticancer drugs, supportive care, immunotherapy
- Beyond BCG
- New treatment options for drug-resistant TB
- Research ethics: are there two standards?
- Anti-retrovirals: access in resource-poor settings
- HIV management: parallels with tuberculosis?
- Immunomodulation: where is its place?
- Sexually transmitted infections and HIV: what have we learnt?
- Advances in malaria chemotherapy and prophylaxis
- Out of Africa: treating tropical diseases

For further information, please contact:

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E-mail: icc2003@congrex.nl; www.congrex.nl/icc2003