ESCMID NEWS
European Society of Clinical Microbiology and Infectious Diseases

ESCMID

2 Editorial
3 Assembly of Members 2006 – Minutes
6 New ESCMID staff
7 CMI: New impact and other factors
24 Highlights from 16th ECCMID in Nice
26 European Council 2006 – Minutes
30 ESCMID awards and fellowships 2007
39 New ESCMID members in 2006
41 ESCMID membership form
43 – FEMS/ESCMID research fellow 2006 – ESCMID/ERS dual membership

Scientific

8 Is Europe prepared for Clostridium difficile PCR ribotype 027?
11 Management of Helicobacter pylori infection
14 Molecular diagnosis of zygomycosis?
16 Conference report: Extended beta-lactamases
17 ESCMID Study Group on Biofilms
18 GRACE Network of Excellence
19 Role of bacteriocins in reducing medical device infection
20 16th ECCMID report: Trees and fruits: spoilt for choice
43 Acinetobacter 2006

Health Policy

23 Infectious diseases at G8 summit

Education

27 Review of the ESCMID Summer School 2006 Santander
29 Course report: Metallo-beta-lactamases

Features

32 Spreading of antibiotic resistance by gene-manipulated plants?

Excerpts

34 What's new in infectious diseases?

Calendar

44 Forthcoming events

Assembly of Members 2006 – Minutes

CMI: New Impact and Other Factors

Is Europe Prepared for Clostridium difficile PCR Ribotype 027?

Management of Helicobacter pylori Infection
ESCMID Is Good for Europe

The role scientific societies play in the Western world is important. This began in 1660 with the foundation of the Royal Society in the United Kingdom, followed by other learned societies in most European countries and North America. In the beginning their main purpose was to witness experiments and discuss scientific topics among their members. Soon publishing scholarly texts became equally important. Later learned societies expanded their activities by promoting the public understanding of science and raising the status of scientific disciplines. Scientific societies are deeply rooted in Western culture. They have profound merits in establishing science and technology as a foundation of our way of life, view of the world and economic welfare. Scientific societies are part of civil society. They have contributed much, and continue to do so, to nation building.

Most scientific organisations such as ESCMID maintain a portfolio of activities pertinent to professional training and education, scientific conferences, research and publication as well as professional practice and policy. If they do their job right they act as platform for the interaction of all professionals in their field, which involves academia and universities, hospitals, industry as well as funding and regulatory governmental agencies. There is no doubt that the medical profession greatly profits from this exchange, even to the extent that modern science and medical practice can hardly be conceived without scientific societies.

Nowadays this scenario must be expanded by the inclusion of another stakeholder of science and medicine: the public. Until not too long ago science was the exclusive domain of scientists. Hiroshima and Chernobyl have definitively changed this. Since then non-scientists demand that science benefits society and contributes to solving all sorts of problems: social, environmental, economic and medical. The ongoing public debate on genetically modified organisms, therapeutic cloning, biodiversity, nanotechnology and global warming shows that science and technology are very much in the focus of media and politics. Lobbyists often seem to put the onus of problem resolution onto science, an approach that makes science more political rather than policy more scientific. Politicisation of science will always be part of political advocacy; its proponents simply disregard the fact that “science” alone does not provide a sufficient basis for decision-making since decisions depend on values and interests alike. The challenge for scientists in providing advice is thus to distinguish between science and policy. It is in this context that modern scientific societies have a role to play in the public debate: to guard against the politicisation of science they must take responsibility for assessing the significance of scientific results for policy. In the infection fields a first step towards this goal is offering the public a place on the “platform” by maintaining a dialogue with the media, politicians and patient groups. If ESCMID is to establish itself as a leading society in these disciplines it must pursue an agenda in the realms of educational, scientific and professional affairs as well as in public relations. The recent extension of the Executive Office (page 6 of this issue) must be seen in this context. ESCMID will meet its objectives if the fostered exchange between all parties shaping infection medicine will eventually improve medical practice and public health for the benefit of the patient. If we succeed, Europe and its citizens will benefit.

Peter Schoch
Managing Director

Front page: Clostridium difficile cultured from a stool sample obtained during an outbreak of gastrointestinal illness, and extracted using a 0.1µm filter. Courtesy of Lois S. Wiggs, CDC, Atlanta, US. See the article from Ed J. Kuijper on the emerging Clostridium difficile PCR ribotype 027 in Europe.
Assembly of Members 2006

Minutes

1 Welcome and President’s report

Ragnar Norrby welcomed the 67 ES-CMID members to the 2006 Assembly. He noted that the minutes of the Assembly 2005 have been published in ESCMID News 2-2005 and that the invitation and agenda for the Assembly 2006 had been correctly sent out as stated in the Statutes.

Ragnar Norrby emphasised ESCMID’s stable finances and healthy situation. Our current savings equal now the expenses of about 2 years. We could thus keep on even if an ECCMID would completely fail. This situation will allow us to increase our spending for education and scientific activities in the future. Some of the key points mentioned by Ragnar Norrby in his review of the past year were the following:

Membership and Governance

- Slow but steady growth of the ESCMID membership also in 2005
- Newly formed European Council of European societies in the infection field to become active and provide input this year
- Dr Hélène Aubry-Damon from Maisons Alfort, France, co-opted by the Executive Committee as new Professional Affairs Officer for Clinical Microbiology
- Positive financial situation, based on a series of successful ECCMIDs, allowing the Executive Office in Basel to expand and increase our educational and scientific activities as well as involvement in EU projects

Science

- Active study groups contributing to science and education in their fields
- Successful EUCAST with excellent working relations to EMEA: Europe has now a working system for setting susceptibility breakpoints for old and new antibiotics.

Clinical Microbiology and Infection further grew in stature and volume.

Education

- Highly praised Summer School 2005 in Szeged, Hungary: a follow-up is planned in 2006 in Santander, Spain
- Expanding programme of educational activities consisting of postgraduate courses across Europe and workshops held prior to ECCMID

Professional Affairs

- Close contacts with UEMS for the development of training curricula and CME accreditation systems
- Support for full recognition of Clinical Microbiology and Infectious Diseases in individual countries and Europe

Cooperation

- FEMS: jointly arranged ESCMID/FEMS conferences on specific scientific topics
- ISC: joint 17th ECCMID/25th ICC 2007 in Munich
- ERS: joint responsibility for the educational platform of GRACE
- SHEA: joint annual postgraduate course in hospital epidemiology

EU Relations

- Representation in the ECDC Advisory Forum by Elisabeth Nagy
- Responsible with ERS for the educational platform of GRACE, a Network of Excellence on community-acquired lower respiratory infections, funded by the European Commission
- Participation in other EU funded projects (EUCAST, IPSE)
- The relationship and cooperation with ECDC will expand in the near future by the organisation of a joint conference in 2006 on infectious disease control and the increasing use of ESCMID study groups by ECDC.

2 Report of the Secretary General

The membership figures were reported by Patrick Francioli. As of 17 March ESCMID had 3023 regular members, 383 thereof at reduced rate. The best represented country is the UK with 224 members, followed by Germany (207) and Italy (193). Currently 37 societies, mostly national societies for clinical microbiology and/or infectious diseases, are affiliated with ESCMID.

ESCMID now represents about 15’000 professionals across Europe.

Question: Richard Bax, London, UK, asked about the Executive’s intention concerning membership development: How many members should ESCMID have and how do you want to achieve this goal? Patrick Francioli responded that we would like to have as many members as possible from the professionally active specialists working in the infection field. Since almost everyone is member of his/her national society, ESCMID as a “supernational” organisation will never have all European specialists on its membership list. This is one of the reasons why we have started the affiliation programme. In addition, some fields such as HIV have gone their own way and founded separate organisations. But still, we will continue to improve our services and try to recruit new members. Ragnar Norrby added that CMI will grow in importance and be a real asset for ESCMID members. In addition, the ESCMID website also should develop into a resource of information for members (e.g. guidelines, educational material, etc).

3 Presentation of the ESCMID research fellowships

Marc Struelens, Chair of the ESCMID Awards Committee, had the pleasure and honour to present the ESCMID research fellowships 2006, including a cheque of EUR 5000, to the following ESCMID members:

Surbhi Malhotra-Kumar, born 1972 in Sirsa, India; PhD, Belgian Reference Centre for Group A Streptococcus, University of Antwerp, Belgium. She has also been selected to receive the joint ESCMID/FEMS Research Fellowship, which consists of an additional EUR 1000 added by FEMS. Her project: Analysis of novel genetic elements and resistance mechanisms, fitness costs and compensatory adaptations in macrolide-, ketolide-, and fluoroquinolone-resistant Group A Streptococcus. Surbhi Malhotra-Kumar, who made her apologies for family reasons, was represented by Herman Goossens.

Rocus R. Klont, born 1970 in Oldenzaal, the Netherlands; MD, Department of Medical Microbiology, Radboud Univer-
sity Medical Centre, Nijmegen, the Netherlands. His project: Development of a serological system for the diagnosis of invasive zygomycoses.

- Sofia K. Kasiakou, born 1975 in Athens, Greece; MD, Research Fellow at the Alfa Institute of Biomedical Sciences, Maroussi, Greece and Resident in Internal Medicine at the Sotira General Hospital, Athens, Greece. Her project: A multicenter, randomised, double-blind, controlled trial of the effectiveness and safety of intravenous colistin with or without intravenous meropenem in ICU patients for infections other than pneumonia due to colistin-only-sensi

tive bacteria. Sofia K. Kasiakou, who was unable to attend, was represented by Matthew Falagas.

Marc Struelens congratulated the recipients for their success (applause).

4 Financial report of the Treasurer

Elisabeth Nagy presented the detailed but still preliminary profit and loss accounts for the year 2005. With expenses of EUR 777'783 and an income of EUR 1'298'493 the result of 2005 was a net profit of EUR 520'710. The main source of revenue is, as in previous years, the annual ECCMID. The expenses, grouped into the main activity fields, were as follows:

- Executive Office and Membership Services 159'069
- Executive Committee 50'267
- Publications and Website 207'045
- Educational and scientific activities 177'125
- ESCMID awards, fellowships, and grants 73'155
- Professional and European affairs 52'681
- Other 38'842
- Taxes 9'499
- Total expenses 777'783

The balance sheet showed a profit carried forward as of 31 December 2005 of EUR 2'135'775.

Elisabeth Nagy then cited from the accounting report by the tax accountant Karl Haas, Lorrach, Germany, testifying that ESCMID account books are in order.

5 Approval of the accounts (vote)

Ragnar Norrby asked for a hand vote of approval of the financial report. It was approved unanimously.

6 Report of the Education Officer

In 2005 the following educational activities were held as reported by Javier Garau:

i) 4th ESCMID School, Szeged, Hungary, 25 June – 2 July 2005, organised by the ESCMID Education Committee, directed by Elisabeth Nagy, Szeged, Hungary. 21 students attended.

ii) Three postgraduate courses were held under the auspices of and supported by ESCMID:

- Training Course on Multilocus Genotyping of Mycobacterium tuberculosis, organised by ESGM and the Institute Pasteur in Lille, France: Lille, France, 23 – 28 May 2005
- Clinical Challenges in Diagnosis and Management of Atypical Pneumonia: Riga, Latvia, 20–21 June 2005
- Training Course in Hospital Epidemiology, organised by ESGM, ESCMID and SHEA: Beaune, France, 6–9 November 2005

iii) During 15th ECCMID 2005 in Copenhagen 17 meet-the-expert sessions and 8 pre-ECCMID educational workshops, organised in collaboration with ESCMID study groups, were organised.

7 Report of the Professional Affairs Officer, Clinical Microbiology

The new Professional Affairs Officer for Clinical Microbiology, Hélène Aubry-Damon, has been “on duty” for 2 days only. It was thus Elisabeth Nagy, who held this office for the last 3 years, who reported about the activities in 2005.

- The evaluation of the second questionnaire about the status of Clinical Microbiology in Europe is almost finished. According to data shown by Elisabeth Nagy almost 70% of all European countries recognise Clinical Microbiology as a full medical specialty. In most of the remaining countries Clinical Microbiology is practised as a subspecialty; in three countries (Belgium, Luxembourg, Portugal) only polyvalent laboratory medicine exists without providing any formal status to Clinical Microbiology. A summary will be published in ESCMID News.

- ESCMID participated in the revision of the UEMS Core Curriculum for Clinical Microbiology. It is available on the UEMS and ESCMID websites.

- EBACM (European Board for CME Accreditation in Clinical Microbiology), a joint venture between the Microbiology Commission of the UEMS Section of Medical Biopathology and ESCMID, has started operations and accredited several meetings.

- The Dutch Society of Medical Microbiology has asked ESCMID for support in creating an independent monospecialist Section of Clinical Microbiology within UEMS. Elisabeth Nagy commented that the ESCMID Executive is sympathetic to this idea but that any official proposal must be submitted by a national medical association which is member of UEMS. The issue was discussed during the European Council meeting on 1 April 2006 during which ESCMID agreed to coordinate certain activities towards this goal.

8 Report of the Professional Affairs Officer, Infectious Diseases

Robert Read, who joined the Executive Committee in 2005, gave his first annual report. He defined his job, which was discussed and approved by the Executive, as follows:

- ESCMID representative in the UEMS Section of Infectious Diseases, dealing with issues such as recognition of Infectious Diseases as a medical specialty, training curriculum, professional qualification and accreditation

- Accreditation of CME through EBAID/EACCME

- Trainee exchange placement, also for scientists returning to Europe: build-up of an internet-based professional mobility platform on the ESCMID website

- Medical practice guidelines and standards of care: definition of procedures, and development of guidelines where needed. In addition, the ESCMID website should become a repository of European medical guidelines, approved or not-approved by ESCMID.

9 Report of the Scientific Affairs Officer

Jordi Vila, who was not able to attend the Assembly for professional reasons, had his report given by Peter Schoch.

- In the past year ESCMID organised a successful conference in cooperation with FEMS on: Lessons from Escherichia coli: from basic research to clinical aspects, Villars-sur-Ollon, Switzerland,
4–8 September 2005. 53 participants attended.

ESCMID has currently 13 active study groups. The most recent one is the ESCMID Study Group on Biofilms (ESGB). For details he referred to the ESCMID website.

A survey among the study groups indicated that the vast majority published a paper and organised one or several scientific meetings or educational courses during the reporting period. More than 50% of the study groups carried out one or several research projects. This proves that the ESCMID study groups are highly active.

10 Report of the Chair of the Publications Committee

As Chair of the Publications Committee Marc Struelens reported on the key figures of CMI which again developed favourably thanks to the excellent work of the editorial team and authors during the past year:

- In 2005 12 regular issues were published with a total of 1056 pages and 209 articles.
- The number of submissions continued to increase, which was accompanied by an inevitable increase in the rejection rate (currently about 75%).
- CMI has achieved an international authorship and broad subject coverage.
- Consortia access increased by 39% and downloads of articles by 22%.
- The citation impact factor increased to 2.361, which positions CMI almost within the best third of related journals in its field.
- Six supplements were published in 2005, some of them highly profitable.
- In 2005 CMI produced for the first time in several years a net income for the Society.
- In 2006 plans are to increase the annual page budget to 1200 pages, to slightly raise the subscription fee, to enlarge the editorial team and to offer authors the option of immediate open access to their paper from the time of publication for payment of a publication fee.
- The ECCMID Abstract Book 2006 was for the first time published as an online supplement and searchable CD-ROM only. The CD also contained a large number of posters.

ESCMID News: Last year three issues in colour print were published. In addition, a short online version was produced for distribution also to affiliated societies. In future the scientific and educational content should be expanded.

Comment: Matthew Falagas, Athens, Greece, thinks that the CD-ROM with the official abstracts should not need to be picked up from a sponsor’s booth. RN agreed and promised that this will not happen again.

11 Report of the President of the 16th ECCMID

Pierre Bellamondica expressed his satisfaction with the success of the 16th ECCMID. With 6128 delegates, 312 accompanying persons and some 860 exhibitors this was the largest ECCMID ever. There were a total of 137 scientific sessions, 1439 posters and 80 exhibiting companies. He thanked his colleagues from the Organising Committee for their support and the participants for coming to ECCMID and extended his best wishes to the new crew, which is already in the starting blocks for the preparation of the 17th ECCMID / 25th ICC 2007 in Munich.

Questions: Panayotis Tassios, Athens, Greece, wanted to know how many ESCMID members did attend the Congress. In his reply Peter Schoch mentioned that the figures for this year are not available yet, but that the average from earlier years indicates that about 25% of the delegates are ESCMID members. If this is true also this year some 1530 delegates at this year’s ECCMID are ESCMID members (corresponding to about 50% of our membership).

Matthew Falagas, Athens, Greece, acknowledged that the quality of the poster sessions improved but thinks that the rejection rate should be further increased. Ragnar Norrby responded that we are already now close to the practice of ICAAC and will explore this issue through the online questionnaire after ECCMID.

12 Report of the Chair of the 16th ECCMID Programme Committee

Andreas Voss used the occasion to inform about the abstract reviewing and selection process: A total of 2560 abstracts were received, blindly reviewed by at least 3 experts and rated 1 (reject), 2 (poor), 3 (fair), 4 (good), 5 (very good) or 6 (excellent). Only abstracts which were rated with an average 3.2 or better were selected for poster or oral presentations (65.9%). Abstracts rated between 2.6 and 3.0 were accepted for publication (18.5%), abstracts rated 2.5 and lower were rejected (15.6%). He was also convinced that the quality of the poster sessions improved and that it will further increase. It remains to be seen whether next year we will slightly increase the rejection rate or not. Andreas Voss thanked the members of the Programme Committee and the Abstract Review Board for their excellent work.

Question: Maja Rupnik, Maribor, Slovenia, and Panayotis Tassios, Athens, Greece, were both concerned about the parallel scheduling of many study group meetings and study group scientific sessions on Saturday afternoon of the first Congress day and asked whether it would not be possible to spread them over several days so that there is less overlap of meetings of interest to the same people. Andreas Voss responded that the traditional ESCMID study group symposia cannot be held next year at the joint ECCMID/ICC but that the study group business meetings might be better distributed.

13 Approval of the Statutes

The main reason for this approval is the need to have a clean version of our Statutes recorded at the Munich register of societies. Ragnar Norrby explained the few changes of the Statutes as they are appended to the invitation for the Assembly and asked the members for a hand vote of approval. There was unanimous consent without dissenting votes or abstentions.

14 Proposal of new membership fees

In 2006 the annual Clinical Microbiology and Infection (CMI) page budget will increase from 1056 to 1200 pages. This leads to increased production costs by Blackwell, which the Executive must defer onto the members for legal reasons based on our charity status. The new fees as proposed would become effective in 2007 (current fees in parentheses):

- CMI print & online EUR 88 (85)
- CMI online EUR 58 (57)

Reduced rate fee (<35 years, retired)
- CMI print & online EUR 68 (65)
- CMI online EUR 38 (37)

The Assembly approved the new fees unanimously.

ESCMID NEWS 2-2006
Formal approval of the actions of the Executive Committee

Ragnar Norrby asked for a hand vote about the exoneration of the Executive Committee. This was approved unanimously.

Other business

No request to speak.

Close of the meeting

Ragnar Norrby thanked the members for attending. He adjourned the meeting at 19:00 h.

New Staff in the ESCMID Executive Office

Henri Saenz's main responsibility in the ESCMID Executive Office will be to support the Education and the Scientific Affairs Officers. This includes, among others, planning and setting up the ESCMID Postgraduate Courses, Workshops and Summer School as well as the GRACE Educational Programme, which is being implemented in close collaboration with ERS. In addition, Henri will be involved in reviewing and establishing new ESCMID Study Groups, in implementing various scientific projects and in administering the Society’s programme for grants, fellowships and awards. His overall goals will be achieved when the ESCMID educational and scientific activities considerably expand in the upcoming months.

Karin Werner's main task at ESCMID’s headquarters will be the support of the Professional Affairs Officers, the President and other members of the Executive Committee in their output related to professional and public affairs. Focus areas will be: the liaison with the European Commission to monitor health action and framework programmes and the support of ESCMID groups in drafting project proposals; the implementation of an agenda of the European Council in cooperation with our affiliated societies; the development of medical practice guidelines; the set-up of an electronic exchange platform for trainees and training centres; and last but not least, the interaction with the Executive and a communication agency to render ESCMID a voice in the international debate of public health issues.

Henri Saenz

Henri Saenz was appointed as ESCMID Education and Science Manager. He was born in Ingolstadt, Germany, and studied biology at the Eberhard-Karls-University in Tubingen, Germany, focussing on medically relevant pathogens in the fields of bacteriology, parasitology and virology. Henri graduated in 2000 with a study on the regulation of biofilm formation in human-pathogenic staphylococci performed under the supervision of Prof. Friedrich Götz. After moving to the Biozentrum of the University of Basel, Switzerland, he earned his PhD working on human-pathogenic bacteria of the genus Bartonella in the group of Prof. Christoph Dehio. His work led to the discovery of a wealth of new virulence factors in the species he studied. During a one-year post-doctoral research period, he linked the pathogenicity data with comparative genomics to form a comprehensive view on the evolution of Bartonella pathogenesis. His findings were presented in several international conferences and will be published in peer-reviewed journals.

Karin Werner

Karin Werner has joined the Executive Office as ESCMID Professional Affairs and Public Relations Manager. She was born in Villingen-Schwenningen, Germany, and studied chemistry at the Albert-Ludwigs-University Freiburg, Germany, focussing on biochemistry. Karin received a PhD in 1999 with a study on the arachidonic acid metabolism in human reproductive tissues. During a two-year postdoctoral research period at the University of Cambridge, UK, she worked on gene function in the epithelium of the uterus. Having worked for different research funding organisations, Karin Werner is already familiar with research administration and public relations. For the VDI-Technology Center, Düsseldorf, Germany, she managed a public relations project in the field of international cooperation funded by the German Federal Ministry of Education and Research. In her position at the Ministry of Science and Research North Rhine-Westphalia, Düsseldorf, Germany, she was responsible for organising several meetings and workshops as well as coordinating all regional Stem Cell Network activities. At her last position at the University of Freiburg she was the EU liaison Officer of the Faculty of Medicine and assisted members of the faculty for participating in European research projects.

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Peter Schoch

ESCMID Managing Director
New Impact and Other Factors

Authors whose papers have been published in CMI and prospective authors alike will be pleased to know that the Impact Factor calculated for CMI this year increased again, placing the journal within the top twenty microbiology journals publishing original research (Fig. 1).

Submitting authors may be interested to see the breakdown concerning editorial decisions (Fig. 2). Those whose papers have been accepted will see that they fall within one quarter of the total, and those whose papers have been declined will understand that the current submission rate continues to push up the rate of rejection.

Concerning scope, CMI primarily attracts papers describing original research (Fig. 3). Ninety percent of submissions during the past three years have been full or concise accounts of research studies. Submitting authors should be aware that unsolicited reviews and editorials are welcome, and may be an appropriate format for clinical findings that would not fall within the current scope of the journal if presented as case reports or series.

It is not surprising that, although CMI is the official publication of a European society, the origins of submissions are widespread and are clearly not limited to Europe. Readers may be surprised to learn, however, that among the 83 countries from which submissions have been received during the past three years, the United States is sixth in terms of number of submissions.

Judith Crane
CMI Managing Editor

We have been successful in making a 30-day reduction in the delay between acceptance and appearance in a citeable format via Synergy/Online Early, and will continue efforts to make papers available even sooner.

In addition to pre-publication availability to subscribers, all published articles are now available on-line to non-subscribers, free of charge, at the end of the year following the year of publication. Further, in line with current trends toward open access, the Society has accepted a proposal from Blackwell that authors be given the option of making their articles freely available immediately upon publication for a fee of GBP 1250 (EUR 1835). This decision was prompted by the existence of open access journals such as BioMed Central and our awareness that certain grant-awarding institutions (e.g., UK Research Councils and US National Institutes of Health) expect grant-holders to ensure that published articles are made freely accessible within six months of publication. Some of these institutions have proposed to assume publication charges for authors in order to make grant-related results available to the public as early as possible. Other journals have put similar policies in place, and we are pleased that our publisher is willing to take this initiative with a lower fee than some.

Manuscripts received according to category
Manuscripts submitted to Clinical Microbiology and Infection, July 2003 – July 2006

Manuscripts received according to decision
Manuscripts submitted to Clinical Microbiology and Infection, July 2003 – July 2004

Clinical Microbiology and Infection
Impact Factor progression 2002 – 2005

Current impact factor places CMI among the Top 20 microbiology journals publishing original research

Pre-publication online access / Post-publication open access

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Is Europe Prepared for the New Emerging *Clostridium difficile* PCR Ribotype 027?

Since March 2003, outbreaks of severe cases of *Clostridium difficile*-associated disease (CDAD) have been reported in hospitals in Montreal and southern Quebec in Canada. In 2004, institutions in the region of Quebec experienced a sharp rise in CDAD incidence involving more than 14,000 patients with CDAD. In January 2005, 30 hospitals in Quebec reported rates of nosocomial CDAD five-fold greater than their historical average. A new, more virulent variant strain was associated with this increase. Surveillance reporting is now mandatory in Quebec. Up to June 2006, the strain has been spread to 7 provinces in Canada with still the highest incidence in hospitals in Quebec of 13 per 1000 admissions. Quebec has also the highest case-fatality rate of 7.9%; the mortality rate has increased by 400% resulting in more than 1400 deaths since 2003 (1).

Before 2003, CDC (Atlanta) already reported a steady increase of CDAD from 2.7 per 10’000 hospital days in 1987 to 4.2 in 2001. The increase is also clear from the data of the US hospital discharges, since the numbers of CDAD doubled between 1996 and 2003. The CDC also recognised the new highly virulent strain associated with high morbidity and mortality during outbreaks in hospitals in at least 17 states (www.cdc.gov/ncidod/dhqp/index.html). Furthermore, reports from CDC mention an increase in severe community-acquired CDAD in populations previously considered to be at low risk (2).

The new epidemic strain was characterized as PCR-ribotype 027 and belonged to toxinotype III, North American PFGE type 1, and restriction-endonuclease analysis group type BI (3). Until March 2004, this strain was considered to be an unimportant and very rare type in the US, Canada and Europe. The new epidemic strain contains the binary toxin gene *cdtB* and has an 18-bp deletion in *tcdC*. In the strains isolated in Canada, an additional single-base-pair deletion has been detected in the *tcdC* sequence at position 117 (4). The exact role of the binary toxin and genetic variations in *tcdC* gene are unknown, but the 117 mutation may be of special importance since it represents a frameshift and premature stop in the early portion of the gene, resulting in a major disruption of *tcdC* function. In non-outbreak situations, binary toxin genes are present in up to 10% of all *C. difficile* isolates, and correlate well with variant toxinotypes. Deletions in *tcdC* are also not specifically associated with type 027. For instance, we have recently found 39 bp deletions present in 11% and 18 bp deletions in 17% of 64 toxigenic isolates collected in a national surveillance study in the Netherlands (manuscript submitted).

The new emerging 027 strain has a characteristic antimicrobial susceptibility pattern, since it was resistant to erythromycin (MIC >256 mg/l), resistant to ciprofloxacin (MIC >32 mg/l), and susceptible to clindamycin (MIC = 4-6 mg/l). This pattern may be of benefit for the microbiological laboratories to recognise the 027 strain.

In the period February to June 2004, the PCR ribotype 027 strain was recognised in the UK in an outbreak involving 150 patients with 12 deaths at the Stoke Mandeville Hospital (5). Interestingly, a second outbreak occurred between October 2004 and June 2005 in the same hospital with 160 new cases and 19 (12%) further deaths. Shortly thereafter, other hospitals also reported an increase of CDAD and submitted isolates to the Anaerobe Reference Laboratory in Cardiff (Jon Brazier). Up to April 2006, 450 isolates of type 027 have been referred to the Reference Laboratory from 75 hospitals. Some were from clinically recognised outbreaks, others from the routine submission of isolates as part of the mandatory surveillance of CDAD in England. Retrospectively, the 027 strain was already present in 2002 as a causative agent of an outbreak. Similarly as observed in the US, the incidence of CDAD was already increasing before outbreaks due to 027 occurred, since the Communicable Diseases Surveillance Centre (CDSRC) for England and Wales had noticed that the number of CDAD reports had risen from 1000 in 1990 to 15’000 in 2000 and 35’500 in 2003. A recent health statistics report on the deaths involving *C. difficile* in England and Wales, revealed an increase from 975 in 1999 to 2247 in 2004 (6). The report examined trends in those deaths that involved *C. difficile* as a contributory factor using the specific ICD-10 code A04.7. Among deaths that occurred in NHS general hospitals and nursing homes CDAD made up to 0.52 and 0.45%, respectively. Most of the deaths are in those 65 years and over and are usually patients who are already very ill due to their underlying disease. These data are in agreement with the observation that CDAD was already increasing and do not reflect a more severe course of disease type 027.

In July 2005, the first outbreak due to type 027 was recognised in a hospital (Figure 1) in Harderwijk in the Netherlands (7). A second epidemic occurred in another hospital 30 km from the first hospital and was probably related to the first outbreak through a transferred patient with CDAD. In response to the outbreaks the Center for Infectious Disease Control at the National Institute for Public Health and the Environment (RIVM) in Bilthoven instituted an outbreak management team with experts in the fields of microbiology, infectious diseases, infection control, and epidemiology. National hospital guidelines relevant for infection control and treatment of CDAD were formulated and dispersed. Surveillance plans were made to register and monitor new outbreaks and a reference laboratory was appointed at the Leiden University Medical Centre. In the period between September 2005 and June
In September 2005, the PCR ribotype 027 strain was isolated from four patients with CDAD in Leper, Belgium (8). Subsequently, the same pattern was identified among strains from 3 outbreaks that had occurred in Brussels in 2003–2004. Other outbreaks were found in Ostende and Libramont. Until July 2006, type 027 has been identified as causative agent of outbreaks in 11 hospitals in Belgium. Two additional health care facilities had 027 without a spread. The Belgium Reference Laboratory received 181 C. difficile isolates and typed 81 as toxinoype III with a 18 bp deletion. In June 2006, a national surveillance programme started in Belgium to monitor spread of type 027.

On 27 March 2006, a cluster of CDAD cases was reported to the Institut de Veille Sanitaire (InVS) by a hospital in northern France (9). The origin of this outbreak remains unknown, although transfers of patients between French hospitals and Belgian nursing homes are frequent and under investigation. A few other clusters are under investigation in northern France. InVS informed all French regional infection control coordinating centres and healthcare facilities and disseminated recommendations for reporting, investigation, surveillance and control of CDAD (www.invs.sante.fr/display?doc=publications/2006/guide_raisin/index.html).

Figure 2. Research team at the Leiden reference laboratory, from left to right: Inge Schaap (technician), Sunita Paltansing (MD, PhD student), Norbert Vaessen (MD, PhD), Renate van den Berg (PhD student) and Ed Kuijper (MD, PhD)

Is Europe prepared for an early recognition of CDAD due to the 027 type to prevent its further spread?

Unfortunately, there exists a severe underestimation of CDAD in Europe due to lack of clinical awareness, lack of standardised diagnostic strategies and lack of standardised surveillance. A European surveillance study of diagnostic methods and testing protocols for C. difficile among 212 hospitals in eight countries in 2002 revealed marked differences between laboratories concerning the methods and the strategies that are used for diagnosing CDAD (10). In 58% of the cases, laboratories only undertook investigations for CDAD when specifically requested by the physician and only 55% of the laboratories were capable of culturing for C. difficile. In the Netherlands, in a 3-month pilot study using an optimal test algorithm at four university laboratories, a nearly 20% increase in the number of diagnosed CDAD patients was found (manuscript submitted). This algorithm enabled the microbiological laboratories to test all faecal specimens of patients hospitalised more than 3 days who developed diarrhoea, irrespective of the physician’s request.

A second European surveillance study has been performed in 2005 among 38 hospitals from 14 European countries (principal investigator: Frédéric Barbut, Unité d’hygiène et de Lutte contre les Infections Nosocomiales, Hôpital Saint-Antoine, Paris) using the participation of the members of the ESCMID Study Group on C. difficile (ESGCD). All participating laboratories collected clinical information and C. difficile isolates of patients with CDAD during 2 months surveillance. The incidence varied considerably from 0.14 to 7.1 per 10’000 patient-days. C. difficile PCR ribotype 027, toxinoype III was found in UK, Belgium, the Netherlands and Ireland. However, only 3 laboratories per country participated and laboratories from 11 European member states were not included in this survey. It is therefore necessary to create a network of laboratories encompassing all European member states, National Institutes of Health, and the European Center of Disease Control in close collaboration with ESGCD. The laboratories should be capable of participating in epidemiological surveillance studies of CDAD. The network should be led by one to two laboratories that are also active in the development of new and improved typing systems for C. difficile.

In January 2006, a workshop was organised on the new emerging C. difficile by ECDC in collaboration with ESGCD and CDC, Atlanta, USA. It was decided to prepare a background paper with a collection of all known information on the new emerging strain. This review will appear as a special supplement in Clinical Microbiology and Infection (CMI) in August/September 2006. All experts emphasised that the focussed interest on type 027 may be temporary and other new virulent types may also arise. In fact, some preliminary reports from Ireland, Argentina, Poland, and the Netherlands suggest that the TcdA negative type 017 strain is also causing outbreaks, sometimes simultaneously with type 027 (7). All agreed on the building of a surveillance system to monitor the incidence of CDAD and the spread of type 027 in Europe. Interim recommendations for CDAD case definitions have been prepared and discussed.

An alarming MMWR report indicated that community-acquired CDAD is increasing in populations previously at low risk (2). A recently completed surveillance study in the Netherlands also revealed a high incidence of CDAD with a community onset in 36% of all diagnosed CDAD patients (manuscript submitted). However, of 31 patients admitted to the hospital with CDAD, 13 patients (33%) had been hospitalised in the previous month and 5 (46%) of them experienced CDAD as a recurrence. This stresses the importance of appropriate definitions for surveillance and classification.
of cases’ origin. Bruno Coignard (Medical Epidemiologist, Saint-Maurice, France) has therefore prepared interim definitions (Figure 3) which are based on published experiences in Canada and the USA and will appear in the special supplement to CMI.

**Definitions**

**Healthcare onset CDAD:** Symptoms start during stay in health care facility
- **Community- or healthcare-associated case:** a CDAD case patient with onset of symptoms within 48 hours (<48h) following admission to a healthcare facility.
- **Healthcare-associated case:** a CDAD case patient with onset of symptoms at least 48 hours (≥48h) following admission to a healthcare facility.

**Community-onset CDAD:** Symptoms start in community outside health care facilities
- **Healthcare-associated case:** a CDAD case patient with onset of symptoms in the community within 4 weeks following discharge from a healthcare facility
- **Unknown case:** a CDAD case patient who was discharged 4-12 weeks from health care facility before the onset of symptoms.
- **Community-associated case:** a CDAD case patient with onset of symptoms outside of healthcare facility, and no discharge from a healthcare facility within the previous 12 weeks.

**Prospectives**

It is very likely that other new virulent types of *C. difficile* will appear in the future, but it is important to concentrate now on early recognition and prevention of spread of PCR ribotype 027. An increasing number of reports mention the occurrence of CDAD due to PCR ribotype 027 in animals, leading to the hypothesis that CDAD due to type 027 can also manifest as a community-acquired zoonotic disease. European countries should develop early warning and response capability with support of ECDC and guidelines should be formulated and dispersed for recognition of CDAD, infection control measures and prevention.

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Guidelines for the Management of Helicobacter pylori Infection

The Maastricht-3 2005 Consensus Report

Introduction
The European Helicobacter pylori Study Group (EHSG) was founded in 1987 to promote multidisciplinary research into the pathogenesis of Helicobacter pylori. The EHSG has organised successful annual meetings since then. The group also has arranged task forces on paediatric issues and clinical trials on H. pylori. Consensus meetings have convened on who, how and when to treat patients with H. pylori infection. The most active area of research is the link of H. pylori with gastric cancer. Gastric cancer is a major public health issue. The most recent consensus meeting held this year was divided into three panels: 1. Who to treat? 2. How to diagnose and treat H. pylori? 3. Prevention of gastric cancer by H. pylori eradication. Chairmen and selected experts were chosen to participate for each of these panels based on their contribution to the published literature. The chairmen met to choose topics relevant to their panel. They developed statements that needed clarification and debate. The international faculty who attended reflected on the global problem of H. pylori infection. Each of the panelists was asked to review different topics and to provide key references on these topics.

Who to treat?
The starting point when considering who to treat are the previous guidelines published by EHSG, Maastricht 2000. (See Table 1).

Dyspepsia
There is need to define non-investigated and investigated dyspepsia and to consider them separately. Treatment of non-investigated may be different if the incidence of H. pylori is low as occurs in developed countries. The increasing awareness of H. pylori as a pathogen in developing countries has stimulated interest in a test-and-treat approach in these areas. Test-and-treat was recommended in adult patients below 45 years of age (the age cutoff may vary locally) presenting in primary care with persistent dyspepsia having excluded those with predominantly gastroesophageal reflux disease (GERD), non-steroidal anti-inflammatory drugs (NSAIDs) consumption and those with alarm symptoms. This recommendation has been vindicated in more recent publications. The definition of low prevalence is a population with an infection rate of less than 20%. The Cochrane review stated that the test-and-treat principle was as effective but less expensive than endoscopy in patients not at risk of malignant disease and likely to be more effective than acid suppression therapy; yet longer-term studies have confirmed this statement. The majority of patients with dyspepsia have a normal endoscopy and in the absence of predominant reflux symptoms, these patients are considered to have non-ulcer dyspepsia. The Cochrane Systematic Review confirmed that there is a small benefit of eradicating H. pylori in this context. Empirical anti-secretory treatment may be less costly if the infection rate is less than 20%.

Dyspepsia: statements and recommendations
- H. pylori test-and-treat is an appropriate option for patients with uninvestigated dyspepsia.
- H. pylori eradication is an appropriate option for patients infected with H. pylori and investigated non-ulcer dyspepsia.
- H. pylori test-and-treat is the strategy of first choice in all (adult) patients with functional dyspepsia in high prevalence populations.
- The effectiveness of H. pylori test-and-treat is low in populations with a low H. pylori prevalence. In this situation the test-and-treat strategy or empirical acid suppression are appropriate options.

Gastroesophageal reflux disease
The second area of controversy that was reviewed was the link of H. pylori and reflux oesophagitis. In the previous guidelines it was thought advisable to eradicate H. pylori when long-term antisecretory treatment is necessary for the management of GERD. This recommendation was based on a report that such treatment may accelerate the progression of H. pylori-induced atrophic gastritis in the fundus of the stomach. Observational studies have suggested that H. pylori may protect against GERD but the results could be due to bias or confounding factors.

In randomised controlled studies the relapse rate in GERD symptoms was the same in the H. pylori-treated as the placebo-treated GERD patients (83% of both groups) and treatment of H. pylori did not affect the efficacy of proton pump inhibitors (PPIs). More recent studies do not support that H. pylori eradication leads to the development of erosive oesophagitis or worsening of symptoms in patients with pre-existing GERD.

Most H. pylori positive GERD patients have a corpus-predominant gastritis and treatment with a PPI eliminates gastric mucosal inflammation and induces regression of corpus glandular atrophy. H. pylori did not worsen reflux or lead to increased maintenance dose confirming the benefit of eradication of H. pylori in GERD patients.

Table 1

<table>
<thead>
<tr>
<th>Strongly recommended indications for Helicobacter pylori eradication therapy</th>
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<tbody>
<tr>
<td>Peptic ulcer disease (active or not, including complicated ulcer)</td>
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<tr>
<td>Atrophic gastritis</td>
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<tr>
<td>Post-gastric cancer resection</td>
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<tr>
<td>Patients who are first-degree relatives of gastric cancer patients</td>
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<tr>
<td>Patients’ wishes (after full consultation with their physician)</td>
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...
GERD: statements and recommendations

- *H. pylori* eradication does not cause GERD.
- Profound acid suppression affects the pattern and distribution of gastritis favouring corpus-dominant gastritis. It may accelerate the process of loss of specialised glands leading to atrophic gastritis.
- *H. pylori* eradication halts the extension of atrophic gastritis and may lead to regression of atrophy. The effect on intestinal metaplasia is uncertain.
- There is a negative association between the prevalence of *H. pylori* and GERD in Asia but the nature of this relationship is uncertain.
- *H. pylori* eradication does not affect the outcome of PPI therapy in patients with GERD in western populations. Routine testing for *H. pylori* is not recommended in GERD. *H. pylori* testing should be considered in patients on long-term maintenance therapy with PPIs.

*H. pylori and non steroidal antiinflammatory drugs*

The relationship between *H. pylori* and NSAIDs is complex. Both account for nearly all peptic ulcers. They are independent factors for peptic ulcer and peptic ulcer bleeding. *H. pylori* eradication is insufficient to prevent recurrent ulcer bleeding in high risk NSAID users. It does not enhance the healing of peptic ulcer in patients taking anti-secretory therapy who continue to take NSAIDs.

In one study among patients with *H. pylori* infection and a history of upper gastrointestinal bleeding who are taking low dose aspirin, the eradication of *H. pylori* was equivalent to treatment with a PPI in preventing recurring bleeding. However, PPI was superior to the eradication of *H. pylori* for preventing recurring bleeding in patients who are taking NSAIDs.

In another study from Hong Kong, among patients positive for *H. pylori* or who had dyspepsia and history of an ulcer before beginning NSAID treatment, *H. pylori* eradication reduced the risk of bleeding but was insufficient to completely prevent NSAID ulcer disease. Clopidogrel is also associated with an increased risk of a gastrointestinal bleed. The role of *H. pylori* in this situation has not been assessed. The combination of aspirin and clopidogrel merits further studies. These drugs have a synergistic beneficial effect on cerebral vascular disease. Among patients with a history of aspirin-induced ulcer bleeding whose ulcer had healed, aspirin and a PPI was superior to clopidogrel in the prevention of recurrent ulcer bleeding. Therefore the current recommendation that patients with GI intolerance to aspirin be given clopidogrel cannot be sustained.

An emerging topic was Cox 2 inhibitor and NSAIDs is complex. Both account for nearly all peptic ulcers. They are independent factors for peptic ulcer and peptic ulcer bleeding. The role of *H. pylori* gastritis and iron deficiency anaemia in the absence of peptic ulcer disease.

**NSAIDs: statements and recommendations**

- *H. pylori* eradication is of value in chronic NSAIDs users but is insufficient to completely prevent NSAID-related ulcer disease.
- Patients who are naïve NSAIDs users should be tested for *H. pylori*, and if positive receive eradication therapy to prevent peptic ulcer and/or bleeding.
- Patients who are long-term aspirin users who bleed should be tested for *H. pylori* and if positive receive eradication therapy.
- In patients on long-term NSAIDs and peptic ulcer and/or ulcer bleeding, PPI maintenance therapy is superior to *H. pylori* eradication in preventing ulcer recurrence and/or bleeding.

**Paediatrics**

In paediatrics it was agreed that there are other indications than peptic ulcer disease for eradication of *H. pylori*. Although recurrent abdominal pain in childhood is not an indication for a test-and-treat strategy it was recognised that children who have a positive family history of peptic ulcer and gastric cancer should be tested after exclusion of other causes. Similar to adults, children with unexplained anaemia and no other obvious cause for it should be treated for *H. pylori* infection.

**Paediatrics: statements and recommendations**

- There are other indications than peptic ulcer disease for eradication of *H. pylori* infection in children and adolescents.

**Other disease areas: statements and recommendations**

- *H. pylori* infection should be sought for and treated in patients with:
  i) Idiopathic thrombocytopenia
  ii) Unexplained iron deficiency anaemia
- *H. pylori* has no proven role in other extra-alimentary diseases.

**How to diagnose and treat?**

The management of *H. pylori* infection has been well established during the last 10 years. Recommendations were made in the Maastricht Conference in 1996, and were updated in 2000. Most of them have been used in other consensus conferences worldwide.

Nevertheless, some points have emerged these past 4 years which led to questions and discussions at the Maastricht-3 Conference.

**Pre-treatment diagnosis**

With regard to diagnostic tests, the discussion focussed on the value of non-invasive tests other than the urea breath test (UBT). A first statement concluded that serology could be considered as a diagnostic test in some situations, e.g. bleeding ulcers, gastric atrophy, MALT lymphoma and current use of PPI or antibiotics. Indeed, PPI are a source of false negative results for all diagnostic tests except serology, and should be stopped at least 2 weeks before performing the test. In contrast, it was stated that neither the doctor tests (near-patient tests) nor the detection of *H. pylori* antibodies in urine and saliva, had any current role in the
management of *H. pylori* infection. The situation is different for the stool test which was considered acceptable, on the same grounds as UBT for *H. pylori* diagnosis, especially in the case of implementation of the test-and-treat strategy.

With regard to invasive tests, the value of a positive rapid urease test during initial endoscopy in patients without previous non-invasive testing or pre-treatment, was considered to be sufficient to initiate a therapy.

The importance of performing culture for clarithromycin susceptibility testing, before using clarithromycin-based treatment as a first line treatment, was hardly debated. Culture was recommended if primary resistance to this antibiotic was higher than 15–20% in the respective geographical area or population, as well as after two treatment failures. The importance of monitoring the primary antibiotic resistance in reference laboratories in different areas was also stressed. In the event that clarithromycin susceptibility testing under such circumstances is impossible, this antibiotic should not be used. In contrast, it was agreed that testing metronidazole susceptibility is not routinely necessary in the management of *H. pylori* infection. Metronidazole susceptibility testing needs further standardisation before being recommended as a first line treatment.

**How to treat?**

The recommended first line therapy therefore remains PPI-clarithromycin-amoxicillin or metronidazole if the primary resistance to clarithromycin in the area is lower than 15–20%. However, it was agreed that there is a small advantage to using metronidazole instead of amoxicillin and therefore, this combination was found to be preferable in areas where the prevalence of metronidazole resistance is lower than 40%. The consensus was also that a 14-day rather than a 7-day treatment duration had a slight advantage in terms of treatment success. The other adaptation of this first line therapy in various geographical regions of the world concerns the doses. Another addition to the Maastricht-2 Consensus is that bismuth-based quadruple therapies, when available, are acceptable as alternative first line therapies.

With regard to second line therapies, bismuth-based quadruple therapies remain the best option. If unavailable, PPI-amoxicillin or tetracycline and metronidazole are recommended.

As previously proposed, the rescue therapy after failure of two courses of different therapies should be based on antimicrobial susceptibility testing.

**Follow-up after treatment**

With regard to patient follow-up after *H. pylori* eradication, UBT remains the preferred test. If unavailable, a laboratory-based stool test preferably using monoclonal antibodies, could be used. The timing of this follow-up should be at least four weeks after the end of eradication treatment.

At this stage, the detection of *H. pylori* pathogenicity factors and host polymorphism was not considered to be helpful in the management of the infection.

### **H. pylori infection and risk of gastric cancer: potential for prevention**

Gastric cancer is a major public health issue and the global burden of gastric cancer is increasing largely at the expense of developing countries. *H. pylori* infection is the prime cause of human chronic gastritis, a condition that initiates the pathogenic sequence of events leading to atrophic gastritis, metaplasia, dysplasia and cancer. Pooled analyses of prospective sero-epidemiological studies have shown that individuals with *H. pylori* infection are at a statistically significantly increased risk of subsequently developing non-cardia gastric cancer. It has also been well established that both histological types of gastric cancer, the intestinal and diffuse type, are significantly associated with *H. pylori* infection. Non-randomised clinical follow-up studies in Japan have shown that gastric cancer rates were significantly higher in patients with *H. pylori* infection than in those with no infection and that second tumour rates were higher in those with infection than in those without following endoscopic resection for early gastric cancer. Thus, it was agreed that *H. pylori* infection is the most common proven risk factor for human non-cardia gastric cancer.

Infection with cagA-positive strains of *H. pylori* increases the risk for gastric cancer over the risk associated with *H. pylori* infection alone. IL-1 gene cluster polymorphisms are associated with higher risk of hypochloridria (Odds Ratio = 9.1), and of gastric cancer (Odds Ratio = 1.9). Potential extrinsic and intrinsic environmental factors in gastric carcinogenesis include: heredity/family history, both direct and indirect (social inheritance); autoimmunity (*H. pylori* may trigger the onset of autoimmune atrophic gastritis in some patients with pernicious anaemia); in diabetes type I occupational exposure to nitrate/nitrite/nitroso-compounds; nutritional (salt, pickled food, red meat, smoking); general factors (low socio-economic status, geography); pharmacological factors (gastric acid inhibition). All these lines of evidence suggest that bacterial virulence factors, host genetic factors, and environmental factors contribute to the risk of development of gastric cancer.

*H. pylori* eradication prevents development of pre-neoplastic changes (atrophic gastritis and intestinal metaplasia) of gastric mucosa. With regard to the possibility that *H. pylori* eradication may reduce the risk of gastric cancer, the following evidence is available: several non-randomised controlled studies in animals and humans showing the preventive effect of *H. pylori* eradication in reducing the occurrence of gastric cancer in very high risk conditions; several randomised control studies showing regression of pre-cancerous lesions or, at least, decrease of progression as compared to control group after *H. pylori* eradication; one randomised control study failing to demonstrate reduction of cancer incidence at five years but showing significant reduction in the group without pre-neoplastic lesions. The consensus report concluded that eradication of *H. pylori* has the potential to reduce the risk of gastric cancer development; moreover, the optimal time to eradicate *H. pylori* is before pre-neoplastic lesions (atrophy, intestinal metaplasia) are present. It was also agreed, that the potential for gastric cancer prevention on a global scale is restricted by currently available therapies. Thus, new therapies are desirable for a global strategy of gastric cancer prevention.

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Towards Molecular Diagnosis of Zygomycosis?

A Collaborative ESCMID Fungal Infection Study Group Project

Background and introduction

Less frequently observed than infections due to Candida spp. or Aspergillus spp., zygomycoses represent severe infections which have a tendency to dissemination. The infection is associated with a high mortality rate of about 40% and mostly occurs in immunocompromised patients in particular in neutropenic or diabetic patients (8). The incidence of zygomycosis has increased during the last decade, especially in solid organ transplant recipients and in allogenic bone-marrow transplant patients. Moreover, Zygomycetes are resistant to most antifungal drugs including recently marketed molecules such as caspofungin (4) and voriconazole (2). It has been shown that the consequences of these resistances are breakthrough zygomycosis in patients with voriconazole prophylaxis against Aspergillus infection (6) or with caspofungin treatment against Candida infection (5). The main human pathogens of the order Mucorales belong to the genera Rhizopus, Mucor, Absidia, Rhizomucor, and Apophysomyces. The most common species found in pathology belong to the genera Rhizopus, in particular Rhizopus oryzae and Rhizopus microsporus. Other species like Cunninghamamella bertholletiae, Saksenaea vasiformis, Sicyphalas trum racemosum or Cokeromyces recurvatus are recovered only rarely from clinical specimens (7). Zygomycetes species exhibit different susceptibility profiles to the antifungal drugs currently used for the treatment of human zygomycosis, such as posaconazole or amphotericin B. To guide antifungal therapy, identification to the species level would thus be of major interest. Yet, identification to the species level by standard microbiological procedures remains difficult and time-consuming and often even requires the expertise of a reference laboratory as the different species share similar morphological characteristics (3). But cultures of infected tissues are often negative, and serological tests for the diagnosis are not routinely available. Diagnosis of zygomycosis depends on histopathology that evidences broad, rarely septate hyphae with right-angled branching (Figure 1). However, identification to the species level is not possible by this means. Recently, molecular approaches have been set up to identify fungal species by amplification and sequencing of small targets in the ribosomal DNA. The regions 18S-ITS-28S-IGS are repetitive sequences in the genome which account for the high sensitivity of the technique (Figure 2). Different targets have been used, including the conserved ribosomal DNA genes and the more variable ITS regions between those genes.

The aim of a recent study (9), which was carried out in the Molecular Mycology Unit (Institut Pasteur, Paris, France), was to validate ITS sequencing as a reliable technique for the identification of Zygomycetes to the species level from pure cultures and to evaluate if species identification is possible directly from tissues of experimentally infected mice. For in vitro studies, a total number of 54 Zygomycetes isolates belonging to 20 species and varieties including the most common species were used. Genomic DNA was extracted from mycelium and complete ITS1 and ITS2 regions were amplified and sequenced using the fungal universal primers V9D and LS266. Alignment of the sequences showed that intraspecies similarity was 99% in a given species, while interspecies variation was high. Sequences were heterogeneous with a similarity between genera of only ≤71% and between species of only ≤95%, except for some varieties and uncommon Mucor species, thus allowing an accurate identification of Zygomycetes to the species level in most of the cases. These results demonstrated that ITS sequencing is an appropriate molecular tool for the identification of Zygomycetes from pure cultures.

After validating ITS sequencing as a tool for Zygomycetes species identification from cultures, an animal model of disseminated zygomycosis was used to evaluate if species identification was also possible directly from infected tissues. Mice were infected with one of six different species (R. oryzae, R. microsporus, Absidia corymbifera, Rhizomucor pusillus, Mucor circinelloides, and Mucor indicus). Brains and kidneys were checked for positive infection under the fluorescence microscope by staining the fungal mycelium with Calcofluor White (Figure 3). Complete genomic DNA was extracted from frozen tissues, amplified and sequenced with V9D and LS266.

Figure 1. Paraffin-embedded kidney of a mouse experimentally infected by Zygomycetes and stained by methenamine silver (Grocott’s staining) (250x)

Figure 2. Scheme of the fungal ribosomal DNA
The presence of hyphae in tissues as proved by fluorescence staining was then compared with the positive PCR results and in at least all cases where the presence of hyphae was proven, the PCR was also positive. Overall, identification of Zygomycetes to the species level is possible from pure cultures and frozen tissues (9).

### Outline of a study performed by EFISG

In clinical practice, paraffin-embedded samples are often the only available samples. Until now only one study evaluated the identification of Zygomycetes to the species level from paraffin-embedded tissues using the 18S gene as target region. The histological diagnosis of zygomycosis was confirmed by PCR in 14 of 23 cases and the infecting species was identified. For 9 samples no amplification was obtained (1). Further evaluation of the sensitivity and the reproducibility of this technique remains to be done.

The main goal of the present EFISG study is to assess the reproducibility of a technique for the molecular identification of different Zygomycetes species from paraffin-embedded tissues obtained from experimentally infected mice through a European interlaboratory exercise. A secondary goal is to broadly assess the sensitivity of the technique by amplification of different quantities of tissues. Overall 7 laboratories from 7 countries are participating in the study. The samples were prepared and provided by the Molecular Mycology Unit in collaboration with the Histotechnology and Pathology Unit, Institut Pasteur, Paris, France. Animals were infected with one of 5 species (R. oryzae, R. microsporus, A. corymbifera, R. pusillus, and M. circinelloides). Brains and kidneys were removed aseptically, and checked for infection under the fluorescence microscope after Calcofluor White staining. Infected tissues (brains and kidneys) were afterwards fixed in formaldehyde for at least 48 hours. Fixed tissues were then included into paraffin blocks. From these blocks, tubes containing 1, 10, or 30 slide cuts (to assess sensitivity) corresponding to animals infected with each species were prepared and mailed to each laboratory. Species identification will be done in the different laboratories from the provided samples using a protocol designed in the Molecular Mycology Unit based on preliminary experiments. Samples will be deparaffinised and complete DNA will be extracted. Because of DNA denaturation during the fixation step, only a short fragment, the ITS1 region which is sufficiently variable to identify the different species, will be amplified and sequenced with the fungal universal primers ITS 1 and ITS 2. Results of positive or negative amplification and species identification will be done in each laboratory. Final analysis will be performed in the Molecular Mycology Unit.

Please check one of the next ESCMID News issues for the results of the study.

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### References


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ESCMID Conference on Extended-spectrum Beta-lactamases

A stimulating ESCMID Conference held in a unique and beautiful setting, namely the Scuola Grande di San Giovanni Evangelista in Venice, Italy, focussed on the problem represented by the extended-spectrum beta-lactamases, widely known under the acronym 'ESBLs'.

The three-day Conference, attended by roughly 250 participants from over 40 different countries, comprised of state-of-the-art lectures and round-tables aiming to put the European situation into a worldwide context. It also provided practical advice on managing the ESBL problem, disseminating current knowledge and best practice in a fast-developing area.

The ESBL problem today

For around 20 years, wider and narrower definitions of ESBLs have been used, some based on spectrum, others on evolutionary history. No definition is perfect and pragmatically, the one proposed during the ESCMID Conference was: “an ESBL is any beta-lactamase, ordinarily acquired and not inherent to a species, that can rapidly hydrolyse, or confer resistance to oximino-cephalosporins (not carbapenems) or any beta-lactamase mutant, within a family, that has an enhanced ability to do so” (David Livermore).

ESBLs have been recognised as a cause of resistance to cephalosporins for 20 years. Initially found among Gram-negative bacteria (such as Klebsiella pneumoniae and Enterobacter cloacae) isolated from institutions particularly at high risk, these enzymes are now commonly found in nursing homes and in long-term care facilities, and even in community-acquired infections caused by the common and widely diffused Escherichia coli. Moreover, newer, ‘CTX-M-type’ ESBLs have started to disseminate in the clinical setting later than the classical TEM- and SHV-type enzymes, and they are now undergoing a rapid and massive spread. The most frequent community-acquired infections caused by ESBL-producing bacteria are urinary tract infections. However, 5–15% of community-acquired infections caused by ESBL-producing E. coli are bacteraemia, and this figure is still increasing. Consequently, the protocols for the empirical therapy of community-acquired sepsis potentially caused by E. coli in areas where ESBLs are prevalent would need to be revised.

Prevalence of ESBLs in Europe and in the rest of the world

Although ESBLs are a universal concern, determinants of bacterial resistance do not operate everywhere in the same way. Although clonal spread of strains of ESBL-producing E. coli has been reported in some countries, in most of them it is the ESBLs themselves that are being spread through mobile genetic elements among clonally unrelated strains.

In Europe, the increase of ESBLs in recent years is mainly produced as a consequence of the spread of CTX-M enzymes both in the community and in the nosocomial setting. However, SHV- and TEM- ESBL producers are still recognised and different surveillance studies have shown the maintenance of particular clones associated to specific ESBLs. Conversely, ESBL production in the United States remains heavily weighted toward TEM and SHV beta-lactamases. Only rarely have CTX-M or OXA ESBLs been identified. In some organisms, multiple ESBLs are observed, usually a TEM with an SHV enzyme. Often non-clonal strains are identified, even within the same institution, but common plasmids are frequently observed within a localised geographical region. In Latin America, ESBLs are more prevalent and belong to different groups than the ones described in Europe and the US. Many factors can be responsible for this high prevalence such as free use of broad-spectrum antibiotics, limited identification of these bacteria in the microbiology laboratories due to economical constraints and a higher possibility of transmission of these bacteria between patients because of patient overcrowding in the ICUs and wards, and failures in contact barriers and hand washing.

Detection of ESBL-producing strains

Antimicrobial susceptibility testing to 3rd generation cephalosporins is based on (1) breakpoints and (2) the performance of screening tests to detect and characterise ESBLs. The number of species with ESBLs, the increase in the number of different ESBLs and an increased variety in the MIC values resulting from the various ESBLs and the ensuing variations needed in ESBL-detection methods have led EUCAST to re-evaluate susceptibility breakpoints of Enterobacteriaceae against 3rd generation cephalosporins. The breakpoints will detect most clinically important ESBLs but will not obviate the need for detection of ESBLs since this is of epidemiological importance.

Therapeutic strategies

Therapy of infections caused by ESBL-producers with most of the beta-lactams to which they appear susceptible in standard in vitro tests, has been associated with treatment failure and increased mortality. The Clinical Laboratory Standards Institute (CLSI) recommends reporting ESBL-producing strains of E. coli and Klebsiella spp. as resistant to all penicillins, cephalosporin and monobactam antimicrobials, but as susceptible to beta-lactam/ beta-lactamase inhibitor antimicrobials, like piperacillin-tazobactam, when they test as such in the laboratory. Clavulanate is critical in ESBL detection tests, but there is scepticism about its potential in therapy. This is partly due to the use of difficult-to-protect penicillin in the marketed combinations.
and partly due to the potential for antagonism of cephalosporins by the induction of AmpC. Sulbactam is commercially available in combination with either ampicillin or cefoperazone. As with other inhibitors, the antibiotic in vitro activity against ESBL-producing bacteria is restored, and one of the particular advantages of this combination is that sulbactam itself has intrinsic activity against Acinetobacter baumannii.

Injective carbapenems are commonly held as powerful drugs for treating infections by ESBL producers. Imipenem and meropenem are active against Enterobacteriaceae and non-fermentative Gram-negative bacilli. In Europe they are both licensed for many indications, covering almost all severe and nosocomial infections. Ertapenem has limited activity against non-fermentative Gram-negative bacilli, and since 2002 it is licensed in the EU for the treatment of intra-abdominal infections, community-acquired pneumonia, acute pelvic infections and soft tissue infections associated with diabetic foot. In Japan and South Korea panipenem and biapenem are also available. Both have in vitro activity comparable to that of imipenem. Other carbapenems such as doripenem are still under development.

Carbapenems with sufficient oral activity for community use have demonstrated broad-spectrum antibacterial activity against common respiratory pathogens, but have never achieved sufficient activity against Pseudomonas aeruginosa. Competition with less expensive, once-a-day agents has made it difficult to identify a competitive agent.

Conclusions

The beta-lactams still constitute the antibiotic class showing the widest flexibility of usage, due to their great versatility in terms of chemical properties, antibacterial spectrum, and administration schedules. The major threat for this class of antibiotics consists nowadays of the ever-growing diffusion of beta-lactamases and in the fact that, out of more than 350 different beta-lactamases identified, almost one third has ESBL characteristics, i.e. hydrolytic capabilities for broad-spectrum cephalosporins and aztreonam.

The ESBL problem is changing now, and increasing, especially in Europe. New ESBLs – particularly ‘CTX-M’ types – are spreading; E. coli is becoming the major host, rather than Klebsiella; and producers are being isolated from community patients, not just in the ICU. These changes challenge the laboratory, the clinician treating infected patients, public health and infection control doctors and pharmaceutical developers, posing a serious threat to the future of antimicrobial chemotherapy.

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ESGB Notes

The ESCMID Study Group on Biofilms (ESGB) was founded during the 15th ECCMID in Copenhagen in 2005. ESGB organised a biofilm symposium and a biofilm educational workshop at the 16th ECCMID in Nice 2006, both of which were well attended.

For the 17th ECCMID/25th ICC in Munich an educational workshop is also being organised. Further planned activities in 2007 are described below.

The 4th American Society of Microbiology Biofilm Meeting will take place in Quebec, Canada just before the ECCMID/ICC Congress in Munich. The biofilm meeting will start with a workshop on Sunday, 25 March 2007 and continue as a regular scientific meeting with key-note talks and oral and poster sessions until Thursday, 29 March. ESGB is highly involved in the organisation and scientific content of this meeting and ESGB contact persons for this meeting are Niels Høiby and Søren Molin.

An ESGB symposium and workshop Bacterial Adaptation Mechanisms: Biofilms, Hypermutability and Antibiotic Resistance will take place in Palma de Mallorca, Spain, 8 – 9 November 2007 by Antonio Oliver (Palma de Mallorca, ES), Oana Ciofu (Copenhagen, DK) and Niels Høiby (Copenhagen, DK). ESGB contact persons for this meeting are Oana Ciofu and Niels Høiby.

The ESGB hopes to see its members and other ESCMID members at these meetings in 2007. More information about these events will be posted on the ESGB website as it becomes available (www.escmid.org/esgb).

I hope you have had nice summer holidays.
Infections of the respiratory tract are leading causes of morbidity, mortality and antibiotic prescribing in the community. This in turn continues to be a powerful driver for selecting antibiotic resistance among respiratory pathogens and the microflora.

The optimum management of respiratory infections is frustrated by fundamental gaps in our knowledge concerning host genetic susceptibility, the microbiology and a clear understanding of the natural history of many of the syndromes captured by the term lower respiratory tract infection (LRTI).

**GRACE**

To address these issues, ESCMID is a partner with the European Respiratory Society (ERS) in a 5-year collaborative research project in the GRACE Network of Excellence funded by the EU Sixth Framework Programme. GRACE (Genomics to combat Resistance against Antibiotics in Community-acquired lower respiratory tract infections in Europe) was launched on 17 March 2006 in Brussels (see photo).

GRACE is an ambitious project which brings together expertise in genomics, molecular microbiology, health economics, IT, laboratory and clinical medicine. The partners are drawn from academic centres from 9 Member States and 5 small-to-medium enterprises (SMEs). The Network will be rigorously managed and IT supported. The GRACE website (www.grace-lrti.org) will be linked to those of ESCMID and ERS.

How will the GRACE project meet its objective of combating antibiotic resistance? The programme of research is based on the establishment of a virtual genomic laboratory network in 8 European countries and a primary care research network in 11 European countries. Human and microbial genomic research will be integrated into a programme of clinical observational and interventional studies. The health economic impact of these community LRTI will be defined. It is anticipated that by launching this Network, a platform for future European clinical and laboratory research into LRTI will be established.

**Role of ESCMID and ERS**

To ensure that disease management is based on best practice, new research findings should be rapidly translated into treatment recommendations. ESCMID and ERS are jointly responsible for organising the educational Work Package (WP12). Outputs will include workshops and postgraduate courses, together with web-based materials and e-learning resources aimed at clinicians and scientists in training and in practice. In order to improve antibiotic use in a sustainable manner, the educational resources will be developed to emphasise the acquisition of appropriate knowledge, skills and behaviour.

EUR 500'000 has been allocated to the educational programme which will be divided between the two Societies in proportion to their agreed commitments. The co-leaders of WP12 are Francesco Blasi (ERS) and Roger Finch (ESCMID). The first GRACE postgraduate courses will take place in Munich at the annual ERS Congress (2 September 2006) and at ECCMID/ICC (30/31 March 2007). The programme for the workshops is under development by the GRACE Curriculum and Education Committee, whose members include Javier Garau, Peter Schoch and Roger Finch for ESCMID, Patricia Haslam, Jean-Luc Eiselé and Francesco Blasi for ERS. The GRACE project is an historic milestone for both Societies.

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The Potential Therapeutic Role of Bacteriocins in Reducing Medical Device Infections

Research Report of a Trainee

The following report summarises work I carried out at the University of Otago in Dunedin, New Zealand whilst on a research visit between March and May this year.

Dunedin was not new to me as I had previously been lucky enough to carry out post-doctoral studies in Professor John Tagg’s laboratory where we looked at a peptide signalling system used to control bacteriocin production in oral streptococci. Since leaving John’s lab, I have developed an interest in bacterial biofilms and the regulatory circuits that control them. These systems also often involve peptide signalling molecules.

The aims of this return visit were to develop molecular systems that may aid detection of peptide signalling molecules involved in bacterial biofilm formation, and to investigate novel peptide inhibitors that may be active against biofilm forming staphylococci.

Infection is known to develop in a significant proportion of the millions of artificial joints, prosthetic heart valves, catheters, heart pacemakers and other medical devices fitted in the UK every year. The causative organisms, often coagulase-negative staphylococci, usually exist in the complex microbial communities we call biofilms and can resist virtually all methods used to remove them.

There have been numerous recent attempts to develop novel approaches to combat device-related infection. These include investigation of quorum sensing inhibitors, as many processes in biofilm formation have been shown to be regulated by these systems, and use of naturally produced antibacterial compounds. One particular group of antibacterial agents that may have potential in this respect are bacteriocins, peptides that usually have inhibitory activity against closely related organisms.

Recently, John Tagg’s group has developed a novel “induction assay” to detect the presence of peptide signalling molecules controlling bacteriocin production in the oral cavity. The approach has been used to demonstrate, for the first time, in vivo production of these signalling molecules in human saliva. The assay has promise for use in detection of other peptide signals, but requires some modification to increase the flexibility and sensitivity as it relies on a secondary, agar plate based assay for visualisation of the effect of any signal present in a sample.

The primary goal of my visit to Dunedin was to become familiar with this assay which should be useful in the search for peptides involved in biofilm formation. Once practiced in conducting the test, I was able to modify the induction assay, improving the sensitivity by the introduction of RT-PCR for detection of reporter gene activity. By looking at the expression of a reporter gene we have shown that use of the system may not be limited to detection of signals controlling bacteriocin production. We now plan to employ the assay in searches for peptide signalling molecules in biofilm assays with clinically relevant staphylococci from cases of prosthetic hip joint infection.

The second aspect of the work involved screening for inhibitory activity produced by staphylococcal strains recovered from John Tagg’s extensive strain collection. John’s lab has become established as leading the field of streptococcal bacteriocin isolation and characterisation and he has exploited one particular strain for use as an oral probiotic. However, inhibitors produced by, and active against, staphylococci have not been examined in great detail in Dunedin. These strains are particularly interesting to me due to their potential for use in combating the staphylococci that cause prosthetic joint infection. A number of strains, both coagulase-positive and negative, were selected on the basis of possible activity against staphylococci. Potential inhibitors were partially purified from two strains and the genetic determinants encoding their production identified using degenerate primer PCR, inverse PCR and DNA sequencing. Full characterisation of these bacteriocins is underway. Their utility as novel therapeutics is also being investigated in Manchester.

I wish to thank all of the lab members in Dunedin who helped make the work possible. Thanks are also due to the European Society of Clinical Microbiology and Infectious Diseases, the Society for General Microbiology and the Otago Dental Research Theme for assistance with funding.

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Trees and Fruits: Spoilt for Choice

Attending a conference as rich as the ECCMID is always a challenge: how does one manage to hear all one would like – and metabolise it usefully? Amongst such an embarrassment of riches, it is also to be expected that each participant’s choice of sessions will reflect his or her interests: whether following news in the field of one’s expertise, or expanding one’s horizons into new areas. The present writer is of course no exception.

The 16th ECCMID started, for me, with a session coupling microbial population biology with molecular epidemiology.

‘Trees’ of evolution and ‘trees’ of typed isolates: friends but not always relatives

Barry Hall (Bellingham, USA) explained the basics of constructing, and deriving meaningful information from, phylogenetic dendrograms: the ‘trees’ which present graphically the evolutionary relationships of different but equivalent taxa: genera, species, or strains. In this kind of trees, different but equivalent taxa: genera, species, or strains. In this kind of tree, there are more ambiguities as to the correct position of the nodes, and, based on the same data, different but equally valid, alternative tree ‘solutions’ can often be arrived at. Whilst there is no formal satisfactory definition about ‘correct’ clustering, therefore, larger datasets can correct for these weaknesses.

‘Fruits’ of evolution I: β-lactamases

Patrice Nordmann (Paris, FR) kicked off this session by stating that strictly human pathogens do not possess chromosomal β-lactamases; but environmental ones do for protection against naturally occurring β-lactam compounds. This explains why β-lactam resistance genes may be detected in river waters or populations unexposed to drugs, such as Amerindians. For human pathogens to acquire these enzymes, the mediation of various genetic vectors is required: insertion sequences and more complex transposons, integrons, plasmids, and phages. This great, vector-assisted genetic ‘promiscuity’ leads, on the one hand, to ‘genes without [species] frontiers’, such as TEM-1 and –2; and on the other hand, to species, such as P. aeruginosa and A. baumannii, that are good gene ‘receptors’. Gene exchange follows observably epidemiological links, even if these occasionally are not entirely straightforward. However, there are still genes whose origin remains unknown, for example, those of the TEM, IMP and VIM families.

The CTX-M family of enzymes, one of the most ‘successful’ in recent years, was first identified in human fecal flora in 1988 (Raphael Cantón, Madrid, ES). It is nowadays commonly encountered in both nosocomial and community infections with Enterobacteriaceae, and in the past five years, has become an ‘epidemic gene’ in areas where it was previously only sporadically seen. The corresponding genes have been ‘captured’ from the chromosomes of at least three Klyvera species, by insertion sequence ISecp1, various transposons – including the well known Tn21 and Tn3-, integrons, plasmids, and phage-related elements. They have found their way into many different phylogenetic groups of E. coli; are frequently associated with other drug resistance genes; and the CTX-M-15 variant also provides resistance to cefotaxime, contrary to the typical identifying characteristic of these ‘cefotaximases’. An increasingly wide variety of integrons – with class 1 remaining predominant – has been found associated with all classes of ESBL genes, amongst a wide spectrum of bacteria. In some cases, like for the blaus gene, it seems that a single integron capture has allowed subsequent diverging evolution of this gene’s ‘cassette’ to give rise to nine known variants. On the contrary, OXA-2 genes or the different VIM and IMP gene lineages, seem to have been introduced into integrons during several independent events. Eventually, integrons with multiple ESBL genes have also been formed.

Finally, the genes themselves had been evolving during their natural history, until they gave rise to ESBLs (Marek Gniadkowski, Warsaw, PL). Amongst Class A enzymes, TEM and SHV proteins have undergone a variety of structural and non-neutral modifications, to the extent that we now recognise approximately 150 TEM1/2 variants, and over 80 SHV1 variants, due to variation in approximately 50 naturally-occurring polymorphic sites in each case. In addition, in vitro experiments have allowed the construction of approximately 200 TEM mutants that retain catalytic activity.Seven amino acids, most of them within the active site, mutated with respect to the parent enzymes and have been shown to be critical for ESBL activity. The expanded substrate spectrum is achieved by conformational changes – such as enlargement of the substrate cavity to accommodate the larger ‘third generation’ cephalosporins, or disruption of the cavity’s ‘neck’. There is, nevertheless, a trade-off for this increased activity against cephalazidime and cefotaxime, since the efficiency against ampicillin goes down, though resistance is retained. Mutations outside of the active site can secure more efficient ‘catching’ of 3GCs, through enhanced affinity for these substrates, or stabilisation of the enzyme structure, once its active site has been mutated. This repertoire of equilibrating/modulating mutations with small trade-offs in both directions, is extremely adapted to an environment of fluctuating antibiotic pressure.
In addition to colonisation, survival in the bloodstream is also essential for disease. Of the 18 known genes needed for this, 17 are involved in the biosynthesis of capsule or LPS, which protect the bacterium from destruction by complement. Lactate permease, mediating intracellular entry of lactate, necessary for the synthesis of sialic acid in both LPS and capsule, was shown to be important, since permease-negative cells can survive in mice deficient in complement C3 convertase, but not wild-type mice. Indeed, immunisation of experimental animals with lactate permease was protective against *N. meningitidis*.

Another pathogen that follows an intracellular invasion pathway, *Shigella flexneri*, activates human gene expression in two successive ‘waves’ (Philippe Sansonetti, Paris, FR). By up-regulating the binding of human transcription factor NFkappaB to promoters of pro-inflammatory genes, it effectively stimulates the human cells themselves to receive it. Expression of IL-8 disrupts the epithelial barrier and facilitates bacterial entry, whilst antimicrobial peptide synthesis is simultaneously turned down. Therefore, blocking the inactivation by ubiquitination of NFkappaB’s inhibitor, IxB, can prevent translocation of NFkappaB to the nucleus, and has an observable anti-inflammatory effect – at least in human tissue culture cell lines. In this case, therefore, it is the modification of a host factor that may have a therapeutic effect.

### Revisiting an old controversy: relationships between antimicrobial drug resistance and virulence

This contentious problem was initially approached through the therapeutic needs against *Mycobacterium tuberculosis* (Stewart Cole, Paris, FR). The DOTS scheme for tuberculosis (combined administration of rifampin, isoniazid, ethambutol and pyrazinamide for at least six months), after achieving an initial fast killing of bacteria, often allows the persistence of slow-growing cells. Therefore, new drugs are needed, which would still be specific for *M. tuberculosis* and compatible with DOTS, but would preferably reduce therapy duration, and be active both against persistent and multi-drug resistant cells. At least four drugs are currently being tested, including newer fluoroquinolones.

All resistance mutations in mycobacteria are chromosomal; therefore good candidates for affecting overall fitness (defined as the ability to survive, reproduce in the host and be transmitted). Of two studied mutations conferring resistance to rifampin, only one affected fitness, and then only by 20%, whilst no such effects could be shown for resistance to ethambutol, pyrazinamide or fluoroquinolones. For isoniazid, even though a guinea pig model in the 1950s had shown that resistance does reduce fitness, major mutations in its target, KatG, have negligible effects, as confirmed by epidemiological studies – once again emphasising the difficulty of extrapolating, even from animal models, to the human situation.

Another node of resistance and fitness is represented by efflux pumps of *P. aeruginosa*: these molecules are both ubiquitous and redundant, but also instrumental in resistance, usually when de-repressed and over-expressed (Jose Luis Martinez, Madrid, ES). Since pump over-expression leads to a reduction in quorum sensing and type III secretion, virulence is simultaneously reduced. Nevertheless, this outwardly optimistic picture is complicated by the fact that MDR strains, though incapacitated for the more aggressive type of acute infection are, by the same token, better adapted for chronic infection.

Similarly, an epidemiological observation suggests that quinolone-resistant uropathogenic *E. coli* strains may be less able to cause invasive disease (Jordi Vila, Barcelona, ES). Whilst among cystitis strains, 20% are resistant, this drops to 8% amongst pyelonephritis and prostatitis strains. Resistance to nalidixic acid reduces fimbria expression, which in turn may hamper biofilm formation; less frequent loss of other functions encoded by the *E. coli* pathogenicity island are also observed. However, the directionality of interactions between virulence gene loss and quinolone resistance is still not entirely clear.

The opposite relationship is obtained for *Neisseria gonorrhoeae*, which possesses four known efflux pumps (William Shafer, Atlanta, US), under complex transcriptional regulation, and with functions including the efflux of antimicrobial peptides synthesised by human neutrophils. A single nucleotide mutation in the promoter of the transcriptional repressor of an efflux pump gene, mtr, can lead to penicillin resistance. An accumulation of five mutations can also lead to tetracycline and erythromycin resistance. Mtr mutants are not recovered as efficiently as wild type strains from a mouse model; conversely, Mtr over-producers outcompete the wild type in recovery.
assays, presumably due to their role in pumping out natural antimicrobial substances and/or in virulence.

...and a new approach to infectious diseases I: bacterial genomics’ impact on the epidemiology and control of infectious diseases

James Musser (Houston, USA) used S. pyogenes as an illustration. At the time of his talk, there were over 200 bacterial genomes fully sequenced, including 12 strains of S. pyogenes, which, among other things, yielded the observation of two to eight prophages per genome (some associated with virulence factors), and many proven or putative virulence factors. In the M3 strain, six prophages coded for one toxin each. The evolution of phage 315 from circa 1920 to 1985, and its association with different virulence factors of M3 strains, was reconstructed. Strep-tolysin A is deemed to have been critical for the recent hypervirulence and epidemic spread of M3 strains in 1992–2002, reaching two peaks in 1995 and 2000. Over that period, six distinct subclones have been defined: two present throughout, two specific to the 1995 peak, with another two specific to the 2000 peak. A more detailed comparison of clone 5 with its ‘ancestor’ clone 1, revealed 61 single nucleotide polymorphisms. One of these SNPs, in the gene encoding Fe- and Mn-acquisition protein MtsR, is thought to be associated with clone 5’s decreased ability to cause necrotising fasciitis.

Furthermore, genome analysis can nowadays be complemented by transcriptome analysis, which, for example, has revealed that some virulence genes are upregulated in invasive M1 strains, whilst fewer are expressed in pharyngitis M1 strains.

...a new approach to infectious diseases II: human and comparative genomics – susceptibility to infection

Amalio Telenti (Lausanne, CH) visited the ever more urgent interaction between basic research and social issues, as related to the susceptibility of humans to infection. The fact that a protective deletion in the gene for a co-receptor for HIV, CCR5, is present in ~5% of the human population is perhaps one of the most famous recent examples. Wider interactions of host genes and antiretroviral drugs are also apparent in, for example, the different extent of hyperlipidaemia, depending on both genotype and drug dosage. Today, none of the host genetic data are in clinical use, but the ‘HapMap’ project, a representation of common human genetic variations is under way: 500’000 SNPs per person will be assessed. This currently translates in USD 1’000’000 per 1000 people over two months. Clearly, there is room for improvement, and the data must be usefully integrated through bioinformatics – and, above all, in a well thought out and propitious legal environment.

A similar project specific to HIV encompasses 700 genes and 300’000 SNPs around the whole genome, testing exposed but non-infected individuals, as well as those that have converted to seronegativity. Overall, whole genome research requires perfect phenotyping and efficient genotyping of patients as well as and powerful analytical tools.

Comparative genomics offers another slant on the issue of host susceptibility: most primates ‘have’ their ‘own’ immunodeficiency viruses, which are sometimes exchanged and recombined between species. However, it seems that humans actually are the only ones that suffer from them. APOBEC3G is a protein which interferes with HIV replication, but whose activity can be compromised by the binding of HIV’s own Vif protein. A single aminoacid difference between the human and primate versions of APOBEC3G changes this protein’s affinity for Vif. Similarly, the human variants of TRIM5alpha, which are unsuccessful in controlling HIV, differ from those of all other primates, where this protein blocks viral entry into cells. Surprisingly, evolutionary genomics suggest that our own ancestral – circa 40’000’000 years ago – TRIM5alpha was as good as other primates’, indicating that that version was eventually lost.

Full circle to microbial typing: a tool for public health

The hepatitis C virus infects 3% of the worldwide population, approximately 170’000’000 people (Oliver G. Pybus, Oxford, UK). By sequencing viral strains from different periods, and comparing them in the light of models such as that of ‘coalescent theory’ – according to which lineages come closer when the population is smaller –, it is possible to infer this rapidly evolving virus phylogeny. Results indicate that endemic subtypes go back centuries and are at prevalence equilibrium, whilst epidemic subtypes date only to the 20th century and their population is still growing. In China, two clusters can be observed: one originating in the 1960’s, the heyday of the ‘cultural revolution’, and one in the 1980’s, which saw the advent of paid-for blood donations. Amongst HIV-seropositive men in the UK, seven clusters are spreading; some may be related to the mid 1990s resurgence of unsafe sex practices, related to the success of HAART.

Genotyping of measles virus strains is being used to monitor the elimination of disease worldwide, for which the WHO has set the year 2010 as its goal (Sabine Santibanez, Berlin, DE). For this however, a > 95% vaccine coverage is required, which has not even been reached in Europe. Amongst its 23 genotypes, four are endemic in Europe. Genotyping can also reveal the replacement of old types by new ones over time, as well as travel and importation of genotypes to and from distinct geographical regions.

Sara Haeggman (Solna, SE) described the design, practice and results of a na-
tional surveillance network for MRSA. Apart from useful epidemiological data, such a system allows an extremely valuable comparison of different typing methods for bacterial strains, 'on the battlefield', as it were: newer methods, such as spa-typing and MLST, are not necessarily better than the 'gold standard', PFGE, at drawing epidemiologically meaningful distinctions amongst isolates.

Finally, an illustration of molecular fingerprinting to manage outbreaks was illustrated by the use of RFLP typing of M. tuberculosis (Gerard de Vries, Rotterdam, NL). The system described was an excellent demonstration of collaboration between descriptive epidemiology and molecular typing, also including a well argued call for, and prudent use of, resources. Due to the nature of the disease, related cases can appear as late as three years after the index patient. Therefore, careful database-building can lead to some astonishing results: for example, though 'cluster 510' was mostly composed of homeless persons and/or drug users, the index case belonged to neither category. Amongst drug users, where 35 strains were known to circulate, a peak of 26 cases in 2003 led to the adoption of x-ray screening; cases have since dropped by half. Thus, DNA fingerprinting can reveal new and unrecognised transmission routes, as well as confirm old ones, and can be used to occasionally convince the authorities of very costly public health measures.

To end, I wish to apologise to all authors of oral and poster presentations, whose work I could not refer to, for reasons of both time at the conference, and space in this brief report. Accepting a personal bias, I would summarise the themes of this conference along four axes: the continuum, due to genetic exchange which is increasingly being revealed, amongst phages, bacteria, viruses, and humans; the intricate interplay amongst virulence, drug resistance and host susceptibility mechanisms; the steady improvement of techniques, not only at the molecular level, but also in more 'traditional' approaches; and the enhanced, 'added-value', collaboration amongst laboratory scientists, clinical doctors, veterinarians and epidemiologists.

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Statement on Infectious Diseases at G8 Summit

Twelve national science academies within the G8 countries and Brazil, China, India and South Africa have issued two unprecedented joint statements for submission to the G8 summit in Russia this July. The initiative was lead by the Royal Society (UK). One statement focussed on the global response to climate change. The other called on the G8 leaders to implement measures on a global scale to better combat avian influenza and other infectious diseases and to re-invent the world’s disease surveillance and response system.

The academies stated that a ‘global surveillance’ plan is essential to monitor, identify and report disease outbreaks and align international responses against global epidemics, but that the current system is too complex and poorly coordinated. It is e.g. unable to provide the geographic coverage required to monitor disease outbreak and spread, and lacks resources both in healthcare and scientific research.

“There is a pressing need for closely coordinated, international planning and surveillance to address the current threat of an influenza pandemic. It is also crucially important for the global community not to forget that, at present, avian influenza is not the most significant disease concern for people globally. It is other emerging diseases and existing infectious diseases such as tuberculosis, HIV/AIDS, and malaria which are causing widespread illness and severe economic harm to developing countries.

The ongoing fight against avian influenza is essential, and will hopefully act as a catalyst to improve the planning, monitoring and response to the threat of other global emerging or re-emerging diseases. Many of the issues relevant to avian influenza, such as improved monitoring of potential human and animal disease sources and human illness hotspots and planning for the production and distribution of adequate vaccines in the case of a pandemic, are applicable to number of diseases”(1).

The academies hoped, through this statement, to inform the discussions taking place at the G8 summit and to highlight the vital role science has in achieving progress on avian influenza and other infectious diseases. The submission by twelve academies met with success. On 16 July the G8 leaders published a comprehensive summit document (2) in which they expressed their determination to achieve tangible progress in the field of infectious diseases and committed considerable funds towards this goal. Among the issues mentioned were: the strengthening of the global network for surveillance and monitoring of infectious diseases; fighting avian influenza; increasing global preparedness for a human pandemic; combating HIV/AIDS, tuberculosis, malaria, polio, and measles; and better access to prevention, treatment and care, particularly in Africa.

The Editors

References
Highlights from 16th ECCMID in Nice

Interaction the Key to Success

- Opera singers at the Opening Ceremony
- Full house at a plenary lecture
- Food and small talk
- ESCMID Excellence Awardee
- Interested listeners
- Speaker making a point
- Messages in the exhibition hall
- Sharing data
- Recreational talks
- Discussion in front of posters
- A successful poster walker
- ESCMID booth = information booth
Results from the Opinion Poll

Following the trend of the last two years the 16th ECCMID 2006 in Nice had a very high turnout with over 6100 delegates attending the meeting. An opinion poll was conducted through the internet soon afterwards. Approximately 2200 delegates were asked by email to fill in a short online questionnaire about the Congress, 563 of which complied.

As in the past the first four questions in the Poll concerned the demography of participants, and the results indicated similar results to previous years. More details from these and other questions/answers can be called up from the ESCMID website (www.escmid.org), Information & Opinions, Opinion Poll.

ESCMID was happy to note that most respondents (about 80%) found the balance between basic science and practical aspects of Clinical Microbiology and Infectious Diseases good and felt they got the latest scientific information in their field (Table 1). The latter clearly shows an improvement over last year’s assessment whereby only 58% of the respondents found that the Programme met this expectation.

Still, many suggestions were made concerning improvements to the scientific programme. Some delegates felt that the industry had too much influence over the Programme. ESCMID is aware of this concern, and has hence revised the guidelines for industry-sponsored symposia to further increase the proper balance between science and marketing. As before, all industry-sponsored symposia must be approved by ESCMID and are clearly marked as such, so that delegates can distinguish industry-from official symposia. ESCMID believes that “biased” information in these sessions is exceptional and that in general the quality of the integrated (industry) symposia is high.

A number of comments were made about the poster sessions. Most reassuring was the opinion of more than 55% of the respondents that the quality of the poster sessions improved, while 44% recognised no change. Some respondents indicated that the poster area was too small and too crowded that there were too many posters for a certain time slot and that the assignment of posters to a given session was not always appropriate. About 70% of respondents supported a further slight or moderate increase in the abstract rejection rate. The feedback concerning poster walks was mixed: some supported more poster walks, others suggested abandoning them altogether for various reasons. Several comments were made about the absence of poster authors and even suggested penalties for absent presenters when submitting an abstract for a future ECCMID. These comments are well taken and will be considered when setting up future poster sessions.

For the first time at Nice the abstracts were published on CD and as an online CMI supplement only. The large majority (>72%) supported this decision of printing no abstract book. Criticism was received regarding the fact that the CD had to be picked up from a sponsor’s desk. We can assure you that at future ECCMIDs the poster CD will be included in the congress bag. In addition we will increase the number of computers to accommodate more electronic viewing of abstracts. We also recommend you to bring your own laptop to the Congress, not only to view the abstract and poster CD but also to go online since we will try to make wireless internet access available to all participants.

Some participants missed interesting sessions due to overlaps. In setting up the programme, we try to avoid the simultaneous scheduling of related topics. Given the size of the congress and the broad range of topics presented in up to 10 parallel sessions, an overlap of interesting symposia can, however, not be avoided. The choice offered at ECCMID is actually one of its strengths. It should not be given up by reducing the number of parallel sessions. But we are happy to report that from 2008 on we will be able to make available all or selected presentations given at ECCMID to the participants on DVD or through the Internet.

This year the congress centre capacity was stretched to its limits. Some congress participants reported being denied entrance to lecture halls as well as overcrowding at the poster sessions and at the exhibition. Some participants also needed to be housed some distance from the congress centre. These comments are taken to heart and will be considered in selecting future congress venues and in planning the layout of the congresses.

It is impossible to cover all your many valuable comments in this overview. The ESCMID Executive Committee, including the ECCMID Programme Director and the Managing Director, have carefully reviewed all of them and will do their best to further improve our annual congress by taking them into consideration. Please check us by attending the 17th ECCMID / 25th ICC, 31 March – 3 April 2007 in Munich. You are very welcome! If you have additional ideas for improving the Congress you would like to share with us, please feel free to let us know.

Peter Schoch
ESCMID Managing Director

Table 1

Did the scientific programme meet your expectations of getting the latest scientific information in your field?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>yes</td>
<td>450</td>
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<td>no</td>
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</tr>
<tr>
<td>partially</td>
<td>88</td>
</tr>
</tbody>
</table>
ESCMID European Council 2006

Minutes

Meeting during the 16th ECCMID 2006, Nice, on 1 April 2006 at 15:00 h

1 ESCMID progress report

Ragnar Norrby, ESCMID President, welcomed the 17 participants to the first meeting of the European Council in its new composition. The purpose of the newly formed body, which consists of representatives from the societies affiliated with ESCMID, is to foster discussion and interaction between European specialist societies and to provide input to the ESCMID Executive.

Ragnar Norrby gave a brief account of the Society’s main achievements during the past year.

ESCMID

Our society has currently some 3100 individual members. The Executive Office in Basel is hiring new staff to support and expand the Society’s activities in the field of education, scientific activities, professional affairs and public relations. ESCMID’s financial situation is healthy due to successful ECCMIDs and effective cost management.

Science

ESCMID is getting increasing attention from the European Commission and others due to its very active Study Groups. Another major success is EUCAST: Europe has now a working system for setting susceptibility breakpoints for old and new antibiotics. Clinical Microbiology and Infection, our journal, is developing well and each year achieves a higher impact factor. A positive sign was the acceptance of ESCMID by the European Commission as an independent specialty separate from Medical Biopathology in UEMS. The current Commission of ESCMID is engaged in a number of collaborative projects with other societies:
- FEMS: annual jointly-organised scientific conferences
- ISC: joint 17th ECCMID and 25th ICC, 31 March – 3 April 2007, in Munich
- ERS: educational platform of GRACE
- SHEA: annual courses in hospital epidemiology.

Education

In the past year the educational programme again comprised a very successful Summer School in Szeged, Hungary, several 2-3-day postgraduate courses as well as a number of short educational workshops arranged as pre-ECCMID events. In addition, ESCMID is responsible with ERS for the educational platform of GRACE, a DG Research Network of Excellence in the field of community-acquired lower respiratory tract infections.

Professional Affairs

ESCMID has been closely collaborating with UEMS for the development of training curricula and CME accreditation in our specialty fields. We also supported the proposal to establish Clinical Microbiology as an independent specialty separate from Medical Biopathology in UEMS. In addition, there is an increasing engagement in the development of practice guidelines, e.g. Guidelines for the Management of Adult Lower Respiratory Tract Infections, developed with ERS.

EU Relations

ESCMID is represented in the ECDC Advisory Forum through Prof Elisabeth Nagy. In addition to GRACE and EUCAST (see above), ESCMID is also involved in IPSE (Improving Patient Safety in Europe), a public health action programme supported by DG SANC. There is an increasing use of the expertise in our study groups by ECDC, e.g. the ESCMID Study Group on Clostridium difficile. EUCAST maintains a fruitful cooperation with EMEA in the field of susceptibility breakpoint determination.

Cooperation

ESCMID is engaged in a number of collaborative projects with other societies:
- FEMS: annual jointly-organised scientific conferences
- ISC: joint 17th ECCMID and 25th ICC, 31 March – 3 April 2007, in Munich
- ERS: educational platform of GRACE
- SHEA: annual courses in hospital epidemiology.

2 Update on the affiliation process

Patrick Francioli, Secretary General, gave a brief overview of the affiliation process: up to now 37 specialist societies have signed an affiliation agreement with ESCMID. This is encouraging since most European countries are now represented in the European Council. Still, there is more to do since the estimated potential is about 60 societies with some 20’000 members. Recent experience showed that we will have to set up eligibility criteria for affiliation candidates based on their Statutes, democratic control, objectives and representation. Part of the affiliation concept is the dissemination of ESCMID Online News through the headquarters of the affiliated societies. Unfortunately, a relatively large number of our affiliates are still unable to forward this electronic newsletter to their members. Patrick Francioli invited the national societies to make more frequent use of ESCMID News for the discussion of issues or dissemination of information which are of general interest to the European professional community. Contributions of interest to our members are welcome!

3a European professional affairs, Clinical Microbiology

Elisabeth Nagy, Professional Affairs Officer for Clinical Microbiology, first referred to the second, still ongoing pan-European survey of the professional situation and clinical practice in Clinical Microbiology and Infectious Diseases. The return and evaluation of the questionnaires is not yet complete; the results will be published in ESCMID News.

An important result of the survey, however, is the finding that Clinical Microbiology is a recognised specialty in almost 70% of the European countries. This implies a curriculum and an examination after training. The Microbiology Commission of UEMS has recently approved a core curriculum in Clinical Microbiology, devoid of clinical chemistry and haematology, but still lacking epidemiology and hospital hygiene. Elisabeth Nagy concurred with the proponents of promoting the establishment of an independent Section of Clinical Microbiology in UEMS since this would much better reflect the situation in Europe and broaden the representation of the specialty in UEMS. The current Commission of Microbiology, which is part of the UEMS Section of Medical Biopathology, is simply not representative of the specialty in Europe. Guis Ruijs, the Netherlands, suggested that ESCMID coordinates the activities towards the goal of creating an independent Section within UEMS. Elisabeth Nagy reminded the audience of the UEMS procedures for forming a new section: the formation must be proposed by a National Association, which is Member of UEMS and ap-
proved by two thirds of the voting members of the UEMS Council. ESCMID cannot take part in this formal process. But she agreed to arrange a meeting during ECCMID in Nice among those participants interested in taking action, to discuss the scenarios and develop a plan.

3b European professional affairs, Infectious Diseases

Robert Read first defined his role as Professional Affairs Officer for Infectious Diseases:

i) As formal representative/observer of ESCMID in the UEMS Section of Infectious Diseases he has responsibility in the field of professional training (curriculum development), accreditation, qualification and registration.

ii) As member of EBAID, which is jointly run by the UEMS Section of Infectious Diseases and ESCMID, he is also involved in the accreditation of CME.

iii) Plans are being made for an electronic platform for the facilitation of exchange visits between centres for trainees in Clinical Microbiology and Infectious Diseases.

iv) ESCMID plans to become more active in developing medical practice guidelines and standards of care.

Questions from the floor:

1 Winfried Kern, Germany, asked about the costs of guidelines development: who will pay? Ragnar Norrby answered that the costs will be borne by ESCMID. If no salaries have to be paid costs will not be very high.

2 Giorgio Palu, Italy, was interested in who is entitled to propose the development of specific guidelines. Robert Read answered that anyone, an individual ESCMID member or an affiliated society, can come up with a proposal. Next question: would ESCMID also review and approve existing national guidelines? According to Robert Read this might be very well possible.

4 Any other issues

Ragnar Norrby expressed his concern that in some countries Infectious Diseases is losing specialists to Paediatrics. We should liaise with ESPID to discuss the situation.

Ragnar Norrby thanked the participants for their participation and adjourned the meeting at 16:30 h.

Basel, 28 July 2006

Signed,

S. Ragnar Norrby
President

Patrick Francioli
Secretary General

Peter Schoch
Managing Director

Review of the 5th ESCMID Summer School 2006 in Santander, Spain

The 5th ESCMID Summer School was held in Santander, Spain, from 10–16 June 2006. It was organised by the ESCMID Education Committee under the auspices of the University of Cantabria and the University Hospital Marqués de Valdecilla, Santander, where the scientific sessions took place.

To attract as many participants as possible the ESCMID Education Committee reduced the tuition fee substantially in comparison to previous School editions: registration was EUR 600 and EUR 650 for ESCMID members and non-members, respectively, and covered the scientific programme, accommodation, breakfast, lunch, wireless internet access and social events during the entire week. The approach met with success: a total of 50 participants registered from 18 countries with previous training in Clinical Microbiology or Infectious Diseases. They were from Albania (1), Belgium (1), Georgia (1), Greece (2), Hong Kong (1), Hungary (1), Italy (1), Macedonia (1), Netherlands (2), Norway (1), Pakistan (1), Portugal (3), Saudi Arabia (1), Slovenia (3), Spain (24), Sweden (1), Taiwan (1), Turkey (2), Ukraine (1) and USA (1).

The School, as in its previous editions, covered five major chapters:

– emerging antimicrobial resistance;
– microorganisms and infection pathogenesis;
– diagnostic and management strategies of major clinical syndromes;
– immunocompromised hosts; and
– epidemiology, infection control, vaccines, and public health.

These topics were dealt with by experts giving plenary lectures in the morning, each followed by a question and answer session.

The faculty for the plenary talks included:

– R. Cantón, Madrid, ES: Clinical implications of PK/PD, and Antimicrobial consumption and impact on resistance
– F. García-del Portillo, Madrid, ES: Type III secretion systems
The afternoon programme consisted of case presentations by individual participants and discussions of selected case studies in groups of 9–10 students led by an experienced facilitator. School attendees had been asked to submit a case (not exceeding 2500 characters) from their professional experience for potential presentation during a plenary session. Cases were selected by the Faculty of the School based primarily upon their educational relevance for the whole group. A total of 20 cases, four per day, were presented and discussed.

In addition, the facilitators J. P. Horcajada, G. Peralta, J. Rodríguez-Baño, G. Schmid, and A. Schwenk, had also prepared illustrative cases with particular educational value and discussed them in small tutorial groups. These were highly interactive sessions with plenty of exchange between facilitators and students.

The social events included a welcome dinner, an excursion to the Altamira cave with its famous prehistoric paintings, followed by a visit to the medieval village Santillana del Mar with official dinner in the Parador, and as the final activity of the School, a boat trip to the Santander Bay.

ESCMID has supported seven students by providing them a grant covering the full tuition fee. The financial support to the School from Merck Sharp and Dohme Spain, Pfizer Spain, Gilead Spain, Wyeth Spain and the Institute for Education and Research Marques de Valdecilla is also gratefully acknowledged.

In addition to the direct educative value, another notable result of the School was the ease of establishing scientific and personal relationships among the students and the faculty from so many different countries. During this week participants got in touch with many groups involved in Clinical Microbiology and Infectious Diseases and could thus build professional networking contacts which may prove important to their future careers.

Participants have expressed a high level of satisfaction with the School, as indicated in an evaluation questionnaire anonymously filled out by all students. The European Board for the Accreditation of CME in Clinical Microbiology (EBACM) has evaluated the programme and faculty of the School and granted 35 European CME credits.

Luis Martínez Martínez
Director of the 5th ESCMID School
Member of the ESCMID Education Committee
Course Report

Detection and Characterisation of Metallo-beta-lactamases

The ESCMID Study Group on Antimicrobial Resistance Surveillance (ESGARS) organised the 36th ESCMID Postgraduate Course on metallo-beta-lactamases, held in Verona, Italy, on 26–28 May, which followed a workshop on the same topic held in Siena, Italy, at the “Certosa di Pontignano”, in November 2005.

A concise expert meeting followed by a postgraduate course seemed to be a timely and effective way of reviewing the present knowledge, discussing open issues, and trying to develop a continental strategy for surveillance and control of these resistance determinants by reinforcing and relating to one another the existing activities set forth by individual efforts, scientific societies, EU-driven networks and similar academic-based projects.

The rationale for these ESGARS initiatives was the rapid spread of metallo-beta-lactamases (MBLs), their increasing diversity and the number of species involved – having recently included some species so far endowed with lower levels of antibiotic resistance. This does not seem to be paralleled by accuracy/standardisation of detection methods, completeness of epidemiological knowledge, and clear understanding of what MBLs entail in terms of hospital infection control and therapy.

This is a matter of concern mostly in Europe, where the greatest proportion of MBLs have been isolated from either individual strains or nosocomial outbreaks, and should elicit a prompt reaction from all those involved in this field, especially in the most affected countries.

The course attendance was limited to approximately 25 participants, the large part of which were granted free tuition from ESCMID.

The programme mainly consisted of interactive sessions and tutorials; formal lectures were kept to a minimum. Since this is one of the fields in which a newer generation of scientists is rapidly emerging in Europe, the faculty mainly consisted of young scientists, many of which had attended previous ESCMID Postgraduate Courses on related topics.

The course dealt with how to effectively detect MBLs in routine testing and how to report their presence to clinicians, and gave the participants basic and integrated elements for understanding the nature of these enzymes, as well as both basic and advanced technical skills for correct identification and reporting. Above all, the course represented a splendid occasion for meeting and establishing sound networks for the future.

Jean-Denis Docquier and Raffaella Koncan
On behalf of ESGARS
ESCMID Awards and Fellowships 2007

ESCMID Award for Excellence in Clinical Microbiology and Infectious Diseases

The European Society of Clinical Microbiology and Infectious Diseases will present the ESCMID Award for Excellence in Clinical Microbiology and Infectious Diseases in the year 2007 to honour a senior scientist for his/her overall achievements in these fields.

Purpose
The purpose of this award is to recognise and reward an outstanding lifetime contribution in the areas of science, education or professional affairs in Clinical Microbiology and/or Infectious Diseases.

Award
The award of EUR 10'000 will be presented by the president of ESCMID at the 17th ECCMID/25th ICC 2007 in Munich. The recipient will be honoured at the occasion of a 45-minute lecture to be given by the awardee. The name of the recipient will be published in the Final Programme, ESCMID News and on ESCMID’s website.

Eligibility criteria
Nominees for the award must be senior scientists who are professionally active and retired from office at least 2 years after resigning from office. Nominees for the award should be born on 1 January 1942 or after. The names of the recipients will be published in the Final Programme, ESCMID News and on ESCMID’s website.

ESCMID Young Investigator Award for Research in Clinical Microbiology and Infectious Diseases

The European Society of Clinical Microbiology and Infectious Diseases will sponsor up to two ESCMID Young Investigator Awards for Research in Clinical Microbiology and Infectious Diseases in 2007 to recognise outstanding research by younger colleagues in these fields.

Purpose
The purpose of these awards is to acknowledge excellence in research, and to stimulate further research of the highest scientific level.

Awards
The awards of EUR 7500 each, which should be used to support further research, prepared to give a 45-minute plenary lecture in their field of research during the 17th ECCMID/25th ICC. Members of the ESCMID Executive Committee are ineligible for at least 2 years after resigning from office.

Nomination procedure
All medical schools and institutions active in the fields of Clinical Microbiology and Infectious Diseases in Europe, ESCMID’s affiliated societies, ESCMID members as well as ESCMID committees and study groups are asked to nominate candidates for the award. Each nomination should include:
1. A biographical sketch of the nominee (maximum two pages, plus an abstract of 150 words)
2. A summary and analysis of the nominee’s major contributions to research in the fields of Clinical Microbiology and/or Infectious Diseases
3. A list of the major original publications in refereed journals
4. The complete postal and e-mail address, phone and fax number, and a colour photograph of the nominee (on paper or electronic)
5. In addition, two letters of support from individuals outside the nominating institution should be mailed directly or together with the nomination to the ESCMID Award Committee.

Selection procedure
The recipient of the award will be asked for a manuscript on the research field to which she/he mostly contributed for publication in CMI.

Nomination procedure
Nominations must be received no later than 15 October 2006. They must be submitted in writing together with proof of the nominee’s age, and include a CV, a complete list of publications as well as up to five original papers published in 2004, 2005 or 2006 or accepted for publication. The nominations should describe the candidate, his/her career, his/her research interests and personal contributions to the various research projects, in which he or she has been participating. At least two
ESCMID Research Fellowships

The European Society of Clinical Microbiology and Infectious Diseases will sponsor the ESCMID Research Fellowships to support further research of young Society members in the fields of Clinical Microbiology and/or Infectious Diseases.

Eligibility criteria
Awards will be made on the basis of a detailed research plan to be part of the application. Eligible individuals must be ESCMID members. They should be born after 1 January 1967 and not be more than five years beyond their training as post-doctoral students or fellows. Appropriate research may be based on laboratory investigations, clinical studies, experimental animal studies, or a combination thereof. Research must be carried out in a European research laboratory or department. If there are collaborators, applicants must make clear their personal role in planning, undertaking and supporting the planned project. Members of the ESCMID Executive Committee are ineligible.

Application procedure
The deadline for submission is 15 October 2006. Applications must be submitted in writing together with a CV, a list of publications, and two supporting letters, including a specific description of the applicant’s present research and a detailed research plan. Applicants must include their complete postal and e-mail address and telephone and fax numbers and send seven copies of all materials plus one colour photograph (on paper or electronic) to the ESCMID Awards Committee, who will select the fellows. Applicants will be notified of the decision by 28 February 2007 at the latest. No correspondence beyond that necessary for the application will be accepted.

ESCMID and bioMérieux Award for Advances in Clinical Microbiology

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) is pleased to announce an award of EUR 10'000 sponsored by bioMérieux to recognise excellence and/or major contributions to the development of clinical microbiology by young scientists from East Central and Eastern Europe.

The award expresses the shared mission of ESCMID and bioMérieux to advance laboratory practice of clinical and diagnostic microbiology across Europe.

Application
Nominations of central and eastern European scientists born in 1967 or later must be submitted in writing. They must contain a description of the nominee’s career, his/her postal and email address, place and date of birth, list of publications, research interests and major contributions to the development of clinical microbiology. Two supporting letters from outside the nominating institution must be included. Self-applications will not be considered. Seven copies of all materials, plus one colour photograph (on paper or electronic) must be sent to the ESCMID Awards Committee.

The selection of the recipient will be made by the ESCMID Awards Committee. Members of the ESCMID Executive Committee are ineligible. No correspondence beyond that necessary for the application will be accepted.

The deadline for submission is 15 October 2006. The recipient of the Award will be notified of the decision by 28 February 2007 at the latest. The Award will be presented at the 17th ECCMID/25th ICC 2007 in Munich.

Please send your application to:
ESCMID Executive Office
P.O. Box 6, Clarostrasse 57
CH-4005 Basel, Switzerland
Phone +41 61 686 77 99
Email peter.schoch@escmid.org
Spreading of Antibiotic Resistance by Gene-Manipulated Plants?

The question, as to whether products of genetically modified crops – from the artichoke to the zucchini – present a health risk, is debatable. While the representatives from industry enthusiastically portray the advantages of the new generation of plants for the farming industry and the consumer – greater yields, longer storage life, standardised characteristic taste and texture – environmental protection agencies, scientists and consumers see a number of health risks. An especially relevant criticism is the fear that antibiotic resistance genes from gene-manipulated plants will be released to the environment and be absorbed by potentially pathogenic microorganisms, which themselves could pose a health threat for humans.

Back in the mid-90’s the UK Advisory Committee for Novel Food and Processes of the British government recognised a health hazard in Novartis’ plan to cultivate transgenic Bt 176 corn with an ampicillin-resistance gene and voted against approval of the plant through the EU. However, the Scientific Committee on Food of the EU Commission did not agree and in 1998 allowed the sale of plants with different antibiotic resistance genes, such as the npt II gene, which carries resistance to kanamycin, neomycin and paromomycin.

Since then, the question has been raised as to whether the large-area cultivation of, for example, gene-manipulated corn leads to ‘polluting’ the environment with gene sequences that encode resistance against certain antibiotics. This could theoretically result in environmental bacteria taking up these genes in their genetic make-up. With this horizontal gene transfer, microorganisms would develop, which are possibly resistant to a number of antibiotics in use today. Since according to current knowledge the geographical spreading of antibiotic resistances for the most part is an ecological problem and is determined by the existence of different environmental resistance reservoirs, the emergence of resistant pathogenic microorganisms in the agriculturally-used areas surrounding habitations could in the long run become a serious infectious disease problem.

The existence of antibiotic resistance genes in transgenic plants is directly linked to the technique of producing such plants (see box below). Currently seven different infectious-relevant DNA sequences are being integrated into transgenic plants, which among others encode resistance to such important antibiotics as ampicillin, tetracycline and amikacin (Table 1).

The fact that an artificial agricultural plant contains an antibiotic resistance marker gene is not, however, proof of a potential health hazard. In order for a health risk to develop, a number of conditions must be fulfilled. First of all, after lysis of the plant cell, DNA sequences must remain intact, which contain at least the entire antibiotic-resistance gene. Secondly, DNA fragments of adequate size must meet up with microorganisms that are principally capable of integrating foreign (plant) DNA in their genome (currently about 50 species are known). Subsequently, the DNA must be taken up and integrated into the genome. And finally, the antibiotic resistance gene must also be expressed, so that it can carry out its function. Only when all steps in this chain of events take place can a health risk be assumed.

It is indisputable that the DNA of a plant cell is released to the environment after its lysis. Although the majority of the DNA is destroyed by nucleases of the plant itself or nucleases from microbes existing in the environment, as well as by mechanical friction, regular intact DNA sequences – also those with an open-reading frame the size of an antibiotic resistance gene – are to be found in the soil and water. These DNA sequences also persist long enough to make contact with receptive bacteria possible.

The same applies to orally-applied DNA. In mice that were fed with plasmid and bacteriophage DNA, approximately 4% of the applied DNA was excreted in the faeces in the form of fragments of up to 100,000 base pairs. Systematic studies with humans do not exist. Interesting is the observance that with ileostomised patients, substantial amounts of a deliberately applied transgene (the epsps gene) could be identified with help of PCR, but not in subjects with a normal intestine.

However, so far no study has yielded convincing evidence that intestinal or soil bacteria actually take up antibiotic-resistance genes from transgenic plants. This possibly relates to the fact that antibiotic resistance markers represent only a very small part of plant DNA that is available in the environment for a possible transformation of bacteria, and that there is competition between the absorption of plant DNA and the DNA from locally-existing dead bacteria.

In order for the absorbed gene to carry out its function, the corresponding DNA fragment must be integrated into the chromosome of the bacterial cell or a resident plasmid. So far it could not be verified that this happens with antibiotic resistance genes that are released from plants. Ultimately, the expression of the antibiotic resistance gene associated with a specific plant promoter requires that the gene is put under the control of a bacterial promoter during insertion. Whether and how often this happens is unknown.

There is no data from field studies with different types of genetically manipulated plants and differing soil and climate, in which the path of a defined resistance gene has been followed from the laboratory via soil and water to the environmental bacteria. The studies performed up until
now were only concerned with individual steps of the microbiological chain of events. Nevertheless, Philippe B. Gan and Stephen H. Gillespie, microbiologists at University College in London, come to the conclusion by the combination of partial probabilities that the health threat from the cultivation of genetically manipulated plants is negligible. The current moving force in the global spread of antibiotic resistance, according to both microbiologists, is still the non-critical prescribing of antibiotics and the mass use of these substances in animal farming and in agriculture (streptomycin, for example, is used as a pesticide in the USA).

The European Food Safety Authority (EFSA) sees the problem as more sophisticated. The EFSA recently performed an evaluation of possible health hazards by antibiotic resistance genes and recommends the classification into three categories (Table 1). The Scientific Panel on Genetically Modified Organisms comes to the conclusion that the npt II gene presents no health risk whatsoever. This gene is naturally found in numerous bacteria that are present in the environment and colonise the human intestine.

However, the picture is different for antibiotic resistance genes, which the EFSA groups into Category II. These gene sequences encode enzymes, which inactivate antibiotics such as ampicillin, streptomycin and chloramphenicol. They are considered to be potentially hazardous, and plants with these marker genes should be cultivated in open land only for research purposes and should not be marketed.

The cell culture of genetically modified plants of the third category is allowed only under strictly controlled conditions in the laboratory. Genes resistant to tetracycline and amikacin belong to this group. These antibiotics are essential to infection medicine. Joachim Schiemann of the Institute for Plant Virology, Microbiology and Biological Security of the Biological Federal Agency for Agriculture and Forestry (BBA) in Braunschweig also shares this view.

“According to all that we know,” says the expert for biological safety, “the npt II resistance gene presents no health risks for humans”.

The United States, where the cultivation of genetically modified plants has been common practice for years, does not, however, adhere to the European recommendations and regulations. Since American farmers use antibiotics in livestock and agriculture on a grand scale, the risk for a health-endangering gene transfer is markedly higher there than in Europe.

Actually, antibiotic resistance genes are in the meantime as needless as a hole in the head and need not be integrated into transgenic plants anymore to select successful transfections. After all, there already are efficient alternative techniques for distinguishing transformed plants from those seedlings, in which the gene transfer did not work out. Hermann Feldmeier Charité University Medicine Berlin hermann.feldmeier@charite.de

Table 1

<table>
<thead>
<tr>
<th>Name of gene</th>
<th>Resistance encoded against</th>
<th>Therapeutic importance of antibiotic in humans</th>
<th>Occurrence of resistance in nature</th>
<th>EFSA category</th>
<th>EFSA conclusion</th>
</tr>
</thead>
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<tr>
<td>NptII</td>
<td>neomycin, kanamycin, paromomycin</td>
<td>topical application for skin, eye, ear infections; preoperative prophylaxis in digestive surgery</td>
<td>ubiquitous</td>
<td>I</td>
<td>no impact on human health, engineered plants can be commercialised</td>
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<td></td>
<td>geneticin</td>
<td>none</td>
<td>unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hph</td>
<td>hygromycin</td>
<td>none</td>
<td>unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CmR</td>
<td>chloramphenicol</td>
<td>only specific indications (eye, ear, skin infections; purulent meningitis); particularly used in developing countries</td>
<td>widespread</td>
<td>II</td>
<td>impact on human health cannot be excluded; plants with these resistance genes should be restricted to field trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(eye, ear, skin infections; purulent meningitis); particularly used in developing countries</td>
<td>widespread in domestic animals</td>
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<td></td>
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<tr>
<td>ampR</td>
<td>ampicillin</td>
<td>many indications</td>
<td>widespread in domestic animals</td>
<td></td>
<td></td>
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<tr>
<td>AadA</td>
<td>streptomycin, spectinomycin</td>
<td>only specific indications (gonorrhoea, tuberculosis, brucellosis), particularly used in developing countries</td>
<td>rare, mostly in areas where used as pesticide</td>
<td></td>
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</tr>
<tr>
<td>nptIII</td>
<td>amikacin</td>
<td>important reserve antibiotic</td>
<td>unknown</td>
<td>III</td>
<td>considerable safety concerns; plants with these resistance genes should only be cultivated in the laboratory</td>
</tr>
<tr>
<td>tetA</td>
<td>tetracyclines</td>
<td>many indications</td>
<td>widespread</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Scientific Panel on genetically modified organisms of the European Food Safety Authority, The EFSA Journal 2004; 48: 1–18
What’s New in Infectious Diseases?

General Clinical Interest

Disease versus disease: how one disease may ameliorate another

In this interesting article Stiehm explores the effect of systemic disease, either genetic or acquired, on the incidence or severity of another disease and concludes that additional exploration of these genetic, infectious, and metabolic influences on disease severity may provide new therapeutic approaches to HIV and other diseases. The best-known examples are Edward Jenner’s use in 1798 of cowpox to prevent smallpox and J.B. Haldean’s 1942 observation that erythrocyte disorders such as thalassaemia and sickle cell disease modify the severity of malaria. Patients with and carriers of cystic fibrosis may have genetic resistance to tuberculosis and/ or secretory diarrhoea. The beneficial effects of undernutrition have led to therapeutic diets for seizures, celiac disease, type 2 diabetes, and inflammatory bowel disease. Finasteride for prostatic hypertrophy was developed after the observation that patients with male pseudohermaphroditism resulting from 5-alpha-reductase mutations do not develop prostatic hypertrophy. Rh immunoglobulin for Rh haemolytic disease prevention followed the observation that ABO incompatibility prevented Rh sensitisation. The natural immunosuppression of measles may cause remission of nephrosis, and that of leprosy prevents psoriasis. Patients with one form of agammaglobulinemia (X-linked) never get Epstein-Barr virus infection, and patients with another form (common variable) are seemingly cured by HIV infection. HIV/AIDS is prevented or modified by co-receptor mutations (notably the CCRDelta32 chemokine mutation), HIV-2, or GB virus C infection.

Stiehm ER. Disease versus disease: how one disease may ameliorate another. Pediatrics 2006;117(1):184–91

Evidence for louse-transmitted diseases in soldiers of Napoleon’s Grand Army in Vilnius

During recent excavations of a mass grave of Napoleon’s soldiers in Vilnius, Lithuania, Raoult et al. grasped the opportunity to investigate the possibility that many soldiers in Napoleon’s Grand Army died of infectious diseases during its retreat from Russia. Segments of 5 body lice, identified morphologically and by PCR and sequencing, were found in earth from the grave that also contained fragments of soldiers’ uniforms. DNA of Bartonella quintana (the agent of trench fever) was identified in 3 of the lice. Similarly, dental pulp from the remains of 35 soldiers revealed DNA of B. quintana in 7 soldiers and DNA of Rickettsia prowazekii (the agent of epidemic typhus) in 3 other soldiers. The authors concluded that louse-borne infectious diseases affected nearly one-third of Napoleon’s soldiers buried in Vilnius and indicate that these diseases might have been a major factor in the French retreat from Russia.


Clinical perspectives of emerging pathogens in bleeding disorders

As a result of immunological and nucleic-acid screening of plasma donations for transfusion-transmissible viruses, and the incorporation of viral reduction processes during plasma fractionation, coagulation-factor concentrates (CFC) are now judged safe in terms of many known infectious agents, including hepatitis B and C viruses, HIV, and human T-cell lymphotropic virus. However, emerging pathogens could pose future threats, particularly those with blood-borne stages that are resistant to viral-inactivation steps in the manufacturing process, such as non-lipid-coated viruses. This review by Ludlam et al. concludes that despite progress in understanding pathophysiology of infectious diseases, the processes of zoonotic transmission and genetic selection or modification warrant that plasma-derived products will continue to be subject to infectious concerns. Manufacturers of plasma-derived CFC have addressed the issue of emerging infectious agents by developing recombinant products that limit the need for human plasma during production.


Statins reduce risk of sepsis

Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are potent lipid-lowering agents but also have anti-inflammatory, immunomodulatory, antioxidant, antithrombotic, and endothelium-stabilising properties. Recent animal studies have suggested that statins might also prevent sepsis, however the relationship between statins and risk of sepsis in patients with atherosclerosis is unknown. Hackam et al. report a population-based cohort analysis of 141,487 patients older than 65 years who had been hospitalised for an acute coronary syndrome, ischaemic stroke, or revascularisation. They found that the incidence of sepsis was lower in patients receiving statins than in controls even when adjustments were made for demographic characteristics, sepsis risk factors, comorbidities, and health-care use (hazard ratio [HR] 0.81; 95% CI 0.72–0.90). The protective association between statins and sepsis persisted in high-risk subgroups, including patients with diabetes mellitus, chronic renal failure, or a history of infections. No benefit was noted with non-statin lipid-lowering agents (HR 0.95; 0.75–1.22). The authors conclude that statins in patients with atherosclerosis reduced the risk of subsequent sepsis, and that randomised trials of statins for prevention of sepsis are warranted.


Sepsis in European ICUs: results of the SOAP study

In this cohort, multi-center, observational study, 198 intensive care units in 24 European countries were utilised by Vincent et al. in order to better define the incidence of sepsis and the characteristics of critically-ill patients in European ICUs. The study included all new adult admissions to the participating ICUs between 1–15 May 2002. Of 3’147 adult patients, with a median age of 64 years, 1’177 (37.4%) had sepsis; 777 (24.7%) on admission. The lung was the most common site of infection (68%), followed by the abdomen (22%). Cultures were positive in 60% of the patients with sepsis, the most
common organisms being *Staphylococcus aureus* (30%, including 14% methicillin-resistant), *Pseudomonas* species (14%), and *Escherichia coli* (13%). *Pseudomonas* species was the only microorganism independently associated with increased mortality rates. Patients with sepsis had more severe organ dysfunction, longer ICU and hospital lengths of stay, and higher mortality rate than patients without sepsis. In patients with sepsis, age, positive fluid balance, septic shock, cancer, and medical admission were the important prognostic variables for ICU mortality. There was considerable variation between countries, with a strong correlation between the frequency of sepsis and the ICU mortality rates in each of these countries. In addition to age, a positive fluid balance was among the strongest prognostic factors for death. Patients with ICU-acquired sepsis had a worse outcome despite similar severity scores on ICU admission.


### Bacterial Infections

**Clarithromycin resistance and failure of eradication of *H. pylori***

Three point mutations (A2143G, A2142G, and A2142C) have been shown to cause clarithromycin resistance in *Helicobacter pylori*. De Francesco et al. report a comparison of the eradication rates achieved when different point mutations are present, and the efficacy of triple therapy and a sequential regimen according to genotypic resistance.

156 patients with *H. pylori* infection were studied and real-time polymerase chain reaction used to assess clarithromycin resistance. 75 patients were given a 7-day triple therapy (20mg of rabeprazole, 500mg of clarithromycin, and 1g of amoxicillin), 81 were given a 10-day sequential regimen (20mg of rabeprazole plus 1g of amoxicillin for 5 days and 20mg of rabeprazole, 500mg of clarithromycin, and 500mg of tinidazole for the remaining 5 days).

*H. pylori* infection was eradicated in 11 of 23 patients (48%) with the A2143G mutation and in 14 of 15 patients (93%) with either A2142G or A2142C strains (P = 0.004). The authors conclude that the point mutation A2143G is particularly associated with clarithromycin resistance and a low success rate in the treatment of *Helicobacter pylori*. A sequential treatment regimen was found to be more successful than standard therapy in all cases.


**Bilateral blindness from orbital cellulitis caused by community-acquired methicillin-resistant *Staphylococcus aureus***

Rutar et al. recount a case report of a 44-year-old man developing proptosis, ptosis, ophthalmoplegia, and no light perception vision after attempting to lance a nasal pustule. A nasal culture grew MRSA. Imaging showed bilateral orbital cellulitis, pansinusitis, and cavernous sinus thrombosis. The right fundus showed severe ischaemia, but the left fundus was essentially normal. Despite initiation of appropriate antibiotics early in the course of infection, the patient lost sight in both eyes. Surgical drainage of the paranasal sinuses and use of intravenous corticosteroids and heparin led to the resolution of orbital cellulitis. The authors conclude that the new, community-acquired clone of MRSA can exhibit increased potential for tissue invasion and that MRSA orbital cellulitis can progress to irreversible blindness despite antibiotic treatment.


### Industry News

**Rotarix: first vaccine against rotavirus available in Europe**

*London, U.K., and Rixensart, Belgium*

The European Commission has granted approval of Rotarix™ in the European Union (EU), allowing active vaccination of infants from the age of 6 weeks, against the highly contagious rotavirus.

Rotavirus disease causes hospitalisation of 87,000 babies and over 700,000 visits to the doctor each year in Europe. In total an estimated 3.6 million of the 23.6 million children under 5 years of age suffer from rotavirus gastroenteritis (RVGE) in the EU each year. Due to the large number of hospitalisations and outpatient visits, there is a high economic burden associated with RVGE. According to a recent study, the total cost in France is EUR 28 million per year.

The high infectivity of rotavirus makes it difficult to control the spread of the disease. Therefore, vaccination is recognised as the only control measure to have a significant impact on the incidence of severe RVGE and is considered the optimum first-line strategy for disease prevention.

Rotarix is a two-dose, oral vaccine that is administered at approximately 2 and 4 months of age to offer early protection against RVGE before the peak incidence of disease at 6-24 months.

Rotarix is highly immunogenic and can be co-administered with all infant vaccines within the routine infant vaccination schedules across Europe, including oral polio vaccine. It has already been licensed in 33 countries and 1.4 million doses of the vaccine have been distributed since its first launch in Mexico in 2005.

The global clinical development programme has proven that Rotarix protects against the most common circulating strains (G1 and non-G1 rotavirus strains) including the globally emerging G9 strain. The vaccine’s safety was shown in a recent trial that demonstrated that Rotarix caused fewer serious adverse events (SAEs) compared to placebo. The safety analysis of this trial also showed that there is no attributable risk for intussusception, a complication that was observed with a previous marketed vaccine.

Rotarix has been developed by GlaxoSmithKline Biologicals since 1997. Rotarix strain RIX4414 derives from the strain 89–12, which was originally developed by Dr Richard Ward at the Children’s Hospital of Cincinnati, and which was in-licensed from Avant Immunotherapeutics. It is the first licensed attenuated human rotavirus oral vaccine conferring protection against severe rotavirus diarrhoea with data also showing efficacy against emergent strains. The European Marketing Authorisation announced that it will make Rotarix the first rotavirus vaccine available to children in Europe. Furthermore, Rotarix has been filed for approval in 75 countries and GSK is in late stage development discussions...
with the FDA regarding licensure of Rotarix for the US market.

Source: GlaxoSmithKline Biologics

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**Wyeth Pharmaceuticals’ antibiotic Tygacil (tigecycline) receives “Positive Opinion” from European Regulatory Authority**

*Madison, N.J.*

Tygacil, the first in a new class of antibiotics called glycyclines (structurally similar to tetracyclines and may have similar adverse effects) has an expanded broad spectrum of *in vitro* activity against many Gram-positives, Gram-negatives, anaerobes, and MRSA (see What’s new in microbiology and infectious diseases, ESCMID News 2-2005).

Wyeth Pharmaceuticals announced that it has received a “positive opinion” recommending approval for the introduction of its first-in-class antibiotic Tygacil® (tigecycline) to the European market by the Committee for Medicinal Products for Human Use (CHMP).

The introduction of Tygacil to the European market will come at a time when the need for new antibiotic options to combat serious infections is increasing. The “positive opinion” is the final step before formal approval to market Tygacil in the 25 Member States of the European Union, Iceland, Liechtenstein, and Norway. The CHMP recommendation of Tygacil will now be forwarded to the European Commission (EC) for final approval. Specifically in Europe, Tygacil will be indicated for the treatment of complicated skin and soft-tissue infections and complicated intra-abdominal infections. Tygacil received approval for use in the United States by the Food and Drug Administration on 15 June 2005. Since then, Tygacil has been placed on formulary at more than 1,450 of the largest hospitals in the United States.

**SOURCE:** Wyeth Pharmaceuticals

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**Progenics Pharmaceuticals’ HIV Drug, PRO 140, receives FDA “Fast-Track” designation**

*Tarrytown, NY*

Progenics Pharmaceuticals, Inc. announced that PRO 140 has been designated a fast track product by the U.S. Food and Drug Administration (FDA) for the treatment of human immunodeficiency virus (HIV) infection. The FDA Fast Track Development Program facilitates development and expedites regulatory review of drugs intended to address an unmet medical need for serious or life-threatening conditions. PRO 140 belongs to a new class of HIV/AIDS therapeutics — viral-entry inhibitors — that are intended to protect healthy cells from viral infection. PRO 140, currently in phase 1b clinical trials in HIV-infected individuals, is a humanised monoclonal antibody directed against CCR5, a molecular portal that HIV uses to enter cells.

PRO 140 may represent a new treatment paradigm for HIV patients, because it has the potential to address the limitations of currently available therapies, including the emergence of multi-drug-resistant virus, significant side effects, drug-drug or drug-food interactions, and often-complex daily treatment regimens. In a recently completed phase 1 study in healthy volunteers, PRO 140 exhibited dose-dependent binding to CCR5-expressing cells. A single 5 mg/kg dose of PRO 140 significantly coated — and thereby potentially protected from HIV infection — CCR5 cells for as long as 60 days. PRO 140 was generally well tolerated at all dose levels in this study.

**SOURCE:** Progenics Pharmaceuticals, Inc.

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**Pfizer receives FDA approval for Eraxis (anidulafungin) to treat candidemia**

*New York, NY*

Pfizer Inc. announced that Eraxis™ (anidulafungin) has been approved by the U.S. Food and Drug Administration to treat candidemia, one of the most deadly hospital-acquired bloodstream infections, with a mortality rate of approximately 40%.

Patients at high risk for candidemia and systemic candidiasis include those with compromised immune systems, stem-cell and organ-transplant recipients, patients on chemotherapy, patients with catheters, critically ill patients in intensive care units, surgical patients and those on prolonged antibiotic therapy. In the U.S., patients with candidemia on average spend an additional 10 days in the hospital at an average increase in hospital charges of about $39,000 per patient.

Eraxis, an antifungal medicine of the echinocandin class, also was approved by the FDA to treat two additional infections caused by Candida: paronychitis and intra-abdominal abscesses as well as oesophageal candidiasis.

Eraxis builds upon Pfizer’s extraordinary strength in medicines for the treatment of infectious diseases, particularly antifungal treatments. Pfizer’s Diflucan® (fluconazole) has been the longstanding gold standard treatment for candidaemia and other fungal infections, especially opportunistic infections in HIV/AIDS patients. Pfizer’s Vfend® (voriconazole) is a treatment for serious mold and yeast infections. Both Diflucan and Vfend are azole-type antifungal agents.

Eraxis is the only medicine that has demonstrated improved efficacy against fluconazole in a pivotal clinical trial for the treatment of candidaemia. Eraxis was added to the company’s antifungal portfolio through the acquisition of Vicuron in September 2005.

In clinical studies, Eraxis was as well tolerated as fluconazole and the total number of drug-related adverse events was comparable to fluconazole. Eraxis has not been associated with renal toxicity, and has no clinically relevant drug-to-drug interactions.

**Source:** Pfizer Inc.

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**FDA MedWatch: Cefazolin for injection recalled due to microbial contamination of active ingredient**

*Bethesda, M.D.*

Hanford Pharmaceuticals and the United States Food and Drug Administration (FDA) notified healthcare professionals about the recall of four lots (379,975 vials) of Cefazolin for injection, USP, 1 g/10 ml vials, an antibiotic used in a hospital environment to treat skin and skin structure, respiratory and other infections.

The product was distributed by Sandoz, Inc. of Broomfield, Colorado, and Watson Pharmaceuticals, Inc. of Corona, California.

Certain lots of the active ingredient used to manufacture the product have been shown to contain microbial contamination (Bacillus pumilus, Staphylococcus hominis, Propionibacterium acnes, or Micrococcus luteus) which may pose a serious or life-threatening risk for some patients. Hospitals, clinics, and users should stop using the affected lots immediately.

**Source:** The FDA Safety Information and Adverse Event Reporting Program

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**Stronger warnings for Tequin (gatifloxacin)**

*Bethesda, MD*

Bristol-Myers Squibb Co. announced labelling changes for Tequin (gatifloxacin),
an antibiotic indicated for the treatment of patients with pneumonia, bronchitis, uncomplicated gonorrhoea, and various infections including infections of urinary tract, kidneys, and skin.

The labelling changes, announced by the Tequin manufacturer in a letter to healthcare professionals, update the prescription information as a result of continued reports of serious cases of hypoglycaemia and hyperglycaemia in patients receiving Tequin. Since the approval of Tequin in 1999, there have been rare cases of life-threatening events reported globally most of which were reversible when properly managed, but a few had fatal outcomes.

Information about the risks of low and high blood sugar was added to the warnings section of the U.S. labelling in 2002. The changes strengthen the existing warning on hypoglycaemia and hyperglycaemia, add a contraindication for use in diabetic patients, and include information identifying other risk factors for developing low or high blood sugar, including advanced age, renal insufficiency, and concomitant glucose altering medications while taking Tequin.

The FDA will continue monitoring Tequin’s safety to ensure that its benefits outweigh the risks to patients.

Source: Food and Drug Administration

Viral Infections

Avian influenza

HPA

The Health Protection Agency (HPA) in the UK also publishes guidance at www.hpa.org.uk/infections/topics_az/influenza/avian/guidelines.htm, relating to management of suspected human cases of avian influenza, investigation and reporting of such cases, laboratory guidance, microbiological guidance for taking and handling of specimens as well as travel advice. SOURCE: HPA website

Avian influenza virus infections in humans

Wong and Yuen recently reviewed the current status of Avian influenza virus infections in humans. More than 200 human cases of avian influenza virus infection due to A/H5, A/H7, and A/H9 subtypes have been reported, mainly as a result of poultry-to-human transmission, with a > 50% case fatality rate for A/H5N1 infections. A mutant or reassortant virus capable of efficient human-to-human transmission could trigger another influenza pandemic. The recent isolation of this virus in extra-pulmonary sites of human diseases suggests that the high fatality of this infection may be more than just the result of a cytokine storm triggered by the pulmonary disease. The emergence of resistance to adamantanes (amantadine and rimantadine) and recently oseltamivir, while H5N1 vaccines are still at the developmental stage of phase 1 clinical trials, are causes for grave concern. Moreover, the to-be pandemic strain may have little cross-immunogenicity to the presently tested vaccine strain. The relative importance and usefulness of airborne, droplet, or contact precautions in infection control are still uncertain. Laboratory-acquired avian influenza H7N7 has also been reported. The authors also review the epidemiology, virology, clinical features, laboratory diagnosis, management, and hospital infection control measures.


Antivirals for influenza in healthy adults

In this article, Jefferson et al. systematically reviewed the evidence of efficacy, effectiveness and safety of registered antivirals against naturally occurring influenza in healthy adults. 51 randomised controlled trials were included up to October 2005. Amantadine prevented 61% of influenza A cases and 25% of cases of influenza-like illness, but caused nausea, insomnia and hallucinations. In treatment, amantadine significantly shortened the mean duration of fever compared with placebo by 0.99 days, but had no effect on nasal shedding of influenza A viruses. The fewer data for rimantadine showed comparable effects. In prophylaxis, compared with placebo, neuraminidase inhibitors (oseltamivir and zanamivir) had no effect against influenza-like illness and higher doses appeared to make no difference. The efficacy of oral oseltamivir 75 mg daily against symptomatic influenza was 61% (73% at 150 mg daily). Inhaled zanamivir 10 mg daily was 62% efficacious. Oseltamivir induced nausea especially at higher prophylactic doses. In a post-exposure prophylaxis role, it has a protective efficacy of 58.5% for households and from 68% to 89% in contacts of index cases. Oseltamivir at 150 mg daily was effective in preventing lower respiratory tract complications in influenza cases (OR 0.32, 0.18–0.57). There was no credible data on the effects of oseltamivir on avian influenza. The authors concluded that the use of amantadine and rimantadine should be discouraged. Because of their low effectiveness, neuraminidase inhibitors should not be used in seasonal influenza control and should only be used in a serious epidemic or pandemic alongside other public-health measures.


Role of RSV in stable COPD

Respiratory syncytial virus (RSV) causes annual peaks of respiratory infection in children, and is increasingly being recognised as an important pathogen in adults with cardiopulmonary disease. It has been associated with acute exacerbations of COPD and has been detected in the lower airway in the stable COPD, but the consequences of RSV in stable disease have not previously been determined.

Wilkinson et al. have studied the effect of RSV persistence and its effect on airway inflammation and lung function decline. They studied 241 sputum samples from 74 stable COPD patients (FEV1 % predicted: 39.2 (29.6–57.8) %) over 2 years. RSV was detected by PCR, quantitative microbiology performed and inflammatory cytokines were quantified by ELISA.

They found that RSV RNA was detected in 32.8% of sputum samples, and patients in whom RSV was more frequently detected had higher airway inflammation and faster FEV1 decline over the study (p = 0.01). The observed relationship between RSV detection and accelerated lung function decline was independent of smoking status, exacerbation frequency and lower airway bacterial load.

The authors conclude that persistent RSV detection in COPD patients is associated with airway inflammation and accelerated decline in FEV1 and that therapy of chronic RSV infection may alter the natural history of COPD.

Description of a new hepatitis C risk assessment tool

Because of the low prevalence of hepatitis C virus (HCV) infection in the general population, mass screening would be expensive and of low yield. In a cross-sectional study Nguyen et al. aimed to develop a patient-administered tool to assess HCV infection risk. Two hundred seven patients with unknown HCV status from a general medicine practice and 222 HCV-positive patients from a hepatology practice completed a 72-item questionnaire about demographic, social, and clinical risk factors for HCV infection. General medicine patients also underwent HCV serologic testing. Three (1.5%) of 207 general medicine patients had positive HCV antibody test results. These patients plus the 222 hepatology patients were significantly more likely than HCV-negative patients to report an array of factors. In a multivariable model, 7 factors remained significantly associated with HCV infection: sex with a prostitute or an injecting drug user, exposure to blood products, refusal as a blood donor or as a life insurance applicant, witnessing illicit drug use, and self-reported HBV infection. A simplified model that assigned 1 point for each factor present predicted HCV infection as well as a weighted model in a population with a 2% prevalence of HCV infection, whereas those with 4 or more risk factors had a 50% chance. If validated in other primary care populations, this instrument could help target HCV screening.


Parasitic Infections

Strongyloides hyperinfection presenting as acute respiratory failure and Gram-negative sepsis

Newberry et al. conducted a retrospective chart review of complicated strongyloides infections from 1993 to 2002 in Minneapolis and St. Paul, MN. Nine patients, all of Southeast Asian heritage, were identified. Eight patients immigrated to the United States > or = 3 years prior to acute presentation. All patients were receiving antecedent corticosteroids; in five patients, therapy was for presumed asthma. Absolute eosinophil counts > 500/µl occurred in only two patients prior to steroid initiation. Eight patients presented with respiratory distress, and Gram-negative sepsis developed in four patients. Three patients died; all had eosinophil counts of < 400/µl. The authors conclude that serious complications, or death, may occur in patients with chronic strongyloides infection treated with corticosteroids. Strongyloides hyperinfection usually presents as acute respiratory failure and may initially mimic an asthma exacerbation or pulmonary embolism. Southeast Asian patients presenting with new-onset ‘asthma,’ acute respiratory distress, and/or Gram-negative sepsis should undergo evaluation to exclude strongyloides infection.


European Affairs

Update on Framework Programme 7: council reaches political agreement

Ministers reached Political Agreement on the entire FP7 package at an extraordinary Competitiveness Council (CC) on 24 July 2006. The meeting was scheduled by the Finnish Presidency with the intention of reaching Political Agreement on FP7 and keeping the legislative process on track to meet its scheduled launch date of 1 January 2007. The revised text sets a budget for FP7 of EUR 50.5 billion (excluding Euratom) over the period 2007–2013. For more information visit: http://cordis.europa.eu/fp7/.

Funding of European Frontier Research: the Scientific Council of the ERC presents its peer review process

The Scientific Council of the European Research Council (ERC) recently published a strategy note presenting its initial agreement on a peer review process to be used to select projects for funding. The document refers to the structure and composition of the selecting panels and relates to the Starting Independent Researcher Grants that support excellent independent researchers who are at the early stages of their careers. Overall, the designation of the panels will be made according to several ‘overriding principles’ to guarantee that the selection process will be independent and that it will serve the overall objective of the ERC to fund innovative research and support scientific excellence in Europe. For more information please consult: http://ec.europa.eu/erc/pdf/erc-scientific-council_strategy_note_peerreview_panels_en.pdf.

Michael Morgan, MD, FRCPath Consultant Microbiologist michaelmorgan@nhs.net
New ESCMID Members in 2006

Since the beginning of the year, ESCMID has acquired 431 new members. We would like to take this opportunity to introduce and welcome them to ESCMID.
Registration Form

European Society of Clinical Microbiology and Infectious Diseases

Surname ____________________________________________________________ First Name(s) ______________________
Department ____________________________________________________________
Institution/Company ____________________________________________________________
Street & No. __________________________________________________________ P.O. Box ______________________
City ______________________ Postal Code ______________________ Country ______________________
Phone ______________________ Fax ______________________
Email ______________________ Birth date (dd.mm.yy) ________________

Regular membership for 1 year for 2 years Total in EUR
CMI print & online, or ○ EUR 88 ○ EUR 166 ______________________
CMI online ○ EUR 58 ○ EUR 106 ______________________

Regular membership for ERS members for 1 year for 2 years Total in EUR
CMI print & online, or ○ EUR 75 ○ EUR 140 ______________________
CMI online ○ EUR 49 ○ EUR 88 ______________________

The dual membership offer for ERS members is available only to applicants paying the regular fee (above). Please indicate ERS membership number: ______________________

Reduced-rate membership (up to 35 years of age or retired)
incl. CMI print & online, or ○ EUR 68 ○ EUR 126 ______________________
incl. CMI online ○ EUR 38 ○ EUR 66 ______________________

Additional journals (optional, all print & online)
Infection ○ EUR 83 ○ EUR 156 + ______________________
European Journal of Clinical Microbiology and Infectious Diseases ○ EUR 102 ○ EUR 194 + ______________________

Total payment EUR ______________________

☐ EUR ______________________ were transferred by (name) ______________________

☐ to Deutsche Apotheker- und Ärztebank, 80323 Munich, Germany
Account number: 000 236 2368, Bank sorting code: 700 906 06
IBAN: DE61 3006 0601 0002362368, BIC (SWIFT): DAAEDEDD

☐ Bank cheque/international draft payable to ESCMID is enclosed

☐ Please charge my credit card with EUR ______________________

☐ VISA ☐ MasterCard ☐ American Express ☐ Diners Club
Credit Card no.: ______________________
Expiry date (mm/yy): ______________________ Card Verification Code (CVC): ______________________
(The CVC is the 3- or 4-digit number printed on the back or front side of your credit card to the right of the regular credit card number.)

☐ I authorise ESCMID to automatically charge the annual/biannual total as above for each membership period to my credit card.

Start of your membership: ☐ as soon as possible ☐ 1 January next year

Date: ______________________ Signature: ______________________
Please indicate your professional background (multiple entries possible):

**Academic degree(s)**
- MD
- PhD
- other: __________________________

**Specialties in clinical medicine**
- m clinical microbiology
- i infectious diseases
- Z dentistry
- G gastroenterology / hepatology
- J general practice / primary care medicine
- H haematology
- j internal medicine
- k paediatrics
- p pathology
- q pneumology
- s surgical specialties
- O other: __________________________

**Non-clinical disciplines**
- B biomedical sciences (including biochemistry, biology, genetics, microbiology, etc.)
- L chemistry
- D marketing and business administration
- X mathematics
- U medical care (including infection control nurses)
- h pharmacology
- d pharmacy
- W public health medicine
- t veterinary medicine
- O other: __________________________

Please indicate your membership interest in one of the ESCMID Study Groups (multiple entries possible):

- f ESCMID Fungal Infection Study Group (EFISG)
- i European Helicobacter Study Group (EHSG)
- d ESCMID Study Group for Coxella, Anaplasma, Rickettsia and Bartonella (ESCAR)
- q ESCMID Study Group on Antibiotic Policies (ESGAP)
- n ESCMID Study Group on Antimicrobial Resistance in Anaerobic Bacteria (ESGARAB)
- r ESCMID Study Group on Antimicrobial Resistance Surveillance (ESGARS)
- g ESCMID Study Group on Biofilms (ESGB)
- c ESCMID Study Group on Clostridium difficile (ESGCD)
- e ESCMID Study Group on Epidemiological Markers (ESGEM)
- m ESCMID Study Group on Molecular Diagnostics (ESGMD)
- j ESCMID Study Group on Nosocomial Infections (ESGNI)
- t ESCMID Study Group on Toxoplasmosis (ESGT)
- p ESCMID Study Group on Primary Care Topics (ESPRIT)
ESCMID and FEMS offer a joint award to foster outstanding research in microbiology by young European scientists. Every year each organisation selects one individual among their recipients of research fellowships to receive an additional amount of EUR 1000 from the other organisation. We are delighted to announce that the third combined FEMS/ESCMID fellow is Laura Menotti from Bologna, Italy.

Research Interests
Laura Menotti was awarded the FEMS/ESCMID Research Fellowship for her research project entitled: Generation of recombinant herpes simplex viruses retargeted to tumour cells for the design of oncolytic herpes viruses. She has been working on herpes simplex virus since 1995. Her present research focuses on HSV-1 for the production of recombinant viruses to be used in anti-cancer oncolytic virotherapy. She recently generated a recombinant virus retargeted to a heterologous receptor, HER2, specifically overexpressed in mammary and ovary carcinomas.

The ESCMID Awards Committee

Announcement

ESCMID / ERS Dual Membership Programme

ESCMID and ERS (European Respiratory Society), which have recently embarked on a 5-year joint educational project in the field of lower respiratory tract infections (see article on GRACE, page 18 of this issue) signed a dual membership agreement this summer. Under this scheme both societies grant those members, who are also members in good standing of the other society, a discount of 15% on the regular full rate membership fee. ESCMID will launch this dual membership at the end of 2006 with the call for membership renewal for 2007. As ESCMID and ERS share similar missions in their respective fields, this dual membership programme should strengthen their cohesion to the benefit of their members.

ESCMID Executive Committee

Acinetobacter 2006

7th International Symposium on the Biology of Acinetobacter

8 – 10 November 2006
Institut d’Estudis Catalans, Barcelona, Spain

Expert lectures and offered papers on
- Genetic diversity
- Genomics/genome analysis
- Antibiotic resistance
- Genetic regulation
- Epidemiology and risk-factors for Acinetobacter infections
- Bioremediation, biotechnology and metabolism
- Acinetobacter in the environment
- Infection control and therapeutic problems

For further information concerning the scientific programme and registration, please contact Kevin Towner (kevin.towner@nuh.nhs.uk).
Forthcoming ESCMID Events

More detailed information about ESCMID courses and conferences as well as general information about other events can be found on the ESCMID website at www.escmid.org under Courses & Workshops, ECCMIDs & Conferences, or Calendar of Events, respectively.

ESCMID events

8–12 October 2006
ESCMID/EFSM Conference on New Frontiers in Microbiology and Infection Mycobacterial Infections: Basic Research Visits Clinical Experience and Vice Versa
Place: Villars-sur-Ollon, Switzerland
Contact: Martine Moreillon
Email: martine.moreillon@unil.ch

9–10 November 2006
38th ESCMID Postgraduate Education Workshop: Diagnosis of Invasive Fungal Infections: New Approaches and Usefulness of Susceptibility Testing
Place: Madrid, Spain
Contact: Manuel Cuenca-Estrella
Email: mcuenca-estrella@isciii.es

25–28 November 2006
41st ESCMID Postgraduate Education Course: ESCMID-SHEA Training Course in Hospital Epidemiology 2006
Place: Baden/Vienna, Austria
Contact: Alice Haindl
Phone: +43 2268 46541 116
Email: alice.haindl@aesculap-akademie.at
Internet: www.aesculap-akademie.com

30–31 March 2007
2nd GRACE Postgraduate Course: The Place of Rapid Diagnostics in Respiratory Tract Infections: Moving from Empirical Therapy to Directed Therapy
Place: Munich, Germany

21–28 May 2008
8th International Meeting on Microbial Epidemiological Markers
Place: Zakopane, Poland
Contact: Waleria Hryniewicz
Internet: www.immem-8.org

29 April – 4 May 2007
40th ESCMID Postgraduate Education Course: Practical and Theoretical Course on Bacterial Molecular Typing
Place: Oeiras, Portugal

2–4 June 2007
42nd ESCMID Postgraduate Education Course
Role of Anaerobic Bacteria In Infections: Diagnostics, Antibiotic Resistance and New Therapeutic Options
Place: Szeged, Hungary
Contact: C&T Hungary Ltd.
Phone/Fax: +36-62-548-485
Email: congress@congresstravel.hu

19–22 April 2008
18th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)
Place: Barcelona, Spain
Contact: AKM Congress Service
Phone: +41 61 686 77 11
Email: info@akm.ch
Internet: www.akm.ch/eccmid2008

Endorsed by ESCMID

8–10 November 2006
7th International Symposium on the Biology of Acinetobacter
Place: Barcelona, Spain
Contact: Kevin Towner
Email: kevin.towner@qmc.nhs.uk

21–28 May 2008
8th International Meeting on Microbial Epidemiological Markers
Place: Zakopane, Poland
Contact: Waleria Hryniewicz
Internet: www.immem-8.org

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