Oral presentations

Emerging issues in β-lactamase-mediated resistance (Symposium jointly arranged with FEMS)

S1 Class D carbapenemases: origins, activity, expression and epidemiology of their producers

L. Poirel (Le Kremlin Bicetre, FR)

Oxacillinases are class D β-lactamases, grouping very diverse enzymes usually not sensitive to β-lactamase inhibitors. Some oxacillinases hydrolyse only narrow-spectrum β-lactams, some others expanded-spectrum cephalosporins, but more worrying are those oxacillinases hydrolysing carbapenems. Those latter oxacillinases named CHDLs for "Carbapenem-Hydrolysing class D β-Lactamases" have been identified in a variety of Gram-negative bacterial species. They do hydrolyse penicillins and carbapenems at a low level, but their hydrolysis spectrum does not include expanded-spectrum cephalosporins. They are not inhibited by clavulanic acid but are inhibited by NaCl in vitro.

Some CHDLs correspond to naturally-occurring β-lactamases encoded on the chromosome of a variety of species, such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Ralstonia pickettii*. The corresponding genes are often poorly expressed, and the impact of those carbapenemases on the carbapenem susceptibility of the corresponding species seems marginal. However, it has been demonstrated that overexpression of the naturally-occurring blaOXA-51-like gene of *A. baumannii* (linked to insertion of an IS element upstream of that gene) can lead to decreased susceptibility to imipenem.

By contrast, other CHDLs are considered as acquired, leading to esistance to carbapenems. Most of these acquired CHDLs have been identified in *A. baumannii*, being of three types (OXA-23, OXA-40, and OXA-58). Those acquired enzymes may be either plasmid- or cchromosome-encoded. Those oxacillinases have been identified worldwide, always identified in carbapenem-resistant isolates, those latter being very often at the origin of nosocomial outbreaks. Interestingly, the source of the OXA-23-encoding gene has been very recently identified, being the chromosome of the carbapenem-susceptible *Acinetobacter* radioresistens species, in which blaOXA-23 is poorly expressed.

Another acquired CHDL is OXA-48 identified firstly in a carbapenem-resistant *Klebsiella pneumoniae* isolate from Turkey, which has now widely disseminated in Istanbul, responsible for large outbreaks. The blaOXA-48 gene is plasmid-encoded and has been recently evidenced in other enterobacterial species in the same country. Interestingly, the source of that acquired CHDL was shown to be the Gram-negative, environmental and waterborne species *Shewanella oneidensis*.

In conclusion, besides the acquisition of metallo-β-lactamases or even class A carbapenemase suck as the KPC-type enzymes conferring carbapenem resistance in Gram negatives, the current emergence and spread of CHDLs represents a worrying threat. The dissemination of such mechanism is difficult to trace and thus to control, considering that no currently available test allows detection of CHDLs.

S2 Metallo-β-lactamase-producing Enterobacteriaceae: phenotypes, genetics, prevalence and clinical significance

V. Miriagou (Athens, GR)

While production of serine β-lactamases of the molecular classes A and C remains the most clinically significant β-lactam resistance mechanism among enterobacteria, there is an increasing concern as to the dissemination of strains with zinc-dependent class B metallo-β-lactamases (MBLs). These acquired enzymes display an extremely wide spectrum of hydrolysis that includes also carbapenems. The MBL-encoding genes commonly occur as cassettes in integrons carried by a variety of transferable plasmids and enterobacterial chromosomes underscoring their spreading potential. Indeed, a physical linkage of MBL integrons with transposable elements has been, in some instances, documented. VIM and IMP β-lactamases – the main MBL types found in enterobacteria – have already achieved a global spread, the southern Europe and the Far East being the most affected regions. There are quite a few epidemiological studies unveiling the mode of spread of MBL-producing enterobacteria. Nevertheless, our understanding of what MBL production entails in terms of clinical impact is still limited. It is not yet clear if MICs of MBL producers must be consider at face value or these isolates must be reported as potentially resistant to carbapenems. Moreover, performance of the routine detection methods based on EDTA-β-lactam synergy is not optimal and not yet standardised. The aim of this presentation is to discuss recent advances on genetics, epidemiology and clinical significance of MBL-producing enterobacteria.

State-of-the-art treatment of imported parasitic diseases

S6 How to deal with chronic infections of *Trichinella*

C.M. Cretu (Bucharest, RO)

Trichinellosis, parasitic disease due to the presence of *Trichinella* spp. larvae in muscle tissue, is an emerging disease and seems to become a re-emerging disease, as in many endemic countries human clinical cases are related and consequent to a breakdown of local legislation.

In Central and Eastern Europe, *Trichinella* infection still represents an important health problem, according to the statistical data registered by ICT.

Many species of *Trichinella* larvae, encapsulated or not, are responsible for human cases, according to data collected in Reference Laboratory in Rome, each one having a typical clinical appearance and geographical distribution: *T. spiralis*, *T. pseudospiralis*, *T. britovi*, *T. nativa*, *T. nelsoni*, *T. murelli*, *T. papuae*.

In endemic countries, medical attention should be paid on both acute and chronic trichinellosis. Acute trichinellosis is familiar for medical doctors: short incubation period, followed by gastrointestinal phase (20–30 days), acute stage (weakness, chills, fever, headache, sweating, tachycardia, eyelid/periocular/generalised oedema, muscle pain) and, sometime, complications (cardiovascular, ocular, neurological, respiratory etc).

Differentiations between convalescent stage (residual myalgia), sequels or chronic trichinellosis still remain not very well defined.

Chronic trichinellosis is either symptomatic (general discomfort, chronic muscle pain, tingling, neuropsychiatric signs, persistent sweating), in patients with history of trichinellosis, or asymptomatic, accidentally discovered, when muscle biopsy is examined for other reasons (i.e. laryngeal or tongue neoplasm), when residual IgG antibodies level is proved (persistence of residual viable larvae), chronic hypereosinophilia or when bioelectric muscle disturbances persist.

The role of chronic trichinellosis larvae as co-factor in the development of cancer is under debate, but further studies are necessary to be conducted in order to confirm the direct relationship between *Trichinella* larvae and neoplasm (chronic inflammation, direct carcinogenetic role, co-factor in carcinogenesis?).

The algorithms for diagnosis of acute or chronic trichinellosis should be taken into account, in order to initiate the appropriate treatment and to prevent severe complications.
Laboratory diagnosis is simple and relevant during the acute stage, while, during the chronic stage or in people who received corticosteroids, ELISA can be negative and only confirmation tests (imunobloting, multiplex PCR) or muscle biopsy can determine the diagnosis.
Epidemiology should evaluate the geographical regions and the different *Trichinella* species, as clinical evolution of the disease is closely related to the parasitic burden, parasitic species and host immune response.

S7 How to cope with the wormy world? Treatment of helminths

A.M.L. Van Gompel (Antwerp, BE)

Helminth infections are among the most common infections in men.
The different helminthic infections that currently may be imported in our European countries by returning travellers, expatriates, immigrants and refugees coming from endemic countries will be succinctly presented in the following way:

- nematodes or roundworms (intestinal nematodes: ancylostomiasis and other hookworm infections, angiostrongyliasis, ascariasis, capillariasis, enterobiasis, strongyloidiasis, trichostrongyliasis, trichuriasis; filarial nematodes and dirofilariasis; tissue nematodes, e.g.: angiostrongyliasis, cutaneous larva migrans, gnathostomiasis, toxocariasis, trichinosis),
- cestodes or tapeworms (cysticercosis, diphyllobothriasis, echinococcosis, taeniasis and other intestinal tapeworms) and
- trematodes or flukes (chlonorchiasis and opistorchiasis, fasciolasis; intestinal flukes; paragonimiasis; schistosomiasis)

... and their treatment modalities will be highlighted.
The number of effective antihelminthic agents is small relative to the vast array of antibacterial agents. The mechanism of action of most antiparasitic drugs is not always well understood. Especially the role of the following very frequently used anthelmintics will be illustrated: the benzimidazoles (albendazole, mebendazole, flubendazole, triclabendazole), ivermectin, praziquantel and diethylcarbamazine; but other products still in use will also briefly be mentioned. Newer "players" as nitazoxanide, the artemisinin-derivatives (possibly new player for the early stages of schistosomiasis? fasciolase) and doxycycline (adjunctive role in the treatment of filariasis) will be highlighted.
An opportunity to obtain an electronic copy in pdf of the powerpoint will be offered at the end of the lecture.

European MIC breakpoints for antimicrobial susceptibility testing are now harmonised by EUCAST (Symposium arranged with EUCAST)

S9 Why European harmonisation?

D. Brown (Cambridge, UK)

At least seven different MIC breakpoint committee guidelines for antimicrobial susceptibility testing have been used in Europe. Consequently Europe has had several different sets of antimicrobial breakpoints and a range of variations in technical methods. It became increasingly evident that harmonisation of breakpoints was necessary both for therapy and resistance surveillance. ESCMID set up EUCAST in 1997 with a representative from each European country and 6 representatives from industry. In 2002 EUCAST was restructured and the major responsibility for the work of EUCAST was taken on by the active national breakpoint committees in Europe. A Steering Committee was formed, currently comprised of a representative from the 6 active national breakpoint committees, 2 from the EUCAST General Committee (which has a representative from each European country), a Chairperson, a Scientific Secretary and a Clinical Data Coordinator. A decision making process was established whereby proposals made by the Steering Committee are distributed to the EUCAST General Committee, relevant expert groups and industry for consultation. The final decision is made by consensus in the Steering Committee, taking account of any comments made during consultations. In this process the expertise of the national breakpoint committees is utilised, there is wide consultation on proposals and the national committees take responsibility for implementation of decisions. Subcommittees have been set up to deal with specific topics including susceptibility testing of fungi and anaerobes, and expert rules in susceptibility testing. A website has been established (http://www.EUCAST.org) that gives details of EUCAST activities, EUCAST breakpoints and publications. Another website has been developed for the collection of MIC data and its presentation as species-specific wild type MIC distributions. EUCAST has been funded by ESCMID, the national breakpoint committees, a grant from the EU and now by ECDC. Industry does not contribute financially but is asked to contribute data required for determining breakpoints and to comment on proposed breakpoints. EUCAST has achieved harmonisation of most existing breakpoints in Europe. It has a formal relationship with EMEA regarding the setting of breakpoints for new agents and the revision of breakpoints for existing agents. The process has been applied to several new drugs. Documents on various aspects of susceptibility testing have also been published.

S12 Implementation of European breakpoints and the future of EUCAST

G. Kahlmeter on behalf of EUCAST

EUCAST will soon have harmonised European breakpoints for existing antimicrobials. Also, as part of the EMEA process for approval of new drugs, EUCAST has determined breakpoints for several antimicrobials. The work of the committee now enters a wider implementation phase.
Existing classes of drugs: At the end of 2008 there will be a complete set of EUCAST clinical breakpoints and epidemiological cut-off values. By early 2009 the clinical breakpoints will be implemented in the AST systems of BSAC (UK), CA-SFM (France), CRG (Netherlands), DIN (Germany), NWGA (Norway) and SRGA (Sweden).
New antimicrobials: EUCAST determines breakpoints as part of the EMEA approval process for new antimicrobials. EUCAST breakpoints are the only breakpoints included in the Summary of Product Characteristics (SPC). Daptomycin and tigecycline are already approved and another 4–6 drugs will be handled during 2007–9.
Antimicrobial susceptibility testing devices: Work is ongoing to implement EUCAST clinical breakpoints in Phoenix (BD) and VITEK 2 (BioMerieux) and it is expected that EUCAST breakpoints will be available for both in early 2009. The fact that EUCAST breakpoints and national breakpoints will be the same will simplify the development of test panels as well as benefiting users.
EUCAST disk diffusion method: Preliminary results from a questionnaire to determine the expectations of clinical microbiologists in Europe indicate that EUCAST should take the lead in developing a disk diffusion test based on Mueller-Hinton agar.
The future of EUCAST: EUCAST has been financed by ESCMID and the national breakpoint committees of France, Germany, Norway, Sweden, The Netherlands and the UK for many years. Over the last 4 years the EU and ECDC have contributed financially. It is hoped that this will be continued by ECDC.
There is a need to sustain a European Committee on Antimicrobial Susceptibility Testing beyond the breakpoint harmonisation process. New antimicrobials will need breakpoints. Companies with approved antimicrobials will seek approval for extensions of clinical or microbiological indications or modified dosages. New resistance mechanisms occasionally necessitate the review of existing breakpoints. The establishment of a European disk diffusion test is a major undertaking and there will be a need continually to develop it to accommodate new antimicrobials and new resistance mechanisms. All these efforts are best served by a common European committee, EUCAST.