S68 A Global Survey Yeast Susceptibility to Fluconazole

J.M. Torres-Rodríguez [1], G. Quindós [2]. [1] *Grup de Recerca en Micologia Experimental I Clínica, IMIM. /Universitat Autónoma de Barcelona, Spain,* [2] *Dept. Microbiology Fac. Medicine, Euskadi University, Bilbao, Spain*

Fluconazole is currently the azole antifungal drug most used for the treatment of yeast infections because of its high rate of efficacy, low toxicity and simplicity of administration. As a result of the wide use of fluconazole, particularly as prophylaxis and treatment of oropharyngeal candidosis in HIV-infected patients, changes in the susceptiblity of some strains of *Candida albicans* and the emergence of other species less susceptible *in vitro* such as *Candida krusei* and *Torulopsis (Candida) glabrata* have occurred. The significance of these effects on the course of the disease is controversial.

Studies of susceptibility to Fluconazole have been published by many laboratories in several countries, most of them from the USA. In general terms the results seem to be similar but there are differences in methodology and procedure.

In a multicentre survey of *in vitro* antifungal resistance in yeasts of medical importance isolated form Spanish patients, the susceptibility to fluconazole was 90.2%; only 4% of *C. albicans* strains were not susceptible. Most resistance was seen in *C. glabrata* and *C. guilliermondii*. All *C. tropicalis* were susceptible to fluconazole. Conclusions of this study were that resistance to antifungals is very low in Spain and it is related to a few non-*albicans* species.

Glauser *et al* conducted a multicentre study in 23 different countries with 2231 consecutively isolated *Candida* strains in which a fluconazole diffusion assay was performed. The results of this study showed the 97.1% of *C. albicans* strains were susceptible to this antifungal. When other species of *Candida* were studied the susceptibility was lower (83.4%). The results of the diffusion test correlated with MICs (NCCLS proposals) for susceptible or intermediate strains when the zones of inhibition were 18–25 mm.

These results suggested a low *in vitro* world-wide resistance of *Candida albicans* to fluconazole and variable susceptibility depending on the other *Candida* species considered.

Recent advances in HIV pathogenesis

S69 Immunologic and Virologic Factors During Primary Infections: Modulation of the Clinical Course and Therapeutic Implications

G. Pantaleo. *CH*

No abstract available.

S70 T cell dynamics in HIV-1 infections studied by telomere length and CD4+ T cell repopulation kinetics following anti-viral therapy

F. Miedema [1], K.C. Wolthers [1], N.G. Pakker [1], D.W. Notermans [2], S.A. Danner [2], P.T.A. Schellekens [1]. [1] *Central Lab. Neth. Red Cross Blood Transf. Service, & University of Amsterdam, Amsterdam, The Netherlands,* [2] *Infec. Dis., Trop. Med. and AIDS & NATEC, Academic Medical Centre, Amsterdam, The Netherlands*

In a group of 14 HIV-infected persons, mean loss of telomere length in PBMC over 3 to 9 years was significantly increased compared to mean loss of TRF length in 7 healthy controls. Loss of telomere length in HIV infection was found exclusively in CD8+ T cells and not in CD4+ T cells. Loss of telomere length could not be explained by differential telomerase activity. This provides evidence that turnover in the course of HIV-1 infection can be increased considerably in CD8+ T cells, but not in CD4+ T cells. This implies that CD4+ T cell decline in HIV-1 infection might be caused by inhibition of CD4+ T cell renewal. To further study T cell renewal capacity and kinetics we evaluated the repopulation of CD4+ and CD8+ T cell subsets and their functional improvement during the first 36 weeks of treatment with ritonavir, 3TC and zidovudine that induced a strong and persistent reduction of the plasma and lymphoid viral load. A strikingly distinct kinetics for CD4+ CD45RO+ and RA+ cells was observed. CD45RO+ cell repopulation followed a biphasic pattern, with a steep increase in the first 5 weeks and a gradual slow increase the following months. In contrast, the naive CD62L+ cells over the follow up period showed a slow and gradual increase with a mean increase of 10^8 cells per day. In addition, a sustained improvement of T cell function was seen in the patients. Our results demonstrate that immunereconstitution following anti-viral therapy may be slow and may not readily reach normal levels of immunocompetence.

S71 The Impact of potent antiretroviral treatment on viral burden and immune depletion in lymphatic tissues

A.T. Haase. *Department of Microbiology, University of Minnesota, Minneapolis, MN, USA*

Quantitative image analysis of sections of lymphatic tissues (LT) after *in situ* hybridization to reveal viral RNA, or immunohistochemistry to identify subsets of $CD4^+$ T cells affords new opportunities to understand the pathogenesis of infection and response to treatment. I will describe the results of recent experiments on the response to combinations of antiretroviral therapy in LT that define the kinetics and magnitude of this response. I will also describe the rate of $CD4^+$ T cell replacement that suggests a "Red Queen" mechanism of immune depletion in HIV-1 infection.

S72 Rationale for Immuno-Based Therapeutic Intervention in Combination with Antiviral Agents

H.C. Lane. *USA*

No abstract available.

Antibiotic resistance in otitis media: Clinical problem or hypothetical risk?

S73 Otitis Media: Pathogenesis and Medical Sequelae

M.J. Tarlow. *UK*

No abstract available.

S74 Choosing the Antibiotic – Pharmacodynamics

W.A. Craig. *USA*

No abstract available.

S75 Measuring the Antibiotic – Real Life Studies

E. Thoroddsen. *IS*

No abstract available.

S76 Treatment Failures – What Can We Learn?

R. Dagan. *IL*

No abstract available.

4th generation cephalosporins: Microbiological rationale and clinical perspectives

S77 β-lactamase-mediated resistance in hospital pathogens

R.N. Jones. *University of Iowa, IA, USA*

Resistance in Gram-negative bacteria is frequently mediated by β-lactamase production. The four major groups currently recognised on the basis of amino acid sequence (A to D) include 3 with a serine active site (A, C and D). Class A includes the common TEM enzymes, class B the metallo β-lactamases which confer resistance to carbapenems, class C the AmpC chromosomal cephalosporinases and class D the OXA and PSE enzymes which have penicillins as the preferred substrate. Of particular concern are inducible AmpC β-lactamases, found in *Enterobacter*, *Citrobacter*, Serratia, *Pseudomonas*, *Morganella* and *Providencia* spp. and which confer resistance (stably de-repressed mutants) to 3rd generation cephalosporins (3GCs). These pathogens are frequent causes of nosocomial infection and pose an enormous therapeutic challenge to the clinician. Resistance can emerge on treatment. Infections caused by *Enterobacter* have increased during the 1990s: this pathogen was responsible for 6.3% of all infections in a US survey conducted in 1994, and is the fourth most prevalent cause of nosocomial RTI. In Europe and the Far East (1987–91), up to 40% of isolates of *Enterobacter cloacae* and *Citrobacter freundii* produced stably depressed AmpC β-lactamases. This increase in resistance to 3 GCs has been correlated with increased use of some broad spectrum antimicrobials such as ceftazidime. Both 3GCs and carbapenems are potent inducers of AmpC, but 4th generation cephalosporins such as cefpirome and cefepime have low induction potential and affinity for the enzyme. In addition, their high membrane penetration rates and β-lactamase stability make them valuable treatment options as resistance increases in the hospital environment. Extended-spectrum β-lactamases are also increasing in prevalence.

S78 Changing epidemiology of severe nosocomial infections

D. Pittet. *Hopital Cantonal Universitaire, Geneva, Switzerland*

In the setting of the ICU, data on the epidemiology of severe infection are used to monitor the effect of preventive measures and policy changes. The chance of contracting infection correlates with various risk factors including length of stay, antibacterial usage, catheterisation, mechanical ventilation and use of invasive devices. Infection can be classified as community- or hospital-acquired, and early or late in onset. Most early onset infection (≤ 4 days) is associated with *S. pneumoniae* or other streptococci, *H. Influenzae*, enterobacteria or MSSA. Late onset infection (> 4 days) is associated with *Enterobacter* spp., *Serratia* spp., *Pseudomonas* spp., *Acinetobacter* spp., enterococci, MRSA and fungi, and is consequently more difficult to treat. A twelve year (1980–1992) study including 260,834 patients in the USA has confirmed the increase in Gram-positive pathogens at the expense of Gram-negatives, particularly as causal agents of bacteremia, although some new and difficult-treat Gram-negatives are emerging, e.g. *Stenotrophomonas*. Treatment of severe nosocomial infections remains mostly empirical, and with the increase of resistance to existing agents, alternatives are needed. Carbapenems are powerful antibacterials, but the emergence of metallo β-lactamases is of concern. 4th generation cephalosporins, e.g. cefpirome and cefipime, hold promise in view of their broad spectrum, stability to most β-lactamases and enhanced Gram-positive activity. Carefully designed clinical trials are mandatory to assess the respective advantages and impact on host flora of broad spectrum antimicrobials in critical care.

S79 Evolving antibiotic susceptibility of nosocomial pathogens

R.C. Spencer. *PHLS, Bristol, UK*

The emergence of antibiotic resistance in nosocomial pathogens continues to be an important clinical problem. Gram-negative pathogens were more prevalent in the 1980s, and resistance has emerged to 3rd generation cephalosporins (3GCs), quinolones and carbapenems. From the mid-1980s onwards, Gram-positive species have become more prevalent and resistance is increasing, particularly penicillin resistance in streptococci, methicillin resistance in staphylococci (up to 70% in coagulase-negative species causing ICU infections) and vancomycin resistance in enterococci. The reason for this increase is multifactorial, including inappropriate or overuse of broad-spectrum agents and increasing use of prosthetic materials and high-technology medicine. Widespread and sometimes indiscriminate use of antibacterial agents has led to the development of multiple drug resistance mechanisms. Faced with an alarming increase in resistance, rational use of antibacterials and appropriate infection control measures are of paramount importance. However, these measures can only work if supported by adequate surveillance data, particularly in the case of seriously ill patients where antibacterial therapy is mostly empirical. Surveillance must be performed at the local, national and international level. Most data on resistance prevalence are inconsistent and fragmentary. In order to be useful, data should be generated by laboratories using reliable and reproducible testing methods, preferably reporting MICs or zone sizes, rather than susceptibility interpretations. In spite of the obvious problems that increasing resistance will cause, there are no formal collaborative surveillance studies in the developed world which will allow analysis of trends in resistance development.

S80 Clinical experience with 4th Generation cephalosporins in severe infections

M. Wolff. *Hopital Bichat-Claude Bernard, Paris, France*

Fourth generation cephalosporins (4GCs) are structurally related to 3GCs but have advantages including improved membrane permeability, high stability and low affinity for β-lactamases, and enhanced activity against Gram-positive pathogens. Only cefpirome and cefepime are widely available, but no direct comparisons have been made between the two. In severe infections, these agents have been shown to be both efficacious and safe, and at least as effective as ceftazidime. In ICU infections, cefpirome (n = 45) and ceftazidime (n = 52) gave similar clinical success rates (82% and 81% respectively. In febrile episodes in neutropenics (FNE), cefpirome and ceftazidime were similar (92/127 vs 86/119) although pathogens were more likely to be susceptible to cefpirome. Similarly, cefepime is as effective as ceftazidime or piperacillin/gentamicin in FNE. In the treatment of nosocomial pneumonia, cefpirome is as effective as ceftazidime, either as monotherapy (62% success for both antibiotics) or