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LESSONS FROM A SYMPOSIUM ON INFECTIOUS DISEASES AND TRAVEL MEDICINE HELD IN THE COLLEGE ON 4-5 DECEMBER 1997*

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It has only recently been recognised that man will always fail to vanquish all pathogens. Some pathogens have been eliminated because they were, genetically speaking, too stable for their own good and thus were vulnerable to immunisation; however, others mutate faster than we can develop specific therapies against them. Although the battle will be continuous, it will be worth fighting. This symposium identified some of our weaknesses and discussed counter-attack strategies. As a wartime strategist might state, 'The key factor is intelligence. We need to know what the enemy is planning and stop them before they start'.

HUMAN IMMUNODEFICIENCY VIRUS

Dr R. Brettle, from the Infectious Disease Unit in Edinburgh, focused on HIV infection. The measurement of virus load has emerged as an accurate predictor of medium-term risks of mortality and development of opportunistic infections, whereas the CD4 count predicts the immediate risk.

The cumulative number of HIV deaths plotted against time had been a straight line prior to 1994. Subsequently zidovudine monotherapy was shown to be successful in the short term, reducing both deaths and the incidence of opportunistic infections, but the effect had only lasted about 18 months. In 1996 the DELTA trial showed that deaths and opportunistic infections could be further reduced by dual therapy; now it is known that triple therapy is better still.

The use of laboratory markers as outcome measures ('surrogate markers') in trials of clinical care has become the rule as the natural history of HIV infection is too long to await clinical outcomes. Even relatively small reductions in viral load may be beneficial, but the hope is that greater reductions associated with triple therapy will be associated with a longer duration of risk reduction. The absolute level of viral load is seen as important; indeed, aiming for an undetectable viral load is the ideal. However, the reduction in viral load is proportional: the higher the initial load, the less likely that a reduction to undetectable levels can be achieved, even with triple therapy. Quadruple therapy may well prove to be better still but, as with present therapy, patient compliance would be an increasing problem, particularly if patients have to take complex regimens when they are asymptomatic, as well they might be, if treatment began when the viral load was relatively low in an attempt to suppress HIV completely.

Although cost-effective compared to some other medical interventions, the extra cost to the National Health Service would be considerable: in Edinburgh the cost would be about three million pounds a year, every year, if all HIV-positive patients were to be so treated.

Dr A. Pozniak, of King's College Hospital, London, re-emphasised the immediate proportional risk of opportunistic infection associated with a low CD4 count in HIV infection. Cotrimoxazole, used prophylactically in those with a CD4 count of less

*A list of speakers and the titles of their papers presented at this 37th St Andrew's Day symposium is recorded in *Proceedings* Vol.28, p.134.

than 200, has almost eliminated *Pneumocystis carinii* pneumonia in patients known to be HIV-positive; however, undiagnosed patients are still presenting. Cotrimoxazole also reduces the incidence of toxoplasmosis.

It is still uncertain whether increases in CD4 counts brought about by anti-retroviral therapy represents immune restitution, although the 'wasting' syndrome induced by cryptosporidiosis or microsporidiosis had been reduced by anti-retroviral therapy alone. However, there are patients with CD4 counts above the usual risk levels for cytomegalovirus retinitis, achieved by anti-retroviral therapy, who nevertheless still develop the condition.

Mycobacterium avium intracellulare (MAC) infection identifies patients with a poor prognosis. With the use of highly effective anti-retroviral therapy, MAC is now presenting with focal infections rather than the previous early systemic spread with positive blood cultures. Prophylaxis with rifabutin or azithromycin may be possible, but there is concern that such widespread use of rifabutin could result in emergence of rifampicin-resistant *Mycobacterium tuberculosis*. Therapy of MAC usually requires clarithromycin and ethambutol, perhaps in association with other drugs depending on sensitivity testing. It remains unclear as to when, if ever, patients should discontinue therapy.

Mycobacterium tuberculosis infection rates are soaring. In 1990 there were about 7.5 million cases worldwide and it is predicted that at the start of the new millennium there will be just under 12 million cases, mostly HIV-associated, and often presenting in an atypical fashion. The same management principles apply to tuberculosis as to MAC. The principles themselves have been known for years: effective public health interventions. Multidrug resistance to *Mycobacterium tuberculosis* was often found associated with non-compliance and only secondarily with HIV.

The identification of *Herpes simplex virus* type 8, presumably a sexually-transmitted opportunistic pathogen in the HIV-positive patients as a cause of Kaposi's sarcoma, means that it might well be preventable by safe sexual practices.

Overall, on balance, the news is good. Certainly opportunistic infections are disappearing because of improvements in anti-retroviral therapy.

ANTI-VIRAL THERAPY

Dr D. Pillay, from Birmingham Heartlands Hospital, summarised developments in anti-viral therapy. Fifteen anti-viral medications are currently licensed in the United Kingdom, but relevant viruses have shown the ability to develop drug resistance to all agents except ribavirin. A further 16 anti-virals are in clinical trials and yet others are nearing clinical testing.

Lamivudine has shown promise against hepatitis B. During hepatitis B infection the hepatitis B DNA changes to RNA and back to DNA; lamivudine can affect this latter change thereby reducing, but not eliminating, the formation of hepatitis B-directed DNA. Resistant 'escape mutants' have occurred in bone marrow transplant patients and the higher the viral load the greater the resistance experienced. It may be that resting DNA in hepatocytes needs to be activated before lamivudine can be most effective.

Cidofovir may have a role in *Herpes simplex* infections which are resistant to acyclovir (mostly in the HIV-positive) as it does not need to be activated by viral thymidine kinase.

Pleconaril has shown itself to be effective against enteroviral meningitis, leading to recovery in 4 days compared to 9.5 days, with durations of headache reduced from 18.3 days to 6.5 days and of analgesic requirement to 5.3 days from 11.5 days. The need for rapid diagnostic techniques to enable prompt use of such drugs is important.

CREUTZFELDT-JACOB DISEASE AND BOVINE SPONGIFORM ENCEPHALOPATHY

Dr J. Ironside, of the Western General Hospital, Edinburgh, recounted the experience to date of Creutzfeldt-Jacob Disease (CJD) and its relationship to Bovine Spongiform Encephalopathy (BSE). Human routes of exposure to BSE include occupational (contaminated food or BSE infected cattle), environmental (farms, abattoirs), dietary (infected bovine tissue entered the food chain between 1989-1990) and pharmaceutical (potentially infected material used in the production of some drugs). New version CJD (nvCJD) has occurred in younger patients (average age: 26 years, range: 14-49). Early symptoms are psychiatric, persistent parasthesiae or dyasthesiae, ataxia, myoclonus or chorea. Dementia or akinetic mutism are late features. Thirty-seven per cent of the population have an increased genetic predisposition to nvCJD. Treatment of such prion diseases will be difficult if not impossible.

BACTERIAL MENINGITIS

Dr U. B. Schaad, a paediatrician from Basel, gave a comprehensive overview of bacterial meningitis. Significant historical dates for this condition are: 1891 - lumbar puncture was introduced; 1906 - serotherapy; 1940s - penicillin; 1980s - third-generation cephalosporins; 1990 - *Haemophilus influenzae* type b vaccination and subsequent virtual disappearance of *Haemophilus influenzae* meningitis; and, since 1995, pneumococcal resistance to beta-lactams has become an emerging problem. Significant advances have been made in early diagnosis, intensive care management, pathophysiological knowledge, mechanisms of neurotoxicity, and prevention. The timing and choice of antibiotic, the need for imaging and use of steroids (specifically dexamethasone) are still matters for debate.

Whilst the meningeal infection can be treated, the management of the associated inflammation remains a problem. Dexamethasone can down-modulate immune responses and reduce cytokine production, thus reducing cerebral oedema and intracranial pressure. A meta-analysis of ten evaluable trials suggests that dexamethasone given before the first dose of antibiotic reduces the subsequent hearing loss and neurological deficit in *Haemophilus influenzae* type b meningitis and *Strep. pneumoniae* meningitis in children. The potential role of dexamethasone in meningococcal meningitis was uncertain: there was no evidence for it causing a delayed sterilisation of the cerebrospinal fluid. Whether these results apply to meningitis in neonates or adults is not known.

The potential problems with dexamethasone are that other diagnoses might be masked, or that the antibiotic penetration into cerebrospinal fluid might be delayed.

Dr Schaad concluded that immediate treatment was of the essence, that a lumbar puncture was rarely indicated, and that routine head scanning was not required and should certainly not delay treatment.

INVASIVE FUNGAL INFECTIONS

Dr D. Denning, of North Manchester General Hospital, reviewed invasive fungal infections. There has been a 20-fold increase in incidence of candidaemia between 1981 and 1997. With the exception of *Candida tropicalis* which causes a high fever with a diagnostically suggestive rash, the presentations of candidaemia are relatively non-specific with low-grade fever, or general deterioration or lack of improvement during treatment of another condition or even septic shock. Risk factors identified are relatively common and thus unhelpful, and include central lines, patients on two or more antibiotics, a raised serum creatinine concentration or transfer from other hospitals.

Blood cultures may be negative: in only about 60% of autopsy-proven systemic candida infections could the organisms be grown during life. Therefore, even one positive blood culture may be significant.

Candida infection has a changing epidemiology with a 'stunning rise' in resistance to anti-fungal agents of *C. glabrata* and *C. tropicalis*, almost certainly attributable to the widespread use of fluconazole. Ninety-seven per cent of *C. albicans* is sensitive to fluconazole, the drug of first choice if *C. albicans* has been positively identified as the organism responsible; if not, amphotericin should be used initially. Intravascular catheters should be changed and their tips sent for fungal (and bacterial) microscopy and culture.

In immunosuppressed patients Aspergillus should be suspected. Classically there is a fungus ball in a tuberculous cavity; the chest X-ray is an insensitive investigation, CAT scanning is much more useful. All neutropenic patients with pulmonary symptoms should be scanned without delay. Bronchoscopic bronchial lavage misses up to 50% of cases and culture is less sensitive than cytology. No less than two-thirds of patients who die of aspergillosis die without the diagnosis having been suspected during life. If there is focal lung disease near the great vessels, then emergency resection is required. If the lesion is peripheral then immediate diagnostic needle biopsy (providing the platelet count is not dangerously low) and medical treatment are indicated.

The best treatment for invasive aspergillosis is not clear. If oral treatment cannot be given, then amphotericin should be given intravenously. If the patient has a stimulated P450 hepatic enzyme system, for example resulting from phenytoin therapy, then again intravenous amphotericin should be given as, if it is not, absorption from the patient's intestine is not certain. If oral therapy is possible, intraconazole should be given as a 600mg loading dose followed by 400mg daily. Amphotericin is relatively cheap, but if there is significant renal dysfunction then a lipid preparation of amphotericin should be used.

EPIDEMIOLOGY OF TRAVEL-RELATED INFECTION

Dr E. Walker, of Ruchill Hospital in Glasgow, reported a 400% increase in foreign travel over the last 20 years. Travellers at risk of illness include the inexperienced, young children, those with pre-existing illness, the pregnant and the disabled, all of whom now expect to travel unhindered. The incidence of travel-related illness should not be based on those who become unwell upon their return because many longer term visitors have their illness abroad: for example, about 2,000 patients presents annually with malaria after returning to the United Kingdom; this figure remains static despite increased numbers of travellers to malarial areas. The number who have their malaria treated abroad is uncertain. The incidence of hepatitis A in travellers has also been kept static by immunisation.

ADVISING TRAVELLERS AT SPECIAL RISK

Dr K. Smith, from the Foundation for AIDS Counselling, Treatment and Support, London, recounted her experiences of advising travellers with special problems, particularly HIV-positive travellers, and emphasised that in all cases there had to be a risk-benefit discussion with the patient. The pregnant and diabetics deserve special mention. Most airlines are reluctant to transport women who are more than 32 weeks pregnant. Insulin-dependent diabetics can have difficulties with time zones, timing of meals on planes, unpredictable activity levels whilst travelling and, in some countries, explaining why they carry injecting equipment.

A full doctor's letter is an absolute necessity, as is adequate insurance ('adequate' meaning a knowledge that policies would not be invalidated if a claim was made and there were pre-existing risk factors) and contingency plans if patients do become ill while travelling.

ILLNESS IN THE RETURNING TRAVELLER

Dr P. Chiodini, Consultant Parasitologist at the Hospital for Tropical Diseases in London, reminded us that illness in the returned traveller is not necessarily related to the travel nor necessarily of infective origin. At the Hospital for Tropical Diseases, malaria is responsible for 44% of febrile illnesses with 280 cases of *Plasmodium falciparum* infection; typhoid fever was responsible for 5% of febrile illnesses. A detailed history and examination(s) are vital. Blood films and cultures accompanied by urinanalysis, full blood counts, biochemistry, chest X-ray, stool culture and microscopy, and serology will identify the diagnosis in most cases although the role of serology is probably overemphasised. If the diagnosis has not been made by the second week then paired sera, for identification of changes in antibody concentrations, scans and specialised radiology may be drawn into the spectrum of investigations.

Diseases which pose diagnostic challenges include malaria, leishmaniasis, amoebiasis and tuberculosis. The new 'dipstick' malaria tests (ParaSight F and Malaria Pf), based on detecting histidine-rich protein, have high sensitivity and specificity and provide added diagnostic precision, particularly in hospitals where laboratory workers lack experience in examining of blood films for malaria. Schistosomiasis may cause diagnostic problems if it presents with giant urticaria as a Katayama type reaction. The schistosomal ELISA, whilst sensitive and specific, may not become positive for three months after infection.

Particular groups at higher risk of acquiring travel-associated disease include backpackers, voluntary workers, agricultural and health care staff. There are concerns about increasing numbers of young people going to the developing world during a 'gap year' prior to starting higher education, who are also a high risk group, particularly for sexually transmitted disease. One recent clinic-based survey of 757 young travellers found that 20% had new sexual partners whilst abroad, two-thirds had not used condoms, and between 5 and 7% developed a sexually transmitted disease. HIV infection was identified in 2.2%.

Cyclospora is a recently identified, and frequently under-diagnosed, waterborne coccidian protozoon. It has a mean incubation period of 11 days and causes diarrhoea in all of those infected. The symptom pattern is similar to that of *Giardia lamblia*, but vomiting, which is unusual in giardiasis, occurs in a fifth of those with cyclospora. Treatment is with cotrimoxazole.

THE LILLY LECTURE - TRAVEL CLINICS

Dr C. Ericsson, of The University of Texas-Houston Medical School, in the Lilly Lecture, surveyed the practical dilemmas faced by clinicians in travel clinics. The mortality of travellers is actually less than that of matched groups of non-travellers, but this was not a reason to be less vigilant. The test of the effectiveness of travel health advice and prophylaxis is the number of cases averted. For example, this field is continually developing: new vaccines for enterotoxigenic *E. coli*, a frequent cause of diarrhoea in travellers, offer the promise of significant benefit.

New information technology enables the traveller to access comprehensive and up-to-date travel advice, either directly or via the travel industry. Travel health advisors should forge partnerships with the travel industry.