

7 Abstracts from the 7th Western Pacific Congress of Chemotherapy and Infectious Diseases

Organized by the Hong Kong Society for Microbiology and Infection

December 11-14, 2000

Management of Neutropenic Fever

Peter Philips

Division of Infectious Diseases, St. Paul's Hospital, Vancouver, BC, Canada

Febrile neutropenia is a frequent complication in hematology-oncology, BMT, and solid organ transplantation. Approximately 50% of those who develop febrile neutropenia have a documented or occult infection. Febrile patients with severe neutropenia ($<100/\text{mm}^3$) have bacteremia in up to 20% of cases. Initial evaluation should include careful history and physical examination with particular attention to the upper and lower respiratory tract, skin, IV sites, abdomen and perianal area. Choice of initial antibacterial therapy must be individualized and depends upon: clinical findings; most frequent pathogens and resistance profiles for the hospital; use of any recent antibacterials (e.g. prophylaxis), and anticipated duration of neutropenia (i.e. low-risk if expected to be ≤ 10 days). Low risk patients who also meet other criteria may be suitable for outpatient oral therapy. Inpatient management options include: monotherapy (imipenem, meropenem, ceftazidime, or ceftepime), duotherapy (aminoglycoside plus antipseudomonal beta-lactam), or the combination of vancomycin plus one or two drugs for selected patients at particular risk of serious gram positive bacterial infections. Many centres have observed an increasing proportion of infections due to gram positive bacteria in recent years, particularly coagulase negative and positive staphylococci, and alpha-hemolytic streptococci. The presence of polymicrobial infection at some sites (e.g. lower respiratory tract) has been increasingly recognized. Further investigations should be considered for patients who have persistent fevers including CT scan of the chest, ultrasound \pm CT scan of the abdomen; and possibly serologic studies (e.g. *Aspergillus* galactomannan, β -1, 3-glucan). Various adjustments to the initial regimen are more often required in high-risk patients and are dependent upon: the duration of fever and general condition of the patient; development of clinical or culture proven sites of infection, including susceptibility patterns; and drug toxicities. Adjustments to the regimen may include: the addition of vancomycin; addition of second drug for gram negative bacterial coverage; addition of empiric antifungal therapy; and consideration of other interventions (e.g. removal of central venous catheters, or surgical resection of a localized site of invasive fungal

infection encroaching upon a major pulmonary vessel). The duration of therapy is dependent upon specific diagnostic findings, and the duration of neutropenia and fever.

New Antiviral Agents

Paul D. Griffiths

Professor of Virology, Royal Free and University College Medical School, London, UK

Antiviral chemotherapy has progressed to the stage where we now have 29 licensed compounds. This tremendous achievement in a short time-scale has nevertheless brought two problems: (1) the development of resistance as a factor to be considered in patient management; (2) drug-drug interactions, either between two antivirals or between one antiviral and another medication.

Nucleoside compounds which are specifically activated by a virus-encoded enzyme have stood the test of time. The prototypical example is acyclovir, which has proven safe and effective in over 20 years of prescribing. Since resistant strains are metabolically disadvantaged, resistance is not a clinical problem in the immunocompetent host, and still remains uncommon in the immunocompromised.

In contrast, nucleosides which are not specifically activated (with zidovudine for HIV and lamivudine for HBV or HIV being typical examples) are not so successful. Activation by cellular enzymes produces selective pressures against cells. The involvement of only one virus-encoded enzyme in the mechanism of action also facilitates the development of resistance.

Non-nucleoside compounds are extremely potent, yet the allosteric-type activity of the HIV compounds means that resistance can be rapidly selected.

Protease inhibitors profoundly interfere with the replication of HIV, but resistance can develop either in the protease itself or in the cleavage sites of the HIV polyprotein. The proteases of hepatitis C, herpesviruses and rhinoviruses represent targets for novel antiviral compounds.

Two neuraminidase inhibitors are licensed for the treatment and prophylaxis of influenza and further examples are in the pipeline.

Examples of pharmacokinetic interactions are readily found in the therapy of HIV because of the need to administer triple or quadruple therapy as part of highly active anti-retroviral therapy. Examples include the mutual antagonism of zidovudine and stavudine, which compete for intracellular phosphorylation pathways, and the ability of protease inhibitors to inhibit cytochrome P450 isoenzymes. The latter effect can increase the area under the concentration-time curve of plasma levels of protease inhibitors; indeed, ritonavir (the most potent P450 inhibitor) can be used at low-dose to increase the bioavailability of other protease inhibitors, such as lopinavir.

Finally, in addition to neuraminidase inhibitors, other antiviral drugs are in clinical trials which have extracellular sites of antiviral action. These include T20, a synthetic peptide which binds the trimeric hydrophobic membrane-attack complex of gp41, and AG7088, a peptidomimetic inhibitor of the protease encoded by rhinoviruses. Optimisation of the pharmacokinetics of compounds administered directly to the respiratory mucosa may be difficult due to increased respiratory secretions, coupled with the ability of the host to forcibly eject mucus containing the compound. Evaluation of antiviral potency in clinical trials may therefore have to rely on empirical measures.

Enterococci - An Emerging Pathogen?

Bryan P. Simmons

Methodist Healthcare, Memphis, Tennessee, USA

Enterococci are the third most common cause of endocarditis and have emerged as a common cause of nosocomial infections, especially in intensive care units (ICUs). According to the National Nosocomial Infections Surveillance System (NNIS), in the ICU enterococci account for over 10% of pathogens each for blood stream infections (BSI), urinary tract infections (UTI) and surgical site infections (SSI). Enterococcus was the single most common reported pathogen from SSI. Virulence factors include cytolysin and bacteriocin production, adhesion and aggregation proteins, extra cellular superoxide production and altered interactions with host immunity. Over 20% of enterococci from ICUs are vancomycin resistant (VRE). Patients who have enterococcal bacteremia have a high mortality, especially for VRE. Up to one third of *Enterococcus faecium* are resistant to ampicillin, vancomycin, gentamicin and streptomycin in the U.S. Resistant genes can be spread by transposons and plasmids. Animal feeds containing avoparcin in Europe and virginiamycin in the U.S. are blamed for selecting VRE and quinupristin/dalfopristin-resistant enterococci, respectively, for transmission to humans.

Overuse of antibiotics in humans seems to be fueling the increase of VRE in the U.S. Potential control measures for VRE include decreasing antibiotics in animal feeds, hospital infection control, new antibiotics, and vaccines; we must think globally but act locally.

The Explosive Rise of Multi-Drug Resistant *S. Pneumoniae* in Hong Kong

DJ Lyon

Consultant, Department of Microbiology, The Prince of Wales Hospital, Hong Kong

The 1990s have been the rapid emergence of penicillin and multi-drug resistant *S. pneumoniae* in many parts of the world. In East Asia, very high levels of antibiotic resistance have been reported in certain locations in recent years - Korea, Japan, Taiwan and Hong Kong in particular. Current evidence suggests that the rapid dissemination of multidrug resistant *S. pneumoniae* is due in large part to the dissemination of a limited number of clones, in particular strains related to the Spanish serotype 23F clone, although regional clones such as the Taiwan serotype 23F clone have also been described. It is assumed that such clones are being selected by antibiotic usage pressure, but data on antibiotic usage are limited in some areas.

In Hong Kong, the first resistant pneumococcus was described in 1990. Subsequently, the proportion of strains which were insusceptible increased, particularly during the winters of 1993/94 and 1994/95. At the Prince of Wales Hospital, Hong Kong, the prevalence of reduced penicillin susceptibility rose from 10% in 1993 to 50% in 1997, with 85% of these isolates being multidrug resistant. The first period 1993-1995 saw the very rapid rise in the % of antibiotic resistant *S. pneumoniae* with a very high rate of multidrug resistance - the phase of "clonal dissemination". The subsequent period of 1995 onwards has seen a stabilisation of levels of antibiotic resistance - the "stabilisation phase". Studies of *pdp* fingerprint patterns and PFGE profiles showed that most resistant isolates fell into two groups, one expressing serotype 23F or 19F and the other serotype 6B, and within which the strains had highly similar *pbp* and PEGE profiles. These two groups were highly similar to representative strains of the of the Spanish 23F and Spanish 6B clones. Using multilocus sequence typing (MLST), the Hong Kong isolates gave allelic profiles identical to the Spanish 23F clone (for 23F/19F strains) and Spanish 6B clone (or 6B strains). Sequencing of the capsular genes of the serotype 19F and 23F strains has suggested that these represent two distinct lineages within the Spanish 23F clone. It is likely therefore that the rapid spread of drug resistant *S. pneumoniae* in Hong Kong is due to the dissemination of at least 3 imported clones, presumably under antibiotic selective pressure.

Good data on community prescribing of antibiotics are not currently available in Hong Kong, and community based surveillance has only recently been started. Control of drug resistant *S. pneumoniae* will require an active programme to optimise antibiotic usage in the community, but this is not currently in place.

The Present and Future of Fluoroquinolones and Rifamycins in the Treatment of Tuberculosis

W W Yew

Chief of Service, Tuberculosis & Chest Unit, The Grantham Hospital, Hong Kong

The fluoroquinolones were found to possess good *in vitro* activity against *Mycobacterium tuberculosis* in the 1980s. Subsequently they were identified to have clinical efficacy against tuberculosis as well. The current indications for the use of this class of drugs in tuberculosis should be limited to multidrug-resistant tuberculosis (MDR-TB) and tuberculosis in the face of hepatic dysfunction or other serious antituberculosis drug-related intolerance. The potentially advantageous therapeutic characteristics of fluoroquinolones include (1) high peak serum drug concentration: minimum inhibitory concentration ratio, (2) good tissue penetration particularly into the lungs and (3) good tolerance by patients on long-term administration. However, great prudence should be exercised in the use of the existing members to prevent development of cross-resistance among emerging members of the class. This would hamper the clinical usefulness of newer members with greater antimycobacterial activities.

Development of new rifamycins has been slow in the past few decades. Rifabutin only has activity superior to rifampicin *in vitro*. Its early bactericidal activity is lower than that of rifampicin and the clinical efficacy of the 2 rifamycins in drug-susceptible tuberculosis patients is approximately equivalent. Because of its marked cross-resistance with rifampicin, it has very limited role in the management of MDR-TB. Rifapentine is a cyclopentyl rifamycin with a half-life of 14 hours. It has a potential role for use as once-weekly administration in the continuation phase of treatment for tuberculosis, together with isoniazid. This drug thus would further facilitate the delivery of directly observed treatment. Rifalazil, a benzoxazinorifamycin, has much more potent activity than rifampicin and even rifabutin against *Mycobacterium tuberculosis* both *in vitro* and *in vivo*. Human (phase II) trials are on-going. Unfortunately, both rifapentine and rifalazil are unlikely to be useful for clinical management of MDR-TB, because of cross-resistance with rifampicin. The potential of using rifabutin or rifapentine, alone or with other agents as preventive therapy, in at risk patients infected with *M. tuberculosis* remains to be evaluated.

Dengue in Travellers

Wilina Lim

Government Virus Unit, Department of Health, Hong Kong

Dengue is a mosquito-borne infection of major international public health concern. Annually, there are an estimated 50-100 million cases of dengue fever and 250,000-500,000 cases of dengue haemorrhagic fever in the world. The disease is now endemic in more than 100 countries. South East Asia and the Western Pacific are most seriously affected.

Dengue viruses belong to the family of Flavivirus and comprise four distinct serotypes causing illnesses ranging from dengue fever, dengue haemorrhagic fever and dengue shock syndrome. Diagnosis of dengue is established by serology, virus culture and detection of virus with the use of polymerase chain reaction (PCR). Serological diagnosis depends on a rise in antibody titre in paired serum samples or the presence of IgM. Virus culture and PCR are useful to confirm the diagnosis and are essential for typing the virus.

Movement of people from one geographical area to another plays an important role in spreading dengue viruses. Starting from the 18th century, dengue virus was known to spread via sailing vessels used in commerce and slave trade, and when people began moving more frequently between continents. In recent years, airplanes make it easier for dengue virus to be rapidly transported. There is, however, a lack of data regarding the actual frequency of this infection in international travellers. Studies of non-tourists allow for an estimate of roughly one illness per 1,000 travellers. Depending on contact with vectors and duration of stay in endemic areas, the risk among tourists is possibly much lower than 1 in 1,000.

Hong Kong is a dengue non-endemic area with large number of people moving in and out of this area. Though *Ae. aegypti* is not found in Hong Kong, the secondary vector, *Ae. albopictus* is. In 1999, the number of residents visiting other areas and countries were 53 million, with at least a few million visiting endemic neighbouring areas and countries. During the same period, there were 10 million visitors to Hong Kong. From 1995 to 2000, however, there had been only 48 confirmed imported dengue cases. The patients invariably presented with fever, headache, joint pain and thrombocytopenia and were diagnosed as dengue fever in hospitals or clinics. No severe haemorrhagic manifestations or mortality were recorded. The mean age of these patients was 38 (range 7-66), with male and female equally affected. Most had visited Indonesia, Thailand, Singapore and the Philippines. Prevention of dengue spread has been focused on early detection, vector control and health education.

Human Herpesviruses 6 and 7

JSM Peiris¹ and SSS Chiu²

¹Departments of Microbiology and ²Paediatrics, The University of Hong Kong, Hong Kong

Human herpesvirus 6 (HHV-6) and 7 (HHV-7) are recently discovered lymphotropic herpesviruses with tropism for CD4+ T-cells. HHV-6 is associated with exanthem subitum in children and disease in the immunocomprised host. Virus culture has remained the only reliable method of laboratory diagnosis but is not applicable in a routine diagnostic setting. We have developed methods useful for diagnosing primary HHV-6 infection in a single acute blood specimen. These are (a) the profile of viral DNA detected by PCR in peripheral blood in the absence of IgG antibody in the plasma, (b) the detection of HHV-6 DNA in the plasma, and (c) high HHV-6 DNA

viral load in peripheral blood leukocytes. Using these methods, we find that HHV-6 is a major cause of hospitalisation of children during infancy. Some of them do not manifest the typical rash of exanthem subitum and will not be recognised without laboratory investigation. In the immunocompromised, HHV-6 infection or reactivation may lead to pneumonitis and is a treatable cause of myelosuppression and graft failure in the bone marrow transplant recipient. HHV-7 is a more enigmatic virus and its clinical role is still undefined. A minority of primary HHV-7 infections are associated with an exanthem subitum-like illness but most infections remain asymptomatic. Our data suggests that HHV-7 reactivation in the renal transplant recipient is associated with high CMV viral load and the progression to CMV disease. By logistic regression analysis, this association is independent of the level of immunosuppression and the mechanism of such an interaction remains to be defined.



Department of Community & Family Medicine
The Chinese University of Hong Kong
Diploma Programme in Health Services Management
and Public Health

September 2001 intake

The programme provides training in epidemiology, biostatistics, health economics, health management, principles of evidence-based health care and health care systems for practitioners in public health and hospital administration in Hong Kong. It will support candidate's preparation for the Hong Kong College of Community Medicine Part I Fellowship examination in Administrative Medicine and Public Health Medicine.

Admission Requirements

A bachelor's degree in medicine or an approved health related field. For non-professional degree holders, honours not lower than second class are required.

Course Duration & Fees

One year part-time. The fees for the whole course will be HK\$35,000 which is payable in two terms.

Application

- Forms and relevant materials are obtainable either in person or by post from Ms Yu/Miss Shum, Department of Community and Family Medicine, The Chinese University of Hong Kong, 4/F Lek Yuen Health Centre, Shatin, N. T. (For postal requests, please enclose a stamped (\$2.1) self-addressed A5 size envelope)
- Fee: HK\$150
- Deadline of application: 30 June, 2001

For further enquiries, please call Ms Yu/Miss Shum from 2 to 5 p.m. (Mon to Fri) at 2692 8326, or fax her at 2606 3791 or email swyu@cuhk.edu.hk.