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Contents

Immunization of healthcare workers

T.K. Ng, Department of Pathology, Princess Margaret Hospital

Due to contact with patients and their infective materials, healthcare workers (HCW) (including doctors, nurses, medical and nursing students, laboratory staff, auxiliary health profession, administrative staff and hospital volunteers are at risk of exposure to and infection of vaccine preventable diseases. Infected healthcare workers may in turn infect other susceptible patients with grave consequences in some cases.

The immunization programme should be part of personnel health programmes in the hospital. The workers should be evaluated before job placement. This include immunization status and medical history that may predispose personnel to acquiring infectious diseases. Screening for some vaccine preventable diseases may be cost effective. The health record of the individual should be maintained and the confidentiality be ensured.

Decision on which vaccines to include in immunization programme should be made by

1. considering the risk of exposure and the consequence of not vaccinating the personnel;
2. nature of employment, (type of contact with patients and their environment);
3. -characteristics of at risk patient population.

On the basis of documented hospital transmission, the following immunization are highly recommended for all HCW.

Hepatitis B

Hong Kong is an endemic area for hepatitis B virus (HBV) infection with carrier rate of 8% in the general population. It can be transmitted through percutaneous and mucosal exposure to blood or body fluids. The transmission is efficient averaging 30% per exposure depending on the virus load in the source patients. 5-10% of HBV infected HCW may become chronically infected and are at risk for chronic hepatitis, cirrhosis of liver and primary hepatocellular carcinoma. The immune response after a full course of immunization (0,1,6) should be checked. The consensus is that for the responders there is no need to periodically monitor the antibody titre or give booster. For non-responders, a repeat course may be tried. If there is no effect, the HCW should be given hepatitis B immunoglobulin (HBIG) after exposure within 7 days.

Rubella, measles and mumps

There is a combined vaccine that can give protection to all three viruses. Rubella can cause abortion and foetal malformations in pregnant women particularly in the first trimester. HCW should be immune to rubella. There is no need to check antibody before giving MMR. Being a live vaccine, it should not be given to pregnant women and immunosuppressed persons. Women should practice contraception for 3 months after vaccination.

Varicella -zoster virus

Varicella can cause complicated infection in high risk groups such as immunocompromised persons, infants born to susceptible mothers and preterm infants. All HCW should be immune if they have contact with such patients. Screening for varicella-zoster antibody may be cost effective because varicella vaccine is still quite expensive. Those who have no history of chickenpox should be screened for antibody. Two doses of vaccine one month apart are required for adults.

Other vaccines that are worth mentioning:

BCG

The efficacy of BCG in preventing pulmonary tuberculosis (TB) in adult is controversial ranging from 0-80% in various studies although there is evidence that serious infection such as meningitis in children and infant can be minimised. For those few HCW who have not received BCG in childhood and Mantoux test negative most countries recommend giving BCG especially when multiple drug resistant TB are prevalent.

Influenza

Influenza vaccine is recommended for HCW in some countries to prevent transmission to high risk patients and shortage of manpower in high seasons. However annual revaccination is needed which may affect the uptake rate.

Rabies

Pre-exposure vaccination is recommended for personnel who work with rabies virus or infected animals such as laboratory workers. Post-exposure prophylaxis should be given to those who have open wound or mucous membrane exposure to patients saliva.

Adoption of standard precautions in the care of patients should decrease staff exposure to majority of infectious diseases. Provision of immunity to vaccine preventable diseases especially those that are transmitted through droplets or airborne route and percutaneous exposure will enhance the safety and welfare of the healthcare workers. Optimal use of vaccine will prevent transmission and eliminate costly work restriction of susceptible HCW after exposure. It is far more cost effective than case management and control of outbreak.

Molecular analysis of hepatitis A virus in outbreaks

W.L. Lim, P.K.C. Cheng, J.Y.C. Lo, C.W.S. Tse[1] and T.K. Ng[1]
Government Virus Unit, Department of Health, and Department of Pathology, Princess Margaret Hospital[1]

Hepatitis A infection is endemic in Hong Kong. It is seasonal in occurrence with increasing incidence in winter and spring. In the past 20 years, the pattern of hepatitis A infection in Hong Kong has changed. The introduction of higher standards of hygiene has, paradoxically, increased the incidence of hepatitis A in young adults as more people no longer have acquired immunity by the time they reach adulthood. The percentage of immune adults in the 21 – 30 age group decreased from 75% in 1979 to 32% in 1994 (1).

Consumption of contaminated raw or partly cooked bivalve shellfish appears to be an important route of infection. Of the notified cases in 1991/92, half the patients gave a history of consuming bivalve shellfish, among which more than half admitted to having eaten raw or partly cooked shellfish. Experimental study carried out in the Government Virus Unit using oysters spiked with laboratory strain of hepatitis A virus (HAV) HM175 showed that for oysters ranging from 13.9 to 45.9 g, HAV infectivity could be destroyed by boiling for 3-5 min, or deep-frying for 1.5-3 min (2). Due to culinary habits of local residents, this requirement of heat treatment to inactivate HAV is seldom attained in normal preparation of shellfish dishes. It is also very difficult to ensure that bivalve shellfish are safe microbiologically because of the complex channels of supply in Hong Kong.

Starting in the summer of 1999, over a 3-month period, 6 persons residing in one institution were infected with HAV. From December 1999 to February 2000, 17 persons in other institution were also infected with HAV (Figure 1). To determine if the same strain of HAV was responsible for the two outbreaks, HAV RNA were extracted from patients' serum samples and subjected to reverse transcription and polymerase chain reaction (RT-PCR). Seminested PCR was performed using primers chosen to bind to the conserved VP1 capsid region (3). Amplified cDNA was purified and sequenced. By comparing the extent of nucleotide variation within a 140-base region encoding VP1, a measure of the relatedness of individual strains could be made. Nucleotide sequences obtained from 2 samples in the first outbreak and 12 from the second showed they were identical and belonged to genogroup IA (4). Further investigation revealed that there had been patient traffic between the two institutions.

As hepatitis A is endemic in Hong Kong and occurred outside the institutions in the community at the same time as the outbreaks, to determine the genetic relatedness of HAV in the community, HAV RNA in 14 serum samples obtained in each month in 1999 and in the first two months of 2000 were extracted, amplified and sequenced. Genetic comparison showed that though they were all in genogroup IA, they were different from the outbreak strains.

The Government Virus Unit has in the past 3 years regularly analysed shellfish samples to study the level of HAV contamination. An antigen-capture RT-PCR was developed to detect HAV in shellfish samples. Results showed that 15% of local shellfish samples were positive for HAV RNA. cDNA obtained from 37 local shellfish samples were purified and sequenced to determine if they were related to the outbreak strains. Genetic comparison showed that the nucleotide sequence obtained from a batch of clams in May 1999 was identical to the outbreak strain.

In conclusion, genetic sequencing is a useful tool to map out the movement of HAV. Genetic analysis not only showed that the two outbreaks were caused by the same strain of HAV and hence were related, it also showed that the HAV strains from the two outbreaks and clams in May 1999 were identical. Temporally, it could be deduced that shellfish was the probable source of HAV infection in the two institutions and that HAV had been transmitted from person to person in the institutions.

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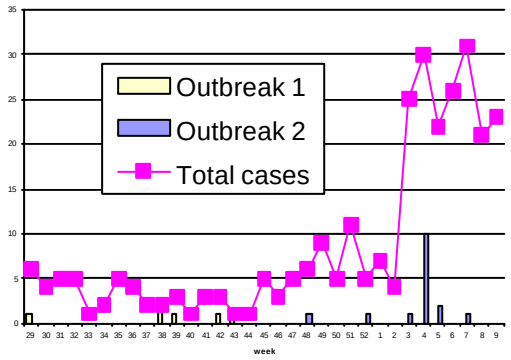
Figure 1. Distribution of time of onset of hepatitis A



Serological tests for syphilis: an update

T.Y. Wong, Department of Medicine and Geriatrics, Princess Margaret Hospital

Two main types of serological tests for syphilis are commonly used nowadays, namely tests for anti-lipoidal antibody and specific anti-treponemal antibodies. Some more specific and sensitive tests are being developed. It is hoped that these tests will facilitate the management of patients with suspected syphilis in the future.

Tests for anti-lipoidal antibody

Anti-lipoidal antibodies, also known as reagin, react with mitochondrial phospholipids extracted from mammalian tissues. Tests in current use include Venereal Disease Research Laboratory (VDRL) slide test and Rapid Plasma Reagin (RPR) test. In VDRL test, the antigen is mixed with heated serum and mechanically rocked on a ringed glass slide. The reaction has to be read with a microscope. By making dilution of the serum a quantitative result can be obtained. On the other hand, RPR is carried out with unheated serum. The clumping is detected by naked eye. An automated version of the RPR test is carried out in an autoanalyser and is particularly useful if large number of predominantly negative sera is to be processed.

The major disadvantage of anti-lipoidal teats is that of false positive reaction. Biological false positive (BFP) reactions are defined as positive reactions with one or more of the anti-lipoidal antibody tests in patients who have no clinical evidence of syphilis and in whom treponemal tests are non-reactive. Acute BFP (lasting less than 6 months) are associated with acute febrile illness, immunization and pregnancy. Chronic BFP reactions are found in association with connective tissue disease (especially SLE), haemolytic anaemia, leprosy, polyarteritis nodosa and other less common conditions.

Test for specific anti-treponema pallidum antibodies

Specific anti-treponema pallidum antibody tests use antigens from virulent Treponema pallidum (T. pallidum). This organism cannot be grown in artificial culture media, but has to be maintained by passage in rabbits. This is expensive and not entirely without hazard. Traditional tests under this category include T. pallidum Immobilisation Test (TPI), Absorbed Fluorescent Treponemal Antibody test (FTA-Abs) and T. pallidum Haemaggluntination test (TPHA). TPI is regarded as the most specific test available. FTA-Abs requires the use of fluorescin microscopy to detect antibodies to treponemes. TPHA detects presence of antibodies by the principle of agglutination of red cells enabling macroscopic reading of result. Thus, it is simple to use and is both sensitive and specific. Enzyme-linked immunosorbent assay (ELISA) gives a quantitative colorimetric result and can be automated.

Positive reactions in both treponemal and reaginic antibody tests can arise as a result of infections with spirochaetes other than T. pallidum. It is impossible to distinguish between yaws, pinta, bejel and syphilis on serological grounds. Borrelial infections, both relapsing fever and Lyme' s disease, will produce positive reactions with both lipoidal and spirochaetal tests for syphilis.

Immunoblotting

Greater precision in the demonstration of specific T. pallidum antibodies can now be obtained by immunoblotting. This technique was developed in the mid-eighties. In this technique a number of specific T. pallidum antigens are presented to test sera on a blotting membrane after separation and purification on an electrophoretic gel. The pattern of antibody responses, rather than the presence of a specific response to one single antigen, is helpful in ascertaining both the stage of an infection and also in differentiating from other treponemal infections.

Recombinant technology

The genes coding for a number of antigens have now been isolated and recombinant proteins produced. These have been incorporated into ELISA tests and promise a new generation of highly specific and sensitive tests for syphilis.

Polymerase chain reactions

This is not a serological technique but is being developed as a test for the diagnosis of syphilis. It detects the presence of T. pallidum specific DNA in tissues or body fluids by amplifying any DNA in a specimen which is complimentary to a specific ' primer' used to detect it. This is highly sensitive. It is being evaluated in the diagnosis of neurosyphilis. It holds a promise of differentiating between syphilis and yaws.

Behaviour of serological tests at various stages of syphilis

Untreated patients

Primary syphilis:

FTA-Abs is the first to become positive. It is positive in 85% of cases. VDRL becomes positive 7-10 days after primary chancre appears. It is positive in about 70% of cases. TPHA becomes positive in about 60 % of cases. A few bands may become reactive on Western blotting.

Secondary syphilis:

All tests are positive, usually to a high titre. Western blotting shows reactivity of many bands.

Latent and late syphilis:

Tests for anti-lipoidal antibody are positive in about 75% of cases. Specific treponemal tests are positive in almost all cases. But the reactions tend to be weaker than in the secondary stage. Western blotting reactivity declines with time.

Treated patients:

After treatment of primary and secondary syphilis, anti-lipoidal antibody disappears in 6 months to 1 year. Tests for anti-treponemal antibody are slower to become negative. If treated, latent and late syphilis anti-lipoidal tests may slowly revert to negative, but anti-treponemal tests remain positive for many years, usually for life. Lipoidal test titres should fall fourfold within a year of successful treatment.

Screening:

Routine sera are traditionally screened by VDRL and TPHA. If either of these is positive, a quantitative VDRL test is carried out and FTA-Abs done to check that the reactions of the screening tests are specific and not biological false positive reactions. ELISA tests using T. pallidum are being used in a number of laboratories for automation reason.

Highlights from Australasian Society for Infectious Diseases Annual Scientific Meeting

T.Y. Tsang, Department of Medicine and Geriatrics, Princess Margaret Hospital

DNA chip technology in infectious diseases practice

DNA microarray technology is poised to revolutionize the study and practice of infectious diseases. This technology is based on the knowledge of the full microbial genome sequences and a large percentage of all human gene sequences and makes possible a rapid, comprehensive assessment of genome structure and function for both pathogen and host. The result has important implications for epidemiology, diagnosis, prognosis, pathogenesis and therapy of infectious diseases. DNA microarrays are high density arrangements on a solid surface of nucleic acid probes with predetermined design and location. The semi-automated detection of hybridized DNA on these arrays is equivalent to tens or thousands of simultaneous, semi-quantitative measurements of genotype and gene expression. They will facilitate microbial strain typing and host susceptibility assessment. They may also facilitate the identification of novel diagnostic and prognostic signatures, based on stereotyped patterns of host gene expression. In this manner, infectious agents may be recognized even before the development of typical disease, and the clinical course for any given patient may be predictable. Finally, DNA array-based data will reveal pathways and molecules which play critical roles in the development of infectious diseases, hence provide novel targets for therapeutic and prophylactic interventions.

Community methicillin-resistant Staphylococcus aureus (cMRSA): an emerging problem worldwide

MRSA continues to be a major problem inside the hospital and frequently causes serious infections. Recently MRSA has been seen in people with no connection to hospitals. These strains are different to hospital strains and are not multi-resistant. The mortality of septicemic cMRSA would be more than 80%. cMRSA has been reported in children in the USA (Chicago and Dallas). Different cMRSA strains have been present in Western Australia for over 15 years. The percentage of cMRSA has been more than 10% in Auckland. cMRSA is disproportionately associated with relatively socially deprived groups such as Aborigines, American Indians and Maoris. cMRSA currently remains sensitive to most non-betalactam antibiotics such as erythromycin, tetracycline and gentamicin. Multi-resistance is likely to develop however. In vitro these strains are not eradicated by betalactams or gentamicin alone. However, the combination of the two results in inhibition. A betalactam in combination with an aminoglycoside may therefore be suitable empirical therapy while awaiting identification and sensitivity results for any community patient who presents with serious Staphylococcus aureus sepsis to a hospital. This is preferable to widespread empirical use of vancomycin.

The role of macrophages in HIV infection

The precise role of macrophages in HIV infection of various tissues and at different stages of disease is still being clarified. Strains of HIV can be classified according to their ability to infect macrophages or T-lymphocyte cell lines. This was initially thought to be defined by the ability of such strains to use the chemokine receptor CCR5 for entry into macrophages and CXCR4 for entry into T-lymphocytes. However there is overlap. Some strains are able to use both CCR5 or CXCR4 (R5 and X4 strains). There is a selection of R5 strains during sexual and blood transmission and a predominance of these strains during asymptomatic infection and even during the phase of immunosuppression. Macrophages are also important target cells for HIV infection in the bone marrow and brain. This may explained why the onset of dementia and peripheral immunosuppression are linked. However in blood and most tissues, especially the lymphoreticular system, T-lymphocytes rather than the macrophages are the dominant infected cells. It is now known that the long lasting latently infected cells which provide a barrier to the successful eradication of HIV by antiretrovirals are quiescent T-lymphocytes. Nevertheless, in the very late stages of HIV infection CD4 lymphocytes are depleted and macrophages are predominant. Furthermore, opportunistic infections of macrophages with mycobacteria or pneumocystis enhance local HIV production. Tuberculosis appears to increase the load of macrophage derived HIV in plasma. Antiretrovirals are also metabolized differently in T-lymphocytes and macrophages. Hence new antiretroviral strategies will need to target both activated and quiescent T-lymphocytes and also macrophages if eradication is ever to be possible.

HIV vaccine

Even in developing countries where antiretroviral drugs are affordable, relapse of HIV infection apparently controlled by antiretroviral combinations is becoming increasingly common. Indeed, transmission of resistant HIV strains is alarming – approaching 10% in many centres and likely to increase. A preventive HIV vaccine would be a quantum advance on current efforts to control HIV infection. While HIV protein vaccine have not shown encouraging efficacy and live attenuated vaccines are unsafe, DNA and fowlpoxvirus vector vaccines are to date both safe and have shown encouraging signs of efficacy. CTL and Th1 responses were dramatically enhanced in both mice and monkeys after giving this DNA/fowlpoxvirus vaccine. High level CTL and Th1 responses to both Env and Gag proteins were observed in all studied monkeys following immunization, reaching levels known to correlate with control of HIV-1 exposure. Inoculation of DNA/fowlpoxvirus vaccinated animals with infectious doses of HIV-1 resulted in very rapid clearance of HIV-1, almost certainly mediated by HIV-specific CTL/Th1 responses. Recently, similar studies in both the USA and UK have broadly confirmed these observations.

Adherence to anti-infective therapy

M.K. So, Department of Medicine and Geriatrics, Princess Margaret Hospital

At the Asia Pacific Postgraduate Forum on highly active antiretroviral therapy (HAART) on 24 - 26 March 2000 in Langkawi, Malaysia, the scientific and practical approaches to strengthen adherence to anti-infective therapy were highlighted.

Dramatic changes have occurred in treatment strategies for HIV during the last several years. These changes have been driven primarily because of potent combination regimens with protease inhibitors and more recently, the non-nucleoside analogues, affording durable viral suppression and restoring immune response for the long-

term. Toxicities with side effects and adverse experiences, however, are not uncommon with the HAART. Mitochondrial toxicities may manifest as neuropathy, myopathy, pancreatitis, hepatic steatosis and lactic acidosis. Metabolic complications with lipodystrophy, insulin resistance and hyperlipidaemia are recognised. Hence the superior efficacy of any regimen could well be due to better compliance and adherence by the patients.

Adherence to chronic therapy is a complex psychosocial and medical issue depending on stage of illness, feedback experience while on therapy, personal belief, knowledge, lifestyle and psychosocial support of an individual , confidence with the therapy prescribed, doctor-patient relationship, peer group influence, just to mention some. This arises invariably in managing other infectious diseases: mycobacterial tuberculosis, chronic hepatitis B, chronic hepatitis C, post-exposure prophylaxis to individual with high risk, malaria chemoprophylaxis, multi-dose vaccination, and even in short course antimicrobial treatment. Various measures can be made use of to improve adherence: interview between patient and doctor, counselling by nurse specialist, more user-friendly regimen, less toxic regimen, workshop, patient hotline etc.

Here are some tips to make it easier to take drugs on time:

- Take your pills with something you do everyday, e.g. brush teeth, eat dinner
- Place your pills near something you use everyday, e.g. your cup, your toothbrush
- Have supplies of your drugs at places where you know you be, e.g. at work, at a friend' s place
- Take supplies with you wherever you go, e.g. backpack, handbag, briefcase, so long as they don' t need to be kept in the refrigerator
- Use a pill box, e.g. carrying pills in a film canister, a pocket pill or dosette box when out and about
- Keep a record of when you need new prescription, e.g. mark in your diary or on a calendar
- If you are always busy or always forget, mark in the diary, use paging reminder service, computer reminders, post it notes, watches anything that trains you to remember
- Find out what to do if you miss a dose or what to do if you miss a meal at pill time, e.g. ask your doctor or a nurse specialist
- Prepare answers for nosy people and talk with friends about your pills, say whatever you are comfortable with, e.g. they are for your long term health, or vitamins, or for allergies
- Think about when and why you miss them, identify doses you may miss regularly

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Extrapulmonary manifestations of *Mycoplasma pneumoniae* infection

Y.W. Kwan, C.W. Leung. Department of Paediatrics, Princess Margaret Hospital

A 10-year-old boy presented with high fever and respiratory distress. He had productive cough for 6 days and high swinging fever (up to 41°C) for 1 week prior to admission. Amoxycillin-clavulanate (Augmentin) was prescribed by his private doctor but no apparent clinical response was observed after 5 days of treatment. He enjoyed good past health and had no history of asthma or chronic respiratory illness.

On physical examination, he was lethargic and tachypnoeic. Decreased air entry and crepitations were noted in the left lung. The cardiovascular system and abdomen was normal. A non-pruritic generalized maculopapular skin rash was present.

After admission, he was treated with intravenous ampicillin and cefotaxime. Chest radiograph showed collapse-consolidation of the left lingular lobe. Haemolysis was detected as evidenced by a drop in haemoglobin level (from 12.0 g/dL to 10 g/dL), a raised reticulocyte count (3.5%) and anisopoikilocytosis in the peripheral blood smear. Erythrocyte sedimentation rate was raised to 76 mm/hr. There was also deranged liver function with an elevated alanine aminotransferase level (628 IU/L) and a decrease in albumin level from 34 to 28 g/L 4 days after admission.

The antibiotic regimen was changed to intravenous clarithromycin and vancomycin in view of the persistence of fever and left lingular lobe collapse. Computed tomography of the thorax was performed and showed pneumonic changes complicated by left lingular lobe collapse and bilateral pleural effusions. Enlargement of bronchopulmonary lymph nodes was excluded.

Serum for anti-mycoplasma IgM was positive and a rise in the convalescent complement fixation titre against *Mycoplasma pneumoniae* was also evident. Sputum for bacteriological culture was negative. The clinical

condition improved on the new antibiotics regimen, with rapid resolution of pneumonia, haemolysis and hepatitis.

Atypical pneumonia was suspected in this patient because of a poor response to the usual β-lactam antibiotics. *Mycoplasma pneumoniae* infection, the commonest cause for atypical pneumonia was serologically confirmed. Two important extrapulmonary manifestations of *Mycoplasma pneumoniae* infection were illustrated by this case, namely haemolysis and anicteric hepatitis. The diagnosis of *Mycoplasma pneumoniae* infection should be suspected in patients presenting with pulmonary infiltrates, with or without pleural effusion, and one or more extrapulmonary manifestations.