PREVENTION OF INFECTION WITH CYTOMEGALOVIRUS, PARVOVIRUS B19, NEW VARIANT CREUTZFELDT-JAKOB DISEASE AND MYCOBACTERIUM TUBERCULOSIS IN CYTOGENETICS LABORATORIES

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RISK OF INFECTION FROM CYTOMEGALOVIRUS (CMV)

Incidence

Congenital cytomegalovirus (CMV) infections remain the leading viral cause of congenital birth defects in the developed world. Despite advances in our knowledge, the epidemiology and natural history of congenital CMV infection are still poorly understood. About 50-85% of the adult population are infected by the age of 40. For most healthy persons who acquire CMV after birth there are few symptoms and no long-term health consequences. Some of those with symptoms experience a mononucleosis-like syndrome with prolonged fever and mild hepatitis. Once a person becomes infected, the virus remains alive, but usually dormant, within the person's body for life. Recurrent disease is rare, but severe impairment of the body's immune system by medication or disease consistently reactivates the virus from the latent state. Infectious CMV may be shed intermittently in the body fluids of any previously infected person without any signs and without causing any symptoms and may be found in urine, saliva, blood, tears, semen, vaginal fluid, faeces, breast milk and amniotic fluid.

Transmission

In children and adults close, intimate contact is required for transmission as the virus is present in bodily fluids and excretions of infected individuals. An oral route of infection is common and infection through contamination of mucous membranes is also a possibility, but the virus probably cannot penetrate intact skin. There is no evidence of airborne transmission. CMV is often spread by sexual intercourse between young adults in developed countries. Intrauterine transmission from a pregnant woman with primary CMV infection to the foetus occurs in about 40% of cases; 10-15% of the infected foetuses are symptomatic at birth. Transmission from women infected at least 6 months prior to conception occurs in only 1% of cases, and the infected infants generally have no significant illness or abnormality, presumably as a result of the maternal immune system. CMV can also be transmitted via breast milk, transplanted organs and, rarely, by blood transfusions.

Congenital CMV

Congenital CMV infection occurs in about 1% of live births, some of whom are believed to be infected perinatally. About 10% of infected newborn cases are symptomatic at birth with multi-organ involvement. Of these, 10-20% will die as a

result of the infection, and 80-90% of survivors will develop major neurological sequelae such as hearing loss, visual impairment and diminished mental and motor capabilities. In addition, 5-10% of the asymptomatic newborns will be afflicted with late sequelae such as mental retardation, deafness and hearing defects, which usually appear during the first two years of life. Nearly all symptomatic cases of congenital CMV result from intrauterine infections in mothers who are infected with CMV for the first time during that pregnancy. CMV is now a more frequent cause of congenital mental retardation than Rubella. There are 3,000 new congenital infections each year in the UK, of which 300 result in subsequent handicap.

Other risk groups

In the majority of adult patients, infections with CMV are not life threatening. However, CMV infections are a major cause of morbidity and mortality in immunocompromised patients despite advances in diagnostic tests and antiviral therapies. CMV is a frequent complication of organ transplantation and presents a spectrum of disease ranging from asymptomatic viraemia to life-threatening tissue-invasive disease. CMV is also lymphotrophic, with the potential to induce autoimmune disease, although immunosuppressive therapy may prevent or attenuate the clinical course in transplant patients. CMV pneumonia is a relatively frequent complication in organ transplant patients. CMV hepatitis can also occur. The spectrum of disease morbidity and mortality amongst HIV patients has altered dramatically since the wide spread use of highly active antiretroviral therapy (HAART). CMV retinitis is the most common ocular opportunistic infection in patients with AIDS, but the incidence of CMV retinitis, once a major cause of blindness in AIDS patients, has been reduced considerably and its clinical course has been altered by the use of HAART.

Opportunistic infections, including CMV infection of the gastrointestinal tract in patients with AIDS, have also diminished greatly. CMV may, however, be a late stage progression factor affecting mortality in HIV adult patients and in children with perinatal HIV infection and very low CD4 lymphocyte counts.

Prenatal investigations

TORCH infections (toxoplasmosis, rubella, cytomegalovirus and herpes simplex virus type 1 and 2) in the mother can lead to severe foetal anomalies or even foetal loss. CMV infection may be known or suspected in samples from certain pregnancies, e.g.,

amniotic fluid samples from pregnancies with an echogenic foetal bowel, where the risk of CMV and other TORCH infections is elevated.

Laboratory containment and precautions

In healthy persons, close contact is required for transmission as the virus is present in the body fluids, secretions and excretions of infected individuals, and an oral or sexual contact route of infection is usual in the adult. CMV is not usually present in blood but may be present in the blood of infected patients who are immunocompromised and in the blood and amniotic fluid of infected foetuses. Adherence to good laboratory hygiene practices to avoid oral contact and to avoid contamination of mucous membranes is therefore essential to minimise risks. Containment level 2+, the standard containment in Clinical Cytogenetics, is appropriate for CMV risk samples. If the standard operating procedures are followed in the laboratory, the risks are therefore extremely low. However, to allay anxiety, local policies could reasonably allow pregnant workers or those at risk of being pregnant, who are concerned, to avoid handling samples at high risk of CMV.

RISK OF INFECTION FROM PARVOVIRUS B19

Parvovirus B19 is the cause of a common childhood illness, erythema infectiosum, characterised by fever and a rash with erythematous cheeks – hence the common name 'slapped cheek'. It is also known as 'fifth disease'. Infection is most common in children aged 6-10 years, but can occur at any age. In adults, especially women, parvovirus B19 infection can be associated with rheumatological manifestations, such as joint pain and swelling. Parvovirus B19 infection in people with haemoglobinopathies can result in transient aplastic crises and chronic infection can occur in the immunocompromised.

Incidence

60% of adults have serological evidence of past infection, which is thought to confer immunity. 40% of adult women are therefore susceptible to infection. The risk of foetal hydrops following maternal infection between 9 and 20 weeks is 3%. If foetal hydrops develops there is a 38% chance that foetal transfusion would be beneficial. The cumulative risk is, therefore, small and most women who are infected with parvovirus B19 during pregnancy have a satisfactory outcome. However, foetal loss has been estimated as occurring in 9% of pregnancies in which infection occurs in the

first 20 weeks of gestation. There is no evidence of B19 associated teratogenicity, or of developmental abnormalities occurring later in childhood.

Transmission

Respiratory secretions (e.g., saliva, sputum, or nasal mucus) are usually involved in transmission. The virus is probably spread usually from person to person by direct contact with those secretions, by activities such as sharing drinking cups or utensils. Infection in adults is normally by daily exposure in the same room (e.g., in a house or classroom or 2-4 bed hospital bay) for a significant period of time (15 minutes or more) to a person infected with parvovirus B19. Infection can also occur less frequently through a single face to face contact with a confirmed case of parvovirus B19 infection during the period of maximum infectivity. Maximum infectivity occurs during the 7 days before the appearance of a rash (the incubation period is estimated to be 13-18 days before the appearance of a rash, which occurs at the end of the period of infectivity). 90% of confirmed maternal infections followed exposure to an infected child. The average risk of infection after outpatient exposure is less than 10%. The virus can also be transmitted parenterally by some blood products and vertically from mother to foetus. Faecal-oral transmission has not been documented.

Laboratory containment and precautions

Parvovirus B19 infection may be known or suspected in certain pregnancies from which amniotic fluid samples are obtained, e.g. in pregnancies where there is unexplained foetal hydrops. The risk of parvovirus B19 infection in such samples is small and the transmissibility of the virus to adults is relatively low. The risk of infection from an infected sample in the laboratory is therefore probably extremely low, although B19 DNA can be demonstrated in serum from infected cases. The number of infections attributable to exposure at work is usually no greater than in the community in general. Containment Level 2+ is appropriate for parvovirus B19 risk samples in Clinical Cytogenetics.

RISK OF INFECTION FROM CREUTZFELDT-JAKOB DISEASE

Creutzfeldt-Jacob Disease (CJD) is one of a group of rare fatal degenerative brain diseases known as Transmissible Spongiform Encephalopathies (TSEs), also known as prion diseases, which occur in humans and certain other animal species. There

have been no confirmed cases of transmission of TSEs to humans as a result of occupational exposure. If TSEs could be transmitted in the occupational setting, it is considered that this would be most likely to occur from exposure to infected tissues or materials by direct inoculation (e.g., puncture wounds, 'sharps' injuries or contamination of broken skin), by splashing of the mucous membranes or, exceptionally, by swallowing.

Currently, therefore, there is no evidence of any specific occupational risk of transmission of CJD. Nevertheless, available information is limited and, as CJD remains a rare disease, it is not possible to draw firm conclusions. It is prudent therefore to have a precautionary approach. Transfusions of whole blood, component blood or blood derivatives have not been shown to transmit the classical CJD agent. However, it has been noted that the new variant CJD (nvCJD) is quite distinct from classical forms of CJD. This difference appears to extend to the pathogenesis of the disease, and it has been suggested that in nvCJD there is more involvement of lymphoreticular tissues possibly involving circulating lymphocytes. The risk tissues may therefore need to be redefined as further research findings emerge and as the estimation of the numbers of nvCJD cases becomes clearer. At present, the number of people incubating nvCJD is not known.

Current ACDP Guidance for Handling Blood and Other Samples

Although nvCJD is classified in Hazard Group 3, derogation from full Containment Level 3 is possible for routine laboratory work in specific circumstances. When considering measures to prevent transmission to staff in the healthcare setting, it is useful to make a distinction between those patients who are *known or suspected* to have CJD or a related disorder, i.e., those with clinical symptoms, and those who are potentially *at risk* of developing one of these diseases, i.e., asymptomatic, but having a clinical or family history which places them in one of the risk groups.

Samples from *at risk* patients

For routine clinical analysis not involving the deliberate intention to work with the agent of CJD, samples from *at risk* patients that are not from the CNS, and are not known to be contaminated with CNS, can generally be handled in the same way as other clinical samples. In general, blood samples from *at risk* patients can be collected, processed and handled as for any other patient.

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Samples from known or suspect patients

When handling specimens from *known or suspect* patients, or CNS specimens from *at risk* patients, particular care should be taken to avoid accidental inoculation or injury. Wherever practicable, disposable equipment should be used and items contaminated by the specimens should be destroyed by incineration, or else autoclaved or disinfected to the required standard (see Table 1).

Table 1. Chemicals and Processes Recommended for Use Against TSE Agents

Chemical disinfectants	Gaseous disinfectants	Physical processes
20,000ppm available chlorine of sodium hypochlorite for 1 hour 2M sodium hydroxide for 1 hour*	none	porous load steam steriliser 134-137 °C for a single cycle of 18 minutes, or 6 successive cycles of 3 minutes each*
for histological samples only, 96% formic acid for 1 hour		

* but known not to be completely effective.

Where disposable equipment cannot be used, the resistant nature of the agents of TSEs is such that standard methods such as autoclaving cannot be relied upon to inactivate the agents completely. The emphasis must, therefore, be on removal of the agents by thorough cleaning, followed by an appropriate decontamination process. However, this does not apply to instruments that have been used in procedures on *known or suspect* patients, or those used on *at risk* patients where there has been contact with brain, spinal cord or eye, as these items must be disposed of by incineration.

Special arrangements may be needed to minimise any residual contamination of equipment. Where a manual technique using disposable equipment is not feasible, and automated equipment is to be used, the potential for residual contamination must be considered and be dealt with appropriately before equipment is serviced. Where stringent decontamination procedures are inappropriate, the equipment should be cleaned and regularly maintained to avoid accumulation of potentially contaminated debris.

The need for cytogenetic investigations on samples from *known or suspect* CJD patients should to be discussed with the referring clinician and balanced against the risk to staff and the potential disruption of the laboratory service.

RISK OF INFECTION FROM MYCOBACTERIUM TUBERCULOSIS

Background

Tuberculosis (TB) causes more deaths worldwide than any other infectious disease. Some 2 billion people, one third of the world's population are infected with the TB organism, *Mycobacterium tuberculosis*. In England and Wales 6,087 cases of TB were notified in 1998. During the 2 to 8 weeks after the initial infection in people with intact immune systems, a T cell mediated response occurs to limit the spread of infection. At the site of infection in the lung specialised cells kill TB bacilli and wall off infected macrophages in tiny, hard greyish nodules known as tubercles. By this time, an infected person's T cells will respond to the tuberculin skin test (PPD/Heaf/Mantoux tests).

Active disease occurs when the bacilli break out of the tubercles in the alveoli when the body's resistance is low because of age, malnutrition and other factors. Each year, 8 million people develop active TB and 3 million die as a result. Active disease is more likely to occur in those with weakened immune systems. Internationally, the HIV epidemic has greatly increased the number of TB cases as HIV represents the greatest risk factor known to cause TB infection to proceed to disease. In the UK, the prevalence of TB has increased slightly in recent years, but this is not believed to be due to the HIV epidemic as the extent of co-infection with HIV infection in TB cases in England and Wales has remained relatively low. However, at least 3% of TB cases in England and Wales were estimated to be HIV infected. TB infection frequently occurs early in the course of HIV infection, tends to progress directly to active disease and often occurs in areas of the body outside the lungs. In many industrialised countries, a large and increasing proportion of TB cases occurs in people born in parts of the world with a high prevalence of TB. In England and Wales in 1998, a National Survey identified that 56% of cases of TB were in people who had been born abroad.

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Routes and sites of infection

TB is normally spread from person to person in microscopic droplets expelled from the lungs when a TB sufferer coughs. Because most infected persons expel relatively few bacilli, it has been estimated that contraction of TB requires prolonged exposure to a person with active TB, either at home or at work (50% risk of infection after 8 hours exposure a day for 6 months or 24 hours a day for 2 months). Patients who have been treated with appropriate drugs for over 2 weeks are not usually infectious, unless the bacilli are multidrug resistant.

In the active form of the disease the bacilli spread from the tubercles in the lung at the initial site of infection to other sites, usually other sites in the lung or local lymph nodes through the lymphatic system or bloodstream. In 15% of cases, the bacilli cause disease in other regions of the body, such as skin or bones. In miliary TB the bacilli are present in the blood of infected individuals.

Immunisation

A national vaccination programme in the UK was introduced in 1953 using an attenuated form of *Mycobacterium bovis*, developed by Calmette and Guerin, which confers immunity to TB infection. BCG (Bacille Calmette Guerin) vaccination however does not provide complete protection from TB infection. Pre-employment and on-employment measures should include recording any history of TB, details of BCG vaccination and presence or absence of a BCG scar, and, if necessary a chest x-ray. A tuberculin test (usually the Heaf test) is only necessary for new employees who do not have either a definite BCG scar or documentary evidence of BCG vaccination. It has been recommended that health care workers, irrespective of age, who are previously unvaccinated and who are negative on Heaf test grade 1 should receive BCG vaccination.

Risk of infection in pathology laboratories and post-mortem rooms

Recently, it has been estimated that staff of laboratories are between 100 and 200 times more likely than the general public to develop TB, although the incidence of TB in clinical laboratory workers remains low, the rate of infection falling from 38 to 18/100,000 person years between 1970 and 1989. Staff in microbiological laboratories and necropsy rooms are at greatest risk. Particular hazards for staff include specimen containers contaminated on the outside, unfixed sputum smears and generation of aerosols during post mortem examination procedures, especially in

patients not diagnosed with TB in life. Staff may acquire pulmonary infection by inhalation of aerosols, and skin and other lesions through contamination of cuts and abrasions, percutaneous injury and contamination of mucous membranes. In contrast to exposure to live patients with active TB, even very brief exposure during necropsies may carry a high risk of infection, in some circumstances.

Treatment of the active disease involves the multiple drug therapy. Multiple drug resistant cases of TB have increased dramatically in the USA in recent years. However, in the UK the multidrug resistance rate in TB cases has not risen in recent years. In 1998, 1.3% of cases of TB were multidrug resistant.

Risk of infection and containment in Cytogenetics Laboratories

Although blood may contain tubercle bacilli during haematogenous spread of the disease, they are usually too few to be found in blood cultures (cultured for tuberculosis bacilli), except in patients co-infected with HIV. Tubercle bacilli were isolated from cultures of blood from 28 of 50 HIV infected patients but not from 8 TB patients not infected with HIV. The likelihood of significant numbers of TB bacilli in peripheral blood samples and probably bone marrow and other samples sent for cytogenetic investigation, in general, would therefore seem to be very low.

Nevertheless, laboratory Containment Level 3 is specified by the ACDP for samples known to be infected or at high risk of being infected with *Mycobacterium tuberculosis* and related organisms that cause TB. As an aerosol route of infection is a possibility with these organisms, there has been no derogation of this containment level for clinical work with samples known to be infected or at high risk of being infected with *M. tuberculosis* and related organisms. Full containment level 3 should therefore be applied to all samples from patients with active TB. Where patients are infected with *M. tuberculosis* but remain undiagnosed, so that their samples are not known to be at high risk, the routine adoption of Containment Level 2+, including the use of safety cabinets to contain aerosols and splashes and the avoidance of the use of sharps, in Clinical Cytogenetics, would reduce the risk very considerably. The risk of occupationally acquired TB infection in staff working in Clinical Cytogenetics, who have received BCG vaccination, is probably extremely low.

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REFERENCES

1. Advisory Committee on Dangerous Pathogens (1996). BSE (Bovine Spongiform Encephalopathy). Background and general occupational guidance. HSE Books; ISBN 0-7176-1212-0
2. ACDP Spongiform Encephalopathy Advisory Committee (1998). Transmissible spongiform encephalopathy agents: safe working and the prevention of infection. The Stationery Office Books; ISBN 0113221665
3. Al-Kouatly HB, Chasen ST, Streltzoff J, Chervenak FA. (2001). The clinical significance of fetal echogenic bowel. Am J Obstet Gynecol; 185(5): 1035-8
4. Collins CH, Grange JM (1999). Tuberculosis acquired in laboratories and necropsy rooms. Commun Dis Public Health; 2(3): 161-167
5. Collins CH (1982). Laboratory acquired tuberculosis. Tubercle; 63: 151-155
6. Crowcroft NS, Roth CE, Cohen BJ, Miller E. (1999). Guidance for control of parvovirus B19 infection in healthcare settings and the community. J Public Health Med; 21(4): 439-46
7. National Center for Infectious Diseases, Centers for Disease Control and Prevention, US Department of Health and Human Services (2002). Cytomegalovirus (CMV) infection. www.cdc.gov/ncidod/diseases/cmv.htm
8. Department of Health and Social Security. (1981 and 1984). The management of patients with spongiform encephalopathy (Cruetzfeldt-Jakob Disease CJD). DA(81)22 and DA(84)16
9. Grist NR, Emslie JAN (1994). Association of Clinical Pathologists' surveys of infection in British clinical laboratories 1970-1989. J Clin Pathol; 47: 391-4
10. Joint Tuberculosis Committee of the British Thoracic Society (2000). Control and prevention of tuberculosis in the United Kingdom: Code of Practice 2000. Thorax; 55: 887-901
11. Public Health Laboratory Service (2001). Tuberculosis briefing. www.phls.co.uk/facts/TB/briefing.htm
12. ACDP Spongiform Encephalopathy Advisory Committee (1994). Transmissible Spongiform Encephalopathies: a summary of present knowledge and research. The Stationery Office Books; ISBN 0-11-242987-4
13. Walker D, Campbell D (1999). A survey of infections in United Kingdom laboratories, 1994-1995. J Clin Pathol; 52(6): 415-8
14. Yaron Y, Hassan S, Geva E, Kupferminc MJ, Yavetz H, Evans MI. (1999). Evaluation of fetal echogenic bowel in the second trimester. Fetal Diagn Ther; 14(3): 176-80