Bulletin of the Hong Kong Society for Infectious Diseases

Vol. 12, no. 1 **March 2008**

Contents

Recognizing dengue infection in the primary care

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Dengue fever (DF) is a notifiable disease in Hong Kong. A total of 72 imported cases was recorded from 1994 to 2001, with 24 imported cases and 20 local cases in 2002, 48 imported cases and 1 local case in 2003, and 31, 31, 31, 58 imported cases in 2004, 2005, 2006, 2007 respectively. Since 2003, all patients have reported visiting an endemic area within 14 days prior to symptom onset, except for one local case reported in 2003. Indonesia, the Philippines, and Thailand are the three countries where most of the imported cases were from. These countries are endemic for dengue fever with larger cyclic epidemics every three to five years. The mosquito vector *Aedes aegypti* is widely distributed in these countries, while *Aedes albopictus* found in Hong Kong is a less efficient vector for the disease transmission. All cases were sporadic and none were associated with outbreaks or secondary cases. The clustering of cases in the summer months may reflect the vacation season in Hong Kong and dengue activity in travelled countries.

Dengue infection presents with a spectrum of clinical illness ranging from being asymptomatic, indistinguishable non-specific flu-like illness, classical dengue fever, to more severe forms of dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) which may be fatal. People with milder illness may not seek medical attention. In country like Thailand

which is hyperendemic for dengue infection concurrent transmission of all four serotypes occur. Primary infections are usually seen in local young children whereas symptomatic secondary infections generally occur in school-age children or young adults. Primary infection may occur at any age for tourists from non-endemic areas. Most reported cases in Hong Kong are of classical dengue fever type. It is characterized by a sudden onset of fever three to fourteen days after being bitten by infected mosquitoes. Typical presenting features include intense headache, retro-orbital pain, generalized maculopapular rash, myalgia, arthralgia. Petechiae may be present. Tourniquet test can be considered in a clinic setting. It is performed by inflating a blood pressure cuff on the upper arm to a point midway between the systolic and diastolic pressure for five minutes. According to the WHO criteria, a test is considered positive when twenty or more petechiae per 1 inch (2.5 cm) square are observed in the ventral surface of forearm. The test is used for detecting capillary fragility and thrombocytopenia. It differentiates poorly between DF, DHF and other febrile illness like chikungunya fever. Chikungunya fever is a disease that can mimic DF in a returned traveller.

To prevent Hong Kong from becoming an endemic area, enhancing clinical awareness among the medical community especially targeting at travellers is a key strategy. Mosquito bites should be prevented during febrile period of the patient. Diagnosis should be suspected when there is a travel history to endemic or outbreak areas within 14 days prior to symptom onset. Confirmation needs laboratory tests such as detection of IgM by day five of illness, virus detection using RT-PCR in the first week of illness, demonstration of a four-fold or greater rise in total antibody titre to any dengue serotype in paired sera two weeks apart. Early laboratory anomalies include leucopenia, neutropenia, thrombocytopenia, mildly elevated liver enzyme. Depending on the epidemiological and individual risk, the list of differential diagnosis include influenza and influenza-like illness, typhus fever and other rickettsial infections, malaria, measles, rubella, typhoid fever, bacterial sepsis, meningococcaemia, leptospirosis, chikungunya fever, viral haemorrhagic fever. Moreover, coexisting infection should always be considered. A returned traveller from southeast Asia who present with fever, headache and maculopapular rash can have both malaria and dengue infection exemplifying the pitfall in its diagnosis and management. The use of aspirin and nonsteroidal anti-inflammatory drug should be avoided whenever DF is suspected because of their anticoagulant properties. Salicylates should be especially avoided in children due to the association with Reye's syndrome.

References:

1. Centre for Health Protection, Department of Health, Hong Kong SAR, Communicable Diseases Watch, Vol 3, Nos 18 & 19 [www.chp.gov.hk/cdw]
2. World Health Organization Regional Guidelines on Dengue/DHF – Clinical Manifestations and Diagnosis [www.searo.who.int/en/Section10/Section332/Section554_2564.htm]
3. USCDC Traveler's Health: Yellow Book Chapter 4- Dengue Fever [wwwn.cdc.gov/travel/yellowBookCh4-DengueFever.aspx]
4. Vagabond virus. Time December 17, 2007 p.38

CNS Infection: Acute Management

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In this article, the authors present two case vignettes illustrating the principle of management of two acute infectious neurological diseases, viral encephalitis and bacterial meningitis.

Case 1

A 53-year-old man presented with fever, headache and productive cough for 2 days. His headache was aggravated by coughing and sneezing. There was no vomiting. He was initially managed with intravenous amoxycillin/clavulanate and oral clarithromycin in another hospital. One week later he developed drowsiness and bowel incontinence, prompting transfer to our hospital. Mild left hemiparesis was detected. MRI brain showed cortical edema affecting the right medial frontal, as well as right anterior and medial temporal lobes (Fig 1 & 2). He developed repeated seizure attacks soon after transferal, which were aborted by anticonvulsants. What is the most likely clinical diagnosis? Does he need immediate treatment?

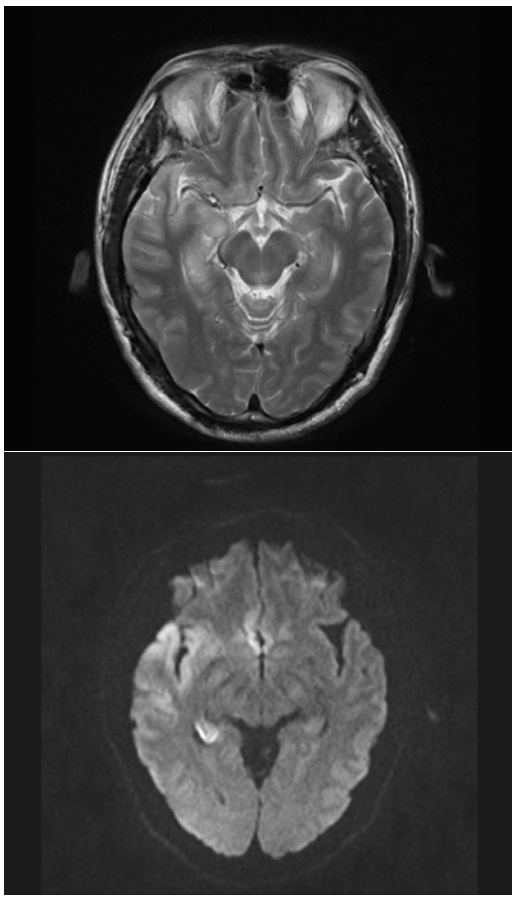

Fig 1 & 2. Axial T2-weighted image and diffusion-weighted image demonstrating cortical edema affecting the right frontal and temporal lobes

Answer: Herpes simplex encephalitis. He was immediately treated with intravenous acyclovir for 21 days. A lumbar puncture done on day 30 of illness showed the following results: opening pressure 18 cm H2O, red cell count 64/mm3, white cell 17/mm3 (100% lymphocytes), protein level 0.8 g/L and glucose level 2.6 mmol/L (serum glucose 8.2mmol/L, making the CSF-to-serum glucose ratio 0.32). Gram stain and acid-fast bacilli stain were negative. His CSF polymerase chain reaction (PCR) for HSV DNA and viral culture were both negative. The CSF antibody titer of HSV was 32. He made an excellent neurological recovery.

Herpes simplex virus encephalitis (HSE) is the commonest fatal sporadic encephalitis in humans. It is the most commonly identified acute viral encephalitis among adults in Hong Kong[1]. The virus has a predilection for the medial temporal and orbital frontal lobes, with involvement of the cingulate and insular cortex. Without treatment, the mortality rate reaches as much as 70% and only 2.5% of surviving patients return to normal neurological function. HSE is primarily caused by HSV-1 infection of the brain (> 90%). HSV-2 infection represents a minority, but more commonly occurs in immuno-compromised individuals such as those with renal transplants or HIV infection[2].

Clinical Features

HSE should be suspected in patients presenting with fever, headache, and altered sensorium. In a local study, fever was found to occur in 94% of HSE patients, followed by headache and confusion (both 44%)[1]. Clinically HSE patients have greater tendency to present with focal encephalitis (focal neurological signs and/or localized abnormalities on neuroimaging) rather than diffuse encephalitis[3]. It is now recognized, by PCR-based study, that up to 20% of HSE patients have mild or atypical diseases.

Investigations

Polymerase chain reaction (PCR) of the cerebrospinal fluid (CSF) is currently the diagnostic method of choice. Being less invasive, it replaces the brain biopsy which

was previously mandatory to make a definitive diagnosis of HSE. Using brain biopsy as the gold standard, PCR was shown to have a sensitivity of 98%, specificity of 96%, positive predictive value of 95% and negative predictive value of 98%. Both timing of the CSF sampling and pre-test likelihood are essential for interpretation of a negative PCR result. If the CSF is obtained more than 72 hours after the onset of symptoms from a patient with low probability of having HSE (absence of typical EEG, typical neuroimaging or CSF pleocytosis), it is safe to discontinue empirical acyclovir therapy. PCR may also be useful to monitor treatment response at completion of therapy[4].

CSF antibody is useful for retrospective diagnosis, when CSF can only be obtained at late times after onset, e.g. when significant cerebral edema and brain shift precludes lumbar puncture at initial presentation. Viral culture is of little value in adults. Serum antibody levels are of no use in the diagnosis of HSE[4].

Neurodiagnostic investigations provide additional support to the diagnosis of HSE. Cerebrospinal fluid typically showed lymphocytic pleocytosis, mildly elevated protein, red blood cells and xanthrochromia. However, normal CSF findings are occasionally seen. Computed tomography of the brain has only 50% sensitivity early in the course of the disease. Magnetic resonance imaging (MRI) of brain demonstrated T2-hyperintensities in the temporal and frontal lobes. Abnormalities may only be detected using FLAIR and DWI sequences when conventional sequences are normal. Normal MRI does not exclude the diagnosis of HSE; about 10% of PCR-proven HSE has normal MRI. Electrocephalography (EEG) may show non-specific slow waves. Periodic lateralizing epileptiform activities (PLEDs) are characteristic but they are not specific for HSE. Our patient had right temporal PLEDs in the EEG (Fig 3).

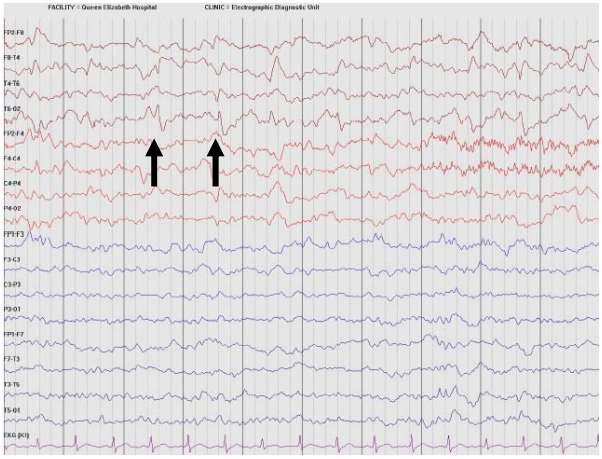

Fig 3. Right temporal PLEDs (arrows)

Management

Intravenous acyclovir (10mg/kg every 8 hours for 14-21 days) is the mainstay of treatment recommended by the International Herpes Management Forum (IHMF) guidelines. Two randomized controlled clinical trials compared the efficacy and safety of acyclovir versus vidarabine in patients with biopsy- and/or antibody-proven HSE[6,7]. Both studies showed superior outcome for acyclovir. Dose adjustment is required in patients with renal impairment. Factors influencing the outcome of acyclovir therapy (favorable factors shown parenthetically) include age (under 30 years of age), Glasgow Coma Scale at the start of therapy (above 10), duration of encephalitis before initiation of therapy (4 days or less) and viral load (less than 100 HSV DNA copies/mm^3).

Seizures are common and occur in 50% of patients with HSE. These should be treated accordingly. For patients with sudden change in mental status during treatment, EEG is indicated to rule out non-convulsive status epilepticus. Other relevant investigations include CT brain to exclude the rare occurrence of intracerebral hemorrhage, and serum creatinine, which reflects the possibility of acyclovir toxicity[7].

In patients who develop massive cerebral edema or hemorrhagic complication, brain herniation and brainstem compression can occur. These can lead to devastating neuro-cognitive sequelae despite early

initiation of acyclovir therapy. In such cases, surgical decompression by craniectomy and duraplasty, with or without anterior temporal lobectomy can result in good or excellent recovery (Glasgow Outcome Scale Score 4 or 5)[8].

Case 2

A 69-year-old man was admitted for right-sided weakness with a power of 4/5. High fever and drop of GCS from 14 to 7 soon developed. Nuchal rigidity was absent. Urgent CT brain showed no mass lesion or brain edema. Lumbar puncture revealed turbid CSF and an opening pressure of 46 cmH_2O. The CSF white cell count was 9200/mm^3 (polymorph 98%, lymphocytes 2%) and Gram smear showed gram-negative bacilli. He required mechanical ventilation. Three days later he developed eye signs as shown in Fig 4. Which organism would you suspect? What else should be investigated?

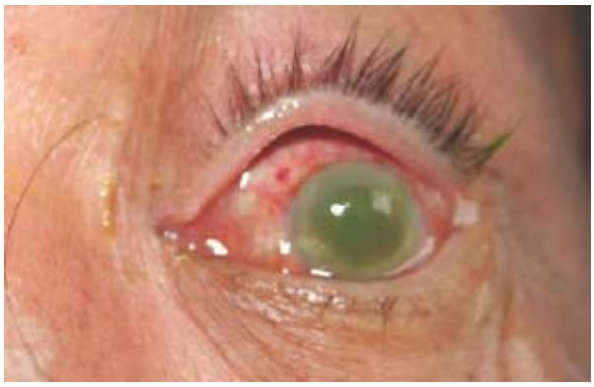

Fig 4.

Answer: Klebsiella pneumoniae meningitis and left endophthalmitis. Blood glucose was normal. Hepatobiliary ultrasonography showed no evidence of liver cirrhosis. However, a liver abscess was detected and percutaneously drained. This patient died despite prompt commencement of antimicrobial therapy and intensive support measures for two weeks.

Patients with bacterial meningitis still suffer from significant mortality and morbidity despite potent antibiotics available in this modern era. We have retrospectively analyzed our own cohort from 1996 to 2005. Combine with other local data, we find the mortality rate of between 20% and 30% in Hong Kong. Leading causative organisms are different from those of Western countries. *Streptococcal suis* is one of the commonest organisms identified in this locality. It takes up about 19% of the total culture-proven bacterial meningitis cases in our center. *Klebsiella pneumoniae*, an important pathogen in countries like Taiwan, ranks the third in another local case series[9]. On the other hand, we have a low incidence of meningitis due to *Hemophilus influenzae and Neisseria meningitidis*.

Clinical Features

The classical symptoms of bacterial meningitis are fever, neck stiffness, altered mental status and headache. The incidence of these symptoms varies considerably among different studies. In our cohort, for example, fever was the commonest finding (present in 80% of patients), followed by confusion (63%), headache (50%) and stiff neck (50%). The “classic triad” of fever, neck stiffness and alterations in mental status was present in only 26% of patients. The traditionally described meningeal signs such as nuchal rigidity and Kernig’s sign have overall poor sensitivity and may not be detected in meningitis[10].

Lumbar Puncture

Lumbar puncture (LP) is the procedure of choice for the diagnosis of bacterial meningitis. One of the issues physicians are faced with in an emergency setting is whether brain computed tomography is required prior to LP to avoid the risk of herniation. The current recommendation by the Infectious Diseases Society of America (IDSA) is based on a prospective study which included 301 adults with suspected meningitis. Features associated with abnormal CT scan included age more than 60 years, history of CNS disease, seizure in past week, immunocompromised state and certain specific neurologic findings. When none of these features were present, the negative predictive value for an intracranial abnormality was 97%[11]. However, the key question is whether abnormal CT scan

findings can really predict the risk of post-LP herniation[12]. There is considerable data indicating that mass effect on CT scan does not correlate with brain herniation after LP. In order to avoid delay in LP and antibiotic treatment, it is not necessary to perform routine CT scan for every patient with suspected meningitis.

Management

Studies suggest poorer clinical outcome with increased delay between presentation and initiation of antibiotic therapy. Although there has not been a study showing a clear beneficial timeframe for administration of antibiotic, the current guidelines recommend that appropriate therapy should be initiated as soon as possible after the diagnosis is considered. In case of delay in performance of LP or when brain CT prior to LP is necessary, empirical antibiotic therapy after blood culture should be commenced first[13].

The initial choice of antibiotic is based on the commonest organism causing the disease according to the patient's age and the clinical setting. Empirical coverage with a third-generation cephalosporin at meningitic dose (cefotaxime 2g q4h or ceftriaxone 2g q12h) is recommended, based on a board spectrum of activity and excellent CNS penetration. Patients over the age of 50 years and who have impaired cellular immunity should have ampicillin 2g q4h or penicillin G 3-4MU q4h added to cover *Listeria*. Addition of vancomycin 1g q12h should be considered when initial tests suggest *S. pneumoniae*[14].

Adjunctive dexamethasone therapy is now advocated in patients with bacterial meningitis. The rationale for its use is the intense inflammatory response to bacterial infection, which is thought to cause significant morbidity and mortality despite effective antibiotic therapy. Dexamethasone is used to modulate this inflammatory response. The dosage is 10mg given every 6 hours intravenously for 4 days according to a randomized, double-blind, placebo-controlled trial. It must be given 15-20 minutes before or with the first dose of antibiotic[15].

References

1. Hui AC *et al*. Herpes simplex encephalitis in Hong Kong: A retrospective review. Neurology Asia 2005;10:35-8.
2. Kennedy PGE, Chaudhuri A. Herpes simplex encephalitis. J Neurol Neurosurg Psychiatry 2002;73:237-8.
3. Domingues RB *et al*. Evaluation of the range of clinical presentations of herpes simplex by using polymerase chain reaction assay of cerebrospinal fluid samples. Clin Infect Dis 2000;31:894-903.
4. Tyler KL. Herpes simplex virus infections of the central nervous system: encephalitis & meningitis, including Mollaret's. Herpes 2004;11:57A-64A.
5. Whitley RJ *et al*. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. N Engl J Med 1986;314:144-9.
6. Skoldenberg B *et al*. Acyclovir versus vidarabine in herpes simplex encephalitis. Randomized multicentre study in consecutive Swedish patients. Lancet 1984;2:707-11.
7. Leep Hunderfund AN *et al*. 73-year-old woman with fever and mental status changes. Mayo Clin Proc 2007;82:874-7.
8. Adamo MA, Deshaies EM. Emergency decompressive craniectomy for fulminating infectious encephalitis. J Neurosurg 2008;108:174-6.
9. Hui ACF *et al*. Bacterial meningitis in Hong Kong: 10-years' experience. Clin Neurol Neurosurg 2005;107:366-70.
10. Fitch MT, van de Beek D. Emergency diagnosis and treatment of adult meningitis. Lancet Infect Dis 2007;7:191-200.

11. Hasbun *et al.* Computed tomography of the head before lumbar puncture in adults with suspected meningitis. N Engl J Med 2001;345:1727-33.
12. Spellberg B. Is computed tomography of the head useful before lumbar puncture? Clin Infect Dis 2005;40:1061.
13. Tunkel AR *et al*. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267-84.
14. Reducing bacterial resistance with Interhospital Multi-disciplinary Programme on Antimicrobial ChemoTherapy (IMPACT), p. 62.
15. de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. N Engl J Med 2002;347:1549-56.

A gentleman presented with fever and stroke

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Case Report

A thirty-nine-year-old gentleman presented with an episode of vertigo for a few seconds one day before admission, which was followed by clumsiness of his left hand and unsteady gait after waking up in the early morning. He also experienced numbness over his left hand and left leg which was subsided later. There was no headache, slurring of speech, loss of consciousness or witnessed convulsion.

He had a past history of heart disease in childhood, which required antibiotic coverage on dental procedure, but long term follow up and medications were not warranted. He also claimed to develop oral ulcer after taking oral penicillin and was labelled allergy to penicillin since then.

He lived with his wife and worked as a clerk. He did not smoke or drink alcohol. On examination the patient was conscious. The temperature was 37.5℃, the pulse was 46 beats per minute and the blood pressure was 128/46 mmHg; the respirations were 18 breaths per minute and the oxygen saturation was 95% while the patient was breathing ambient air. There was digital clubbing but no central or peripheral cyanosis. He had mild left hemiparesis with the power of grade five minus, left ankle clonus and positive Babinski sign. Cranial nerves were grossly intact. There was no nystagmus. Sensation was normal. The heart sounds were normal but there was ejection systolic murmur at the right second intercostal space, radiating to the neck. The remainder of the examination was normal.

Blood-test results showed minimal hypochromic microcytic anaemia (haemoglobin level 12.5g/dL, MCV 73.9fL, MCH 24.8pg), hyperbilirubinaemia (bilirubin 34micromol/L) and raised lactate dehydrogenase (785U/L). Erythrocyte sedimentation rate was 32mm/hr and C-reactive protein 24.9mg/L. Peripheral white cell count, platelet count, serum electrolyte, renal function and aminotransferase level were normal. Fasting blood glucose was 5.3mmol/L, total cholesterol 4.1mmol/L, low density lipoprotein 3mmol/L and total triglyceride 0.9mmol/L. An electrocardiogram revealed complete heart block with ventricular rate of 46 beats per minute. Chest radiograph was clear. The plain computed tomographic scan of the brain was unremarkable.

On the second hospital day, trans-thoracic echocardiography was performed and revealed severe aortic stenosis, mild aortic regurgitation, marked concentric left ventricular hypertrophy and satisfactory left ventricular systolic function (ejection fraction was 75%). There was no septal defect. No vegetation or thrombus was seen. He was treated as ischaemic stroke with aspirin, probably due to cardioembolism. Temporary pacing was implanted for the complete heart block on admission and permanent pacing was performed three days later.

Patient developed intermittent fever during hospitalisation. No source was identified. Sepsis workup including three blood culture and urine culture before starting empirical antibiotic was negative. Patient was treated with ceftriaxone 2 grams every 24 hours without any adverse reaction. Magnetic resonance imaging of brain on the fifth hospital day found multiple infarcts in right corona radiate, parietal lobe and insular cortex, likely due to embolism. Trans-oesophageal echocardiography showed bicuspid aortic valve with calcification, thickened soft tissue attached to aortic cusp, which could be vegetation or thrombus, and severe aortic stenosis and moderate aortic regurgitation. He got persistent fever but was not septic clinically. Ceftriaxone was stopped for the suspected drug fever. Sepsis workup was repeated but still no positive findings. Inflammatory marker levels were still high (erythrocyte sedimentation rate and C-reactive protein). Rheumatoid factor IgM was greater than 33IU/ml, anti-nuclear antibody was negative, complement C3 and C4 were normal. Fever then subsided spontaneously.

Second trans-oesophageal echocardiography four weeks after admission revealed vegetation at both aortic side and ventricular side of aortic valve, mobile thread-like soft tissue structure attaching to aortic valve, no perivalvular abscess formation, normal mitral and tricuspid valves. He was treated as culture negative infective endocarditis with intravenous levofloxacin 500mg every 24 hours and gentamicin 80mg every 8 hours. Serum IgG phase I and phase II antibodies to *Coxiella burnetii* was detected by immunofluorescent assay with high titre of 12800, IgM titre less than 25 and Coxiella burnetii antibody by complement fixation test 1024. On direct questioning, patient used to drink unpasteurised cow milk in Mainland China around 30 years ago. His latest travel was to urban area of Korea in October 2006 in group tour. No contact with wild animals was reported. He denied eating herbs or special food. The final diagnosis was chronic Q fever with infective endocarditis, complicated with embolic stroke and complete heart block. Standard treatment of oral doxycycline 100mg twice daily and hydroxychloroquine 200mg thrice per day was given to the patient. He had an uneventful recovery and was seen in our outpatient clinic with no specific complaints. His inflammatory markers were normalised around ten months after discharge and the antibody titre to *Coxiella burnetii* was decreased to 1280.

Q fever is a worldwide zoonosis which is caused by *Coxiella burnetii,* an obligate intracellular bacteria. Query fever was described in 1935 following an outbreak of febrile illness in an abattoir in Queensland, Australia.

Epidemiology

The reservoirs include mammals, birds and arthropods, mainly ticks [1]. The most commonly identified sources of human infection are farm animals such as cattle, goats and sheep. Pets like cats, rabbits and dogs, have also been demonstrated to be potential sources of urban outbreaks. Human infection can result from inhalation of contaminated aerosols from parturient fluids of infected livestock. Therefore, Q fever is an occupational hazard. At greatest risk are persons in contact with farm animals, individuals downwind from manure, straw or contaminated dust from farms and laboratory personnel who work with infected animals. Mammals shed *C. burnetii* in milk, thus consumption of raw milk could be a source of infection. It has also been proven to occur via transplacental transmission, via intradermal inoculation and via blood transfusion. Q fever occurs at any age, but five times more likely to occur in 15 years old or above than in those below 15 years of age in Switzerland [2]. A study in Greece found that the prevalence in children substantially increased with age [3]. Male to female ratio for the infection is 2.45 in adults [2]. This bias by sex is not found in children in Greece or France. Women and children are more commonly asymptomatic than men and adults, respectively.

Natural History

Following exposure to *C. burnetii*, a non-immune person develops a primary infection that is asymptomatic in 60% of cases [4]. 40% of cases have symptoms which are usually mild. However, 2 to 5% of those symptomatic cases may develop severe disease. Certain conditions like pregnancy, immunosuppression, heart valve lesions and vascular abnormalities predispose individuals to chronic Q fever [5].

Clinical manifestation

The clinical presentation of Q fever depends on the geographic origin of the infection. For instance, pneumonia is more common than hepatitis in eastern Canada, while in southern Spain, pneumonia is rare and hepatitis is very common. In southern France, pneumonia is common and hepatitis very common [1]. The clinical manifestation of acute Q fever is also associated with host factors. Those patients presenting with pneumonia are often immunocompromised. The incubation period for acute infection is 20 days, ranging from 14 to 39 days. Three clinical presentations are typically encountered: a self-limited flu-like illness, pneumonia and hepatitis.

Chronic Q fever is defined as infection lasting for more than six months. It occurs in 1 to 5% of patients infected with *C. burnetii* and may develop insidiously months or years after the acute disease. *C. burnetii* multiples in macrophages and produces a prolonged bacteraemia, resulting in very high levels of persistent antibodies. Typically, the heart is the most commonly involved organ, followed by arteries, bones and liver.

Q fever endocarditis usually occurs in patients with previous valvular damage or those who are immunocompromised. Patients with clinically unknown or mild valve lesions such as bicuspid aortic valve or minimal mitral insufficiency, or those with mitral valve prolapse are also at risk. Of those people with valve lesions, 30 to 50% will develop chronic endocarditis [5]. The clinical picture depends on the diagnostic delay [6]. Q fever endocarditis does not typically resemble acute endocarditis, as fever is frequently recurrent or absent, vegetations may be difficult to detect by echocardiography and routine blood culture are negative. Arterial embolism occurs in about 20% of patients.

Diagnosis

The laboratory findings during acute Q fever are non-specific. The leukocyte count is usually normal but may be elevated in 25% of cases [7]. The erythrocyte sedimentation rate might also be high. Thrombocytopenia is noted in 25% of cases. Liver enzymes are raised in as many as 85% of cases. The increase in transaminase levels is usually moderate, ranging from 2 to 10 times of normal values. During an episode of prolonged fever, the combination of a normal white cell count, thrombocytopenia and elevated hepatic enzymes should raise the diagnosis of Q fever. Creatine phosphokinase is also increased in 20% of patients. Autoantibodies like anti-mitochondrial antibodies, anti-smooth muscle antibodies and antibodies to phospholipids are commonly found in Q fever but their significance is still unknown. In Q fever endocarditis, clinical and biochemical symptoms are related to the predominantly cell-mediated inflammatory response to the micro-organism. Conventional blood cultures remain negative. The laboratory manifestations of an inflammatory syndrome are usual, including anaemia, elevated erythrocyte sedimentation rate and polyclonal hypergammaglobulinemia. The leukocyte count may be normal, increased or decreased. Thrombocytopenia and elevated hepatic enzyme levels are commonly found. Renal involvement is common, characterised by an elevated creatinine level and microhaematuria.

Serology

Since the clinical diagnosis is difficult in most instances, the diagnosis of Q fever is usually made by serology. The most

reliable and commonly used methods are indirect immunofluorescence, complement fixation, enzyme-linked immunosorbent assay (ELISA) and microagglutination [7]. Seroconversion is usually detected 7 to 15 days after the onset of clinical symptoms. Approximately, 90% of patients have detectable antibodies by the third week. As cutoff values in the immunofluorescence assay (IFA), it is recommended that titres of anti-phase II IgG of ≧200 and titres of anti-phase II IgM of ≧50 for the diagnosis of acute Q fever and titres of anti-phase I IgG ≧800 for the diagnosis of chronic Q fever (table 1). IFA titres usually reach their maximum levels four to eight weeks after the onset of acute Q fever and then reduce gradually over the following 12 months. The persistence of high levels of anti-phase I antibodies despite treatment or the reappearance of antibodies may signal the development of chronic infection.

Table 1: Sensitivity, specificity, and positive and negative predictive values of different serological tests for diagnosis of Q fever

Test	Form of disease	Titre	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Reference
Micro-immunofluorescence	Acute	Anti-phase II IgG ≧1:200; Anti-phase II IgM ≧1:50	58.4	95.2	NA	88-96.6	1
	Chronic	Anti-phase I IgG ≧1:800	100	NA	98.6	NA	1
		Anti-phase I IgG ≧1:1600	NA	NA	100	NA	1
ELISA	Acute	Anti-phase II IgG ≧1:1024; Anti-phase II IgM ≧1:512	80 84	>99	NA	NA	2
	Acute (screening)	Anti-phase I IgG ≧1:128 Anti-phase I IgM ≧1:128	NA	97.3-98.7	NA	NA	2
Microagglutination	Acute	1:64	84.6	98.6	NA	NA	3

1. 1994. Q fever serology: cutoff determination for micro-immunofluorescence. Clin. Diagn. Lab. Immunol. 1:189-196.

2. 1995. Validation of an enzyme immunoassay for serodiagnosis of acute Q fever. Eur. J. Clin. Microbiol. Infect. Dis. 14:421-427.

3. 1996. Rapid method for detection of Coxiella burnetii antibodies using high-density particle agglutination. J. Clin. Microbiol. 34:2947-2951.

Culture

C. burnetii must be cultured in biosafety level 3 containment due to its extreme infectivity. The micro-organism can be isolated by inoculation of specimens onto conventional cell cultures.

DNA amplification

Polymerase chain reaction (PCR) has successfully been used to detect *C. burnetii* DNA in cell cultures and clinical samples, including cardiac valves or vascular aneurysm biopsies, liver biopsy, milk, placenta, faetal specimens, ticks and blood samples. Its specificity reaches 100% and it is useful to test patients with acute infection in the first two weeks following the onset of symptoms with sensitivity of 24 %, compared with 14% by serology.

Treatment

Acute Q fever is usually a mild disease that resolves spontaneously within two weeks. Thus, clinical evaluation of the efficacy of antibiotic therapy is difficult and comparative studies are scarce. Consideration of therapy is warranted only in patients who are symptomatic. Doxycycline at 200mg daily for 14 days is the current recommended regimen for acute Q fever [1]. Fluoroquinolones are considered to be a reliable alternative, particularly in patients with Q fever meningoencephalitis, because they penetrate the cerebrospinal fluid.

Although a macrolide compound or co-trimoxazole may be potential effective alternatives, no reliable antibiotic regimen can currently be recommended for children and pregnant women.

Chronic Q fever-associated mortality may be significantly reduced with appropriate antibiotic therapy, but the organism is difficult to eradicate and a prolonged course of antibiotic treatment is necessary. Relapses are frequent despite prolonged antimicrobial therapy and mortality rates can exceed 60%. In vitro data have shown that the pH within the acidified phagosomal compartment in which intracellular *C. burnetii* resides may be responsible for the lack of bactericidal activity of many antibiotics. *C. burnetii* is inherently resistant to β-lactam compounds and aminoglycosides, but the organism is generally susceptible to tetracycline derivatives, cotrimoxazole, rifampicin and the fluoroquinolones. Monotherapy with each of these drugs may be effective in reducing the symptoms associated with chronic Q fever, but relapses are frequent upon cessation of antibiotics, prompting the development of combination regimens [8,9].

In a retrospective multicentre study involving 16 patients with Q fever endocarditis treated with fluoroquinolones and doxycycline, the combination regimen led to a statistically significant difference in mortality compared to doxycycline monotherapy [8]. Hydroxychloroquine, an alkalinising agent of phagolysosomes, in combination with doxycycline has been shown to have in vitro bactericidal activity against *C. burnetii*. In a clinical study involving 35 patients with Q fever endocarditis, the addition of hydroxychloroquine to doxycycline was found to reduce the median duration of treatment by 2 years compared to treatment with doxycycline and ofloxacin, and there were no relapses after 18 months of therapy in the group that received hydroxychloroquine-doxycycline [9]. The mortality rate for both regimens was 5% (table 2) and the major complication associated with each regimen was hypersensitivity to sunlight. Adverse effects of hydroxychloroquine include photosensitivity and retinal accumulation, but only 1 of 21 patients in the doxycycline-hydroxychloroquine group developed retinal toxicity that required the discontinuation of hydroxychloroquine treatment.

The optimal duration of therapy is unknown, based on these findings, the current recommendations for the treatment of chronic Q fever are 100mg of doxycycline by mouth twice daily with 600mg of hydroxychloroquine by mouth once daily for at least 18 months [1]. Serologic testing is recommended on a regular basis during therapy and the main predictive criterion of clinical cure is a decrease of phase I IgG antibody titres to less than 200. Vaccination is advocated for exposed populations, including livestock handlers, abattoir workers, persons in contact with unpasteurised dairy products, veterinarians and laboratory personnel working with *C. burnetii*. Although clinical data are lacking, vaccination should also be considered for persons who are not professionally exposed but who are at higher risk for development of chronic Q fever, including those with cardiac valve defects or prostheses, those with vascular aneurysms and immunocompromised patients

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Table 2: Mortality and failure associated with use of various antibiotic regimens during Q fever endocarditis*

Source	Patients, No.	1, Tetracycline or Doxycycline Alone	2, Tetracycline or Doxycycline and Lincomycin or Clindamycin	3, Co-trimoxazole Alone or Associated	4, Doxycycline and Quinolone†	5, Doxycycline and Hydroxychloroquine Sulfate†
Tobin et al[29]	10	1/2	2/4	1/4	...	...
Varma et al[25]	8	1/3	...	0/5	...	...
Turck et al[28]	16	...	4/14	...	...	...
Haldane et al[36]	5	...	...	2/5	...	...
Wilson et al[22]	16	9/16	...	...	...	...
Ellis et al[37]	8	2/5	1/3	...	...	...
Levy et al[6]	32	6/9	...	1/1	1/16	...
Subramanya et al[34]	1	...	...	1/1	...	...
Present study	...	...	...	...	0/5‡	1/21
Total	...	**19/35** (54%)	**7/21** (33%)	**5/16** (31%)	**1/21** (5%)	**1/21** (5%)

** Data are given as number of deaths or failures/number of treated patients. Ellipses indicate data not applicable.*
† Columns 4 and 5: comparison with column 1, P<.002 (χ^2); comparison with column 2, P<.03 (1-tailed, Fisher exact test); comparison with column 3, P<.05 (1-tailed, Fisher exact test).
‡ Some of the patients were partially described in Levy et al.[6]

References

1. Maurin M, Raoult D. Q fever. Clin Microbiol Rev 1999;12;518-553.
2. Maltezou HC, Raoult D. Q fever in children. Lancet Infect Dis 2002;2:686-91.
3. Maltezou HC, Constantopoulou I, Kallergi C, et al. Q fever in children in Greece. Am J Trop Med Hyg 2004;70:540-44.
4. D Raoult, TJ Marrie, JL Mege. Natural history and pathophysiology of Q fever. Lancet Infect Dis 2005;5:219-226.
5. Fenollar F, Fournier PE, Carrieri MP, et al. Chronic endocarditis following acute Q fever. Clin Infect Dis 2000;33:312-16.
6. Houpikian P, Habib G, Mesana T, Raoult D. Changing clinical presentation of Q fever endocarditis. Clin Infect Dis 2002;34:e28-31.
7. Fournier PE, Marrie TJ, Raoult D. Diagnosis of Q fever. J Clin Microbiol 1998;36:1823-1834.
8. Levy, P.Y., M Drancourt, et al. Comparison of different antibiotic regimens for therapy of 32 cases of Q fever endocarditis. Antmicrob. Agents Chemother. 1991;35:533-537.
9. Raoult D, Houpikian P, Tissot Dupont H, et al. Treatment of Q fever endocarditis: comparison of 2 regimens containing doxycycline and ofloxacin or hydroxychloroquine. Arch. Intern. Med.1999;159:167-173.

Journal review (Mar 2008)

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Metjian TA, Prasad PA, Kogon A, et al. Evaluation of an antimicrobial stewardship program at a pediatric teaching hospital. Pediatr Infect Dis J. 2008; 27:106-11.

Antimicrobial stewardship programs (ASPs), which usually comprise infectious diseases experts and pharmacists with an aim to optimize antimicrobial prescription, are now increasing being established in hospitals both locally and overseas. It is currently unknown whether the benefits seen in adult programs can be extrapolated to the pediatric population. Investigators from a

children's hospital in Philadelphia recently conducted a study to address this issue.

The ASP team consisted of two pharmacists and a director (an infectious disease physician). In addition, two infectious disease fellows assisted in the operation of the program during weekends. Use of non-formulary or targeted antimicrobial agents required approval by the team. Empirical use of antimicrobial was allowed for 48 hours, and continuation of therapy required endorsement by the team. Inappropriate requests were immediately acted upon by the ASP team.

From April through July 2005, the ASP team received 652 calls concerning a total of 856 non-formulary or targeted antimicrobial agents. The ASP team intervened in 294 of the calls (total, 558 interventions). Interventions included 114 recommended changes to target specific or suspected pathogens; streamlining of therapy based on culture and sensitivity data in 52 cases, and narrowing of empiric therapy to fit clinical scenario in 62 cases. The team also made suggestions regarding duration and choice of therapy, and in some cases made arrangements for the patient to be evaluated by the infectious diseases service. Some interventions were made to enhance patient safety (e.g., allergy avoidance and dosage adjustments in patients with renal dysfunction). These changes were estimated to produce savings in excess of US$50,000 in drug-acquisition costs for the institute concerned.

Points to note: ASPs in pediatric hospitals, like those in their adult counterparts, have the potential to promote more appropriate and rational antimicrobial use and can lead to improvements in patient care and safety. In addition, there could be substantial cost savings on the drug budget as a result of its operation. It is anticipated that further studies would be performed in this important area in the near future.

Mavalankar D, Shastri P, Bandyopadhyay T, et al. Increased mortality rate associated with chikungunya epidemic, ahmedabad, India. Emerg Infect Dis. 2008 Mar;14(3):412-5.

Sergon K, Njuguna C, Kalani R, et al. *Seroprevalence* of *Chikungunya* virus (CHIKV) infection on Lamu Island, Kenya, October 2004. Am J Trop Med Hyg. 2008; 78: 333-7.

Panning M, Grywna K, van Esbroeck M, et al. *Chikungunya* Fever in travelers returning to europe from the Indian ocean region, 2006. Emerg Infect Dis. 2008; 14: 416-22.

Chikungunya virus is an *alphavirus* that is carried and spread by vector mosquitoes. Recent data indicated that it has continued to disseminate, causing outbreaks in Asian countries. Three recent investigations provided useful information on clinical course and diagnosis of this disease entity.

In 2006, the government in India reported over 1 million cases of chikungunya fever. Mavalankar and colleagues analyzed monthly mortality rates for 2002–2005 in Ahmedabad, India, and compared them with mortality rates for 2006. The chikungunya epidemic peaked in August and September 2006; the number of deaths reported for August through November 2006 exceeded the average number of deaths for those months in the previous 4 years by nearly 3000. No other obvious cause for excess deaths was identified except for the chikungunya outbreak.

In another article, Sergon et al. reported the findings from a cross-sectional seroprevalence survey conducted on Lamu Island, Kenya, where an outbreak of chikungunya occurred in 2004. In October 2004, investigators administered questionnaires and obtained sera from 288 local residents to test for chikungunya antibodies. *Seroprevalence* rates were high in all age groups (44%–86%), suggesting that the outbreak may have affected as many as 75% of the island's 18,000 inhabitants.

In another study involving 680 returned European travelers with suspected chikungunya fever (many of whom had visited the Indian Ocean region), Panning et al. analyzed the performance of different diagnostic tests. Chikungunya infection was confirmed in 24.4% and 9.9% of those seen during the first and second half of 2006, respectively. Sixty-three of the patients had confirmed chikungunya infection and specimens available from the initial 10 days of illness. Among these patients, reverse-transcription PCR was positive for

all specimens collected during the first 4 days of illness, while none was positive for specimens collected after day 7. Forty-seven PCR-positive samples were cultured on Vero cells; virus was isolated in only 23.4% of these samples. Two patients had coinfections with dengue and chikungunya. Antibodies were detected by indirect immunofluorescence testing as early the first 2 days; all 63 samples were antibody-positive by day 5. High levels of viremia were detected; in particular, viral RNA concentration was significantly higher in antibody-negative than in antibody-positive samples.

Points to note: The high levels of viremia could help explain the rapid spread of infection in susceptible populations. In addition, healthcare workers may also be at risk for infection when caring for patients during their early stages of infection. Moreover, transfusion-associated infection is also a potential risk. Many areas of the world are infested with *Aedes aegypti* and *Aedes albopictus* mosquitoes. It is thus not inconceivable that local transmission may be possible in areas that are vulnerable because of climate and mosquito vector populations, which were not previously considered endemic to the disease. Clinicians should remain vigilant and have low clinical threshold for ordering tests to confirm the diagnosis in patients presenting with compatible clinical syndromes.

Palacios G, Druce J, Du L, et al. A new arenavirus in a cluster of fatal transplant-associated diseases. N Engl J Med. 2008; 358: 991-8.
Whitley R. The new age of molecular diagnostics for microbial agents. N Engl J Med. 2008; 358: 988-9.

Three patients who received kidney or liver transplants from a single donor developed febrile illnesses with encephalopathy, and eventually all of them died within 6 weeks after transplantation. The causative pathogen could not be identified despite extensive investigations. Then a group of researchers from multiple institutions collaborated and used a relatively new technique — unbiased high-throughput sequencing — to evaluate RNA from tissue or body fluids of two of the recipients.
The new diagnostic technique allowed rapid identification of all nucleic acid sequences in the clinical samples assayed, and eventually allowed the researchers to detect a previously unknown *arenavirus* that is related to lymphocytic choriomeningitis viruses. After the new virus was detected, serum from the organ donor was tested and the results suggested acute infection and transmission of the pathogen to all three recipients by the donor. Seroconversion was also evident in serum specimens obtained from one recipient at two time points.
Points to note: This investigation exemplifies the rewards of collaboration among individual experts from different institutions, and is important and groundbreaking in 2 ways: firstly, the researchers identified a novel *arenavirus* that had caused fatal infections in organ-transplant recipients; secondly, this report ushers in a new era of molecular diagnostics for microbial pathogens. Unbiased high-throughput sequencing certainly has the potential of becoming the method of choice for identification of microbial agents in the not-too-distant future.