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Chickenpox in pregnancy

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Introduction & Epidemiology

Chickenpox infection is caused by varicella-zoster virus (VZV) which also causes herpes zoster (reactivation form). Human is the only known reservoir of the virus. The presence of fever and the vesicular rash over body at different stages during the illness pose little diagnostic difficulty. It is by far the most contagious among the members of the herpes virus. The local population usually contract chickenpox before adulthood, 90% occur before the age of 10.

Since 1999, chickenpox became a notifiable disease in Hong Kong. It occurs seasonally and in epidemics. Highest incidence occurs in winters and early springs. Incubation period ranges from 10 to 21 days. The period of communicability is from 2 days (up to 5 days) before rash till all lesions crusted. Three modes of transmission are direct contact, droplets and airborne. For reference, the case fatality rate in the United States in 5-9 age group is 1:100,000, whereas in adults raises to 1:5000. The most serious complications are viral pneumonia, secondary bacterial infections, haemorrhagic complications and encephalitis.

The major problems with chickenpox infection occur in areas housing potentially immunosuppressed patients (paediatrics and oncology units) and pregnant ladies (obstetrics unit).

Maternal risk

In the pre-antiviral era, the mortality in pregnancy was up to 25%. Pneumonia was reported in up to 10% of pregnant ladies with chickenpox.

Fetal risk

Before 20 weeks of gestation

Up to 2% of maternal varicella infections occur before 20 weeks of gestation. Spontaneous miscarriage does not increase if chickenpox occurs in the first trimester.

Fetal varicella syndrome may occur when infection before 20 weeks of gestation. In the skin, there may be dermatomal skin scarring and contractures (76% to 95%). Limb hypoplasia occur in half of the sufferers. Eye complications develop in half of the sufferers. They include microphthalmia, chorioretinitis, cataract, and Horner's Syndrome. Half of the patients may develop central nervous system complications including microcephaly, brain atrophy, paralysis, convulsions or encephalitis. 16% to 29% were mentally retarded. Other organ defects occur in 14% to 18% of sufferers.

Between 20 weeks and 36 weeks of gestation

There is no associated adverse fetal effect. Many patients may present as herpes zoster in the first few years of infant life.

After 36 weeks of gestation

If maternal infection occurs in this period, up to 50% of babies are infected and approximately 23% develop clinical chickenpox infection despite the high titres of passively acquired maternal antibody.

Severe chickenpox is most likely to occur if the infant is born within 7 days of onset of the mother's rash when cord blood VZV IgG is low.

Prevention of chickenpox in pregnancy

In non-immune adult planning motherhood

The most effective way is active immunization of individuals. A live attenuated varicella vaccine is available which is safe and effective in preventing chickenpox in adults. Unlike rubella vaccination, there is no general consensus on immunisation of all susceptible women who are planning a pregnancy for prevention of varicella infection. The vaccine is not available for this purpose anyway. Therefore the current emphasis on the preventive measure is still on contact precaution.

The following advice may be applicable at the initial antenatal visit:

- Enquire about a previous history of chickenpox from the booking visit.
- Advise pregnant women without such history to avoid contact with chickenpox during pregnancy and report to health care worker of any potential exposure.
- Check VZV IgG antibodies if query, although up to 90% pregnant ladies will be seropositive.

A pregnant lady presented to a clinic with an exposure history

The first step is to assess the certainty of the infection which is determined by the infectiousness and degree of exposure. Vesicular rash or development of rash within 48 hours of contact is considered high infectiousness. Any close contact during the period of infectiousness is considered significant. Some authorities take household, face-to-face for five minutes or indoors contact for more than 15 minutes as significant.

The second step is to assess immunity. They should be assumed immune and reassurance for those with a history of chickenpox infection. In case of uncertainty, test for VZV IgG within 24 to 48 hours, or the best to test the stored serum. The presence of antibodies within 10 days of contact is considered a previous exposure before the contact.

A non-immune pregnant lady with a significant exposure to chickenpox while the contact was infectious

Give VZIG as soon as possible when non-immune status was confirmed. VZIG given after ten days may not prevent but attenuate the infection. Maternal death has been reported following the development of varicella pneumonia despite the administration of VZIG.

Pregnant lady with an exposure history should notify if rash develop despite her immune status.

Recommendation for management of pregnant lady who developed chickenpox

Patient should contact her family doctor immediately. The initial assessment should involve the determination if admission is required. Patient should avoid contact with susceptible individuals, i.e. other pregnant lady and neonates until at least five days after the onset or until the lesions have crusted over.

The mainstay of management is symptomatic treatment and hygiene. Secondary bacterial infection of lesions should be actively treated. Patient with the following are considered high risk group, namely chronic lung disease, smoker, taking steroid and in the latter half of pregnancy. Admission is required for high risk group and those with complications (chest symptoms, neurological symptoms, haemorrhagic rash or bleeding, a dense rash with or without mucosal lesions and significant immunosuppression).

The UK Advisory Group on chickenpox recommends the use of oral acyclovir for pregnant lady with chickenpox if they present within 24 hours of the onset of the rash and if they are more than 20 weeks of gestation. Informed consent should be obtained for patient given acyclovir in this context. VZIG has no therapeutic benefit once chickenpox has developed.

Recommendation during peripartum period

Delivery during viraemic period is most hazardous to both mother and the newborn. Supportive treatment and intravenous acyclovir is recommended. It facilitates the resolution of rash, immune recovery and transfer of protective antibodies from mother to the fetus.

If possible delivery should be delayed until five days after the onset of maternal illness to allow for passive transfer of antibodies. Neonates should be given VZIG if delivery occurs five days within maternal infection; or mother developed chickenpox within two days of giving birth.

Infants should be closely monitored for signs of infection for 14-16 days. Acyclovir should be used if infant develops chickenpox. It should be noted that mother who develops herpes zoster around the time of delivery imposes no risk to neonate.

Outbreak control in antenatal clinic

The clinical setting in antenatal clinic in Hong Kong is special. Large numbers of pregnant ladies are seen in the same session in a big consultation waiting hall. They may be of different stages of gestation. The outbreak control measures have to be quick and large volume of work be finished within a few days in order to minimise the possible morbidity and mortality.

To take a case for illustration, a pregnant lady near term developed rash during an ultrasound session at antenatal clinic. The chickenpox vesicular rash became apparent five days later when she presented to the Accident and Emergency Department. She was admitted and the baby was delivered by Caesarean section because of fetal distress. Outbreak response finished within 5 days which involved the identification of 242 contacts, most of them pregnant ladies. 220 contacts were approached, 101 had history of chickenpox infection. 102 patients required blood test to determine immune status. Excluding those who refused blood tests, 72 out of 75 pregnant ladies were tested seropositive. Three contacts required isolation admission during the quarantine period. Fortunately there was no secondary case in this incident.

Another not uncommon scenario is that the pregnant mother comes to the consultation hall with a child who is found to have active chickenpox infection.

Conclusion

Varicella infection is an old recognised infectious disease. Pregnant ladies, fetus / neonates and immunosuppressed are the high risk groups for development of complications.

In addition, the particularly highly contagious nature and the ability for airborne transmission pose special problem for nosocomial outbreak control measures.

In terms of outbreak prevention, the extent and risk of nosocomial spread may be minimised by the following measures:

- Determination of immune status in the initial antenatal visit
- Minimise the waiting time in the consultation hall
- Fragment the large group of pregnant ladies into small groups in different small consultation room (like most of the situation in Western countries)

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Update on varicella vaccination

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Varicella (chickenpox) is a common infectious disease caused by the primary infection of varicella zoster virus (VZV). After the primary infection, the host will usually develop lifetime immunity against reinfection; however, the virus will remain latent within the dorsal root ganglia and may reactivate later in life to cause herpes zoster. Chickenpox is merely a self-limited disease of childhood; nevertheless, complications like ataxia, encephalitis, pneumonitis and bacterial superinfection may occur even in immunocompetent hosts, leading to significant morbidity and mortality. In some developed countries, varicella vaccine had been added to the routine childhood immunization schedule to reduce the incidence of varicella and its related consequences. In this article, the updated information about varicella vaccination and some controversial areas will be discussed.

The vaccine

History

The vaccine virus used (the Oka strain) was isolated three decades ago from an otherwise healthy 3-year-old Japanese boy with varicella. It was attenuated in-vitro through sequential propagation and passage. This live attenuated varicella vaccine has been found to be extremely safe in susceptible children and adults. A total of 9,454 healthy children and 1,648 healthy adolescents and adults have received the vaccine in the prelicensure clinical trials with minimal occurrence of serious adverse events (1). In a double-blind, placebo-controlled study involving 914 healthy susceptible children and adolescents, local symptoms like pain and redness were the only adverse events that occurred significantly more often in vaccine recipients than in placebo recipients. Fever and rash are other frequent reported adverse effects. 3% of the vaccine recipients may develop a varicella-like rash at injection site while a generalized varicella-like rash may occur in up to 5% of recipients. Cases of serious disseminated infections due to the vaccine strain had been reported, which occurred in patients with significant underlying immunodeficiency that was not suspected at the time of vaccination (2). Transmission of the live vaccine virus is another concern. Current data suggested that healthy children are unlikely to transmit vaccine virus to susceptible contacts. However, the risk of transmission may be higher among immunocompromised vaccines, particularly for those vaccines that develop varicella-like rash after vaccination. There is only one report of tertiary spread of the vaccine virus. Contact cases are usually mild or subclinical.

Immunogenicity and efficacy

The vaccine is highly immunogenic. In the prelicensure study, 97% of 6,889 susceptible children aged 12 months-12 years had seroconversion after one dose of vaccine. Significant antibody titer to VZV is present in 97% of children 7-10 years after vaccination. For those aged 13 or above, seroconversion rate was around 80% after the first dose of vaccine, which rose to 95% after a booster dose given at 4-8 weeks later. Antibodies against VZV could be detected for at least 1 year in more than 95% of adolescents and adults who received two doses of vaccine. In general, the vaccine offers 70%-90% protection against infection and 95% protection against severe disease for 7-10 years after vaccination (1). The vaccine may also be given to susceptible individuals after exposure to prevent further cases. The protective efficacy was greater than 90% when children were vaccinated within 3 days of exposure.

Breakthrough cases of chickenpox have consistently been reported following administration of varicella vaccine. Different rates of breakthrough varicella have been reported which may be affected by the vaccine lot and time interval since vaccination. Data from active follow-up of vaccines indicated that varicella developed in less than 1-5% of vaccines per year, with the disease among vaccinated subjects substantially less severe than unvaccinated ones. For vaccines in whom varicella has developed, the median number of skin lesions has been less than 50 (compared with greater than 300 in unvaccinated individuals). In addition, most vaccines are afebrile, with fewer vesicular lesions and shorter duration of illness compared with unvaccinated subjects. The disease manifestations may be so mild that it may be misdiagnosed clinically as non-specific viral illness or rash.

Administration and indication of the vaccine

For children aged 12 months to 12 years, one 0.5mL dose should be given subcutaneously. It may be administered simultaneously with all of the vaccines recommended for children 12-18 months of age. For those aged 13 or above, two 0.5mL doses age should be administered 4-8 weeks apart. In the United States, the vaccine will be routinely given to children at 12-18 months of age except for those who have reliable histories of varicella. The vaccine is also recommended for all susceptible children before their 13th birthday. Those persons aged 13 or above without reliable histories of varicella are considered susceptible. As majority of adults are immune, it may be more cost effective to check for varicella immune status for these “susceptible” adolescents and adults before vaccination. Vaccination of susceptible persons who have close contact with persons at high risk for serious complications like health care workers and family contacts of immunocompromised persons is recommended. Vaccination should be considered for susceptible individuals with high risk of exposure such

as women at child-bearing age and those live or work in environments in which transmission of VZV is likely to occur (e.g. teachers of young children, day-care employees, and residents and staff in institutional settings). Major contraindications to varicella vaccine include pregnancy, severe allergy towards vaccine components and immunodeficiency. Children receiving prednisolone (>2 mg/kg/day or equivalent) for more than two weeks should not be immunised until steroid has been discontinued for at least 3 months (1,2). Although the vaccine is contraindicated in immunocompromised hosts, it may be considered for children with asymptomatic HIV infection and acute lymphoblastic leukaemia in remission.

Effectiveness and cost-effectiveness

The effectiveness of routine varicella vaccine may be evident in the dramatic decline in the mortality related to varicella in the United States since its introduction into the routine childhood vaccination program in 1995. The active surveillance data of varicella in three sentinel counties in Texas, California, and Pennsylvania also support its effectiveness. Vaccination coverage by the year 2000 in these counties ranged from 73.6 to 83.8% among children 19 to 35 months old. During the study, the number of varicella cases decreased by between 71 and 84% in these counties. Annual hospitalisations for varicella per 100,000 persons decreased from 2.7-4.2 in 1995 to 1998 to 0.6 in 1999 and 1.5 in 2000. Incidence of varicella also declined in unvaccinated groups such as adults and infants, which might indicate occurrence of herd immunity.

The cost effectiveness of the vaccine is difficult to assess. It had been demonstrated to be cost-effective in a number of cost-benefit analyses in the developed countries. However, the cost effectiveness of the vaccine may be different when we consider from the societal or payers' perspectives.

Controversial areas about the vaccine

Despite the well demonstrated safety and efficacy of the varicella vaccine, there are still controversies that remain to be solved. First, there are opinions that it is not worthwhile to use too much resource in preventing varicella, which is usually a self-limited childhood disease. Further cost-benefit analyses may be required to answer this question. Second, concern has been raised about the potential risk of waning immunity after vaccination and routine varicella vaccination may actually cause an age-shift of the disease. The argument is that the vaccine may postpone the disease to late adulthood, which results in higher chance of complications. However, existing data so far does not provide solid evidence to substantiate this theoretical risk despite the extensive use of the vaccine for more than two decades. The third debatable area is whether mass childhood vaccination may cause an increase in wild-type zoster in

persons who have had natural varicella. Recent studies suggested that exposure to varicella may be protective against zoster, presumably because of boosting of the immune response to VZV. The routine use of varicella vaccine may reduce the chance of exposure to VZV in those individuals with natural varicella, which in turn increase the chance of VZV reactivation. Close surveillance of the incidence of zoster in countries where routine varicella vaccine is adopted will be necessary to evaluate this potential impact. Ongoing monitoring of the incidence of zoster in sentinel populations has been conducted in countries like the United States. If there is a dramatic increase in the incidence after the introduction of routine vaccination program, interventions may be required. New immunization strategy may be used to boost immunity to VZV and possibly to prevent zoster. Studies had been performed in evaluating the efficacy of varicella vaccine to prevent zoster in the elderly and one large double-blind placebo-controlled study involving approximately 30,000 healthy individuals older than 60 years has been undertaken to evaluate these issues. There are also increasing interests in the use of heat-inactivated varicella vaccine in preventing VZV infection and reactivation.

In summary, experience from many developed countries had demonstrated that varicella vaccine is safe and effective in preventing varicella. As the health infrastructure varies among different places, further evaluation may be required to assess the cost effectiveness of the routine use of this vaccine in Hong Kong.

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Brain abscess

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Introduction

Brain abscess (intracerebral pus collection in a well-vascularised capsule) is not an uncommon clinical condition to both neurosurgeon and infectious disease specialist nowadays. It is one of the most serious complications of head and neck infections. The introduction of antimicrobial therapy, radiological imaging and advanced neurosurgical interventions have significantly reduced the mortality from 50% to less than 20% today. Brain abscesses are now encountered in less than 2% of all intracranial surgeries. Brain abscess can occur at any age, but is most commonly seen in the second to fourth decades due to the higher incidence of mastoid and nasal infection during those years. Around 25% of cases occur in children aged 4-7 years old as a result of the coexisting cyanotic congenital heart disease or from an otic source. Brain abscess can originate from infection of contiguous structures in about 50% of cases (e.g. otitis media, dental infection, mastoiditis, sinusitis), haematogenous spread from a remote infective site in about 25% of cases (e.g. patient with cyanotic heart disease, cystic fibrosis, bronchiectasis, osteomyelitis, intra-abdominal or pelvic infection and pulmonary arteriovenous malformations), trauma related in about 10% of cases and post neurosurgical intervention in about 5 % of cases. In about 15 % of cases, no source can be identified and is named as cryptogenic type. Typically, brain abscess are classified based on the entry point of infection. This allows the determination of likely microbial flora and aids in choosing appropriate empirical antimicrobial treatment (Table 1). Among the intra-cerebral compartments, fronto-parietal is the most common site for infection to arise.

Symptoms and signs

Attempts have been made by several investigators to divide the clinical course into three or four stages in order to predict the outcome. However the clinical presentation is far from stereotyped and clinical alertness is of paramount importance. The clinical course varies from indolent to fulminant and the clinical features of brain abscess can vary significantly, determined by the size, location of brain abscess as well as the virulence of the infecting micro-organism. Subtle presentations are expected in the immunocompromised state because of diminished inflammatory response. Headache (70%) is the most common clinical presentation. If the abscess solely occurs in the brain parenchyma, patient may have no signs of meningism, i.e. absence of neck stiffness cannot exclude parenchymal brain abscess. Different sites of abscess location can give rise to different presentations, e.g. in temporal lobe abscess, patient may have headache over the ipsilateral fronto-temporal region; in cerebellar brain abscess, patient may have coarse nystamus, cerebellar ataxia in ipsilateral arm and leg; in frontal lobe brain abscess, patient may have headache, drowsiness, inattention; in occipital lobe brain abscess, the homonymous hemianopia may be obscured by drowsiness and stupor. Sudden worsening of headache may signify vascular occlusion, new abscess formation in vital regions, rapid oedema formation, co-existing bleeding, herniation or rupture of abscess into a ventricle. For the case of rupturing abscess into ventricles, it usually relieves the CSF pressure temporarily and slightly, and patient will have transient improvement, followed by further deterioration of headache and associated with a high mortality rate (80%) within 10 days afterwards. Fever (40%) alone is not a reliable symptom or sign. It is absent especially after the initial phase when the abscess is being encapsulated. The triad of fever, headache and focal neurological deficit only accounts for <50% of cases upon presentation. Seizures (25%) alone might be the first manifestation and grand mal seizures are particularly common in frontal lobe brain abscesses. Changes in mental status (lethargy progressing to coma) are indicative of severe cerebral oedema and carries poor prognostic outcome. Signs of increased intracranial pressure (papilloedema,

vomiting, 3rd and 6th cranial nerve palsies) are uncommon.

Investigations

With the presence of predisposing condition and clinical symptoms or signs, CT or MRI should be performed. ESR and WCC are not reliable. Blood culture might be positive in 15-30% of patients in particular those cases with remote site of infection. Hence, it is highly recommended to send blood culture in all suspected cases, even in the absence of fever. Lumbar puncture may be dangerous (transtentorial herniation) when intra-cranial pressure is obviously elevated, in which case the information depends mainly on the CT/ MRI and blood culture (or other cultures). CSF examination usually reveals an elevated opening pressure and results consistent with aseptic meningitis. The CSF culture positivity rate varies from 0-37%. The CSF may appear clear but can be cloudy or turbid depending on whether there is any co-existing meningitis, and the CSF cell count varies from 0-1000 cells/mm^3 or even higher. The cell count is usually polymorphonuclear predominant in early unencapsulated abscess near the ventricular or subarachnoid spaces whereas in fully encapsulated cases, the CSF cell count may be normal or only slightly increased. In most cases, the CSF glucose is not lowered. In a few cases, there may be no CSF abnormalities. However, increase in turbidity of CSF, rise in CSF cell count, decrease in CSF glucose and sudden rise in ICP usually signify the rupture of an abscess into ventricles.

Neuroimaging in the diagnosis of brain abscess

MRI and CT scanning with contrast are vital for the diagnosis and subsequent management of brain abscess. Both can identify the different stages of infection, i.e. early cerebritis and encapsulated stages. For cerebritis stage occurring in the first 1-2 weeks of infection, it is shown up as poorly demarcated area with localised inflammation and oedema without necrosis. Whereas encapsulation stage occurs from 2nd week onwards which usually show up as thick and diffuse ring enhancement with central necrosis and liquefaction following contrast injection. The ring of contrast enhancement represents breakdown of the blood brain barrier. MRI has been extensively evaluated in the diagnosis of brain abscess and is the first choice in the evaluation of a patient suspected of having this disorder. MRI is more sensitive than CT and therefore offers significant advantages in the early detection of cerebritis, including greater contrast between cerebral oedema and adjacent brain, more conspicuous spread of inflammation into the ventricles and subarachnoid space, earlier detection of satellite lesions as well as better visualization of the brainstem than CT scanning with contrast. On T_1-weighted images, the abscess capsule often appears as a discrete rim that is isointense to mildly hyperintense. Contrast enhancement with gadolinium provides the added advantage of clearly differentiating the central abscess, the surrounding enhancing rim, and the cerebral oedema surrounding the abscess. On T_2-weighted images, the zone of oedema that surrounds the abscess is one of marked high signal intensity, while the capsule appears as a well-defined hypointense rim at the margin of the abscess.

The subsequent management of brain abscess

Whether the patient requires surgical intervention will largely depend on the size and location of the abscess, the response to empirical anti-microbial therapy as well as the concurrent medical condition of the patient. If the abscess is large, easily accessible and is away from the important region, free-hand needle aspiration can be done. If it is small, or is in close proximity to vital region (brainstem or spinal cord), difficult to be accessed, then CT guided stereotactic aspiration might be another option. Though CT-guided aspiration provides rapid, precise and safe access to virtually any intracranial points nowadays, it is still an invasive procedure, and should be considered seriously before contemplating its application. Empirical antibiotic therapy can be initiated in the operating theatre once specimen for culture

is obtained. The choice of empirical antibiotics is based on presumptive pathogens from primary focus of abscess encountered and the Gram's stain results. Early surgical evacuation is recommended, especially in cases with abscesses located close to the ventricles that could rupture. In some patients who are poor surgical candidates or those with surgically inaccessible lesions, best medical management is appropriate. This is particularly true if the microbes can already be identified from other source, e.g. blood culture, serology study and also if serial imaging has already shown that the size of the brain abscess is decreasing upon antibiotic treatment. Today, open craniotomy is rarely performed but may be reserved for patients with more resistant pathogens such as fungi, Nocardia or those with multiloculated abscesses or traumatic brain abscesses that required complete removal.

Most of the brain abscesses that arise from intracranial extension of sinus infections are usually caused by microaerophilic streptococci or anaerobic organisms, therapy with high dose penicillin G or cefotaxime (2g IV Q6H) or other cephalosporins (ceftriaxone 2g IV Q12h) in combination with metronidazole (15mg/kg IV as loading dose, followed by 7.5 mg/kg Q6-8H) may appear to be highly effective in the empirical treatment of brain abscesses. Metronidazole has excellent cidal activity against anaerobes and high intralesional concentration. Most of the Gram positive and Gram negative organisms are covered. Among the streptococcal species, *Streptococcus anginosus / milleri* (*Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius*) is the commonest isolated species instead of *Streptococcus viridans* and *Streptococcus pneumoniae*. It is mainly because of their presence of proteolytic enzymes to induce abscess formation. Some organisms secondary to dental procedures or dental abscess (e.g. Actinomyces species) may require treatment with intravenous high-dose penicillin G (20 to 24 million units daily divided by q4H). Special consideration of antimicrobial coverage (ceftazidime 2g IV Q8H or cefepime 2g IV Q8H) should be made when an otogenic source of brain abscess is suspected, particularly when *Pseudomonas aeruginosa* are identified as the causative agent. Alternative antibiotic therapy, particularly for Nocardia and ESBL positive organism, has been successfully reported with imipenem. Use of meropenem, with similar broad-spectrum coverage, however, may have less neurotoxicity and epileptogenic. Additional of vancomycin (1g IV Q12H) is indicated when MRSA, *Staphylococcus epidermidis* and *Clostridium* species are suspected in head trauma and post-neurosurgical cases. It has excellent concentration in brain abscess fluid (90% of serum concentration). The usual pathogens (*H. influenzae*, *S. Pneumoniae*, Listeria monocytogenes) isolated in bacterial meningitis are not commonly seen in brain abscess (<1%). Some pathogens (*L. monocytogenes*, *Citrobacter diversus*, *Proteus species*, *Serratia marcescens*, or Enterobacter) are prone to cause concomitant meningitis and bacteraemia.

In the immunocompromised patient (e.g. diabetic patients or those receiving steroids or other immunosuppressed states such as patients with profound neutropenia and malignancy), the chance of getting fungal brain abscess is increased substantially. In such cases, constitutional symptoms may be few but fever is common. Often the lesions lack ring enhancement on brain scan due to inadequate inflammatory response. *Candida*, *Aspergillus*, *Cryptococcus*, *Mucormycosis*, *Pseudallescheria boydii*, *Coccidioides* species are commonly encountered. Among them, Candida species remain the most prevalent. The treatment of choice is combination of amphotericin B plus 5-flucytosine. Cerebral aspergillosis accounts for 10% to 20% of all invasive aspergillosis and rarely presents as isolated brain infection. Both amphotericin B (0.8 to 1.5 mg/kg/day) and voriconazole (8mg/kg) q12h are shown to be effective in cerebral aspergillosis. Mucormycosis (zygomycetous fungi) is well recognised as the most acute, fulminant fungal infection by invasion of vasculature and causing host tissue infarction. It is commonly found in patient with diabetes mellitus (70% of cases), metabolic acidosis, post-transplantation, concurrent deferoxamine / steroid therapy, rhinocerebral form

of mucormycosis as well as in normal hosts (5%). The mainstay of treatment is amphotericin B and aggressive surgical debridement. Of course, some rare but important bacteria, mycobacterium and protozoal species should also be considered such as *Listeria monocytogenes*, *Bacillus cereus*, *Rhodococcus equi*, *nocardiosis* and *toxoplasmosis*.

In patients with AIDS, the most common cause of brain mass lesion is toxoplasmosis, and empirical pyrimethamine / sulfadiazine or pyrimethamine / clindamycin therapy should be initiated. Patients who fail to respond to 1-2 weeks antimicrobial therapy or have negative serology may still have toxoplasmosis, although the differential diagnosis may include other infections or neoplasms (e.g. CNS lymphoma). Definitive diagnosis will be much relied on early surgical brain biopsy. Other reported causative agents for brain abscess in AIDS patients include *L. monocytogenes*, *Nocardia* species, Mycobacterium species, *coccidioidomycosis*, *blastomycosis*, *histoplasmosis*, *cryptococcus*, *Candida* and *Aspergillus*.

In general, intravenous antibiotics should be given for a total of 6 to 8 weeks, followed by an additional 2- to 3-month course of oral antibiotic therapy. The need to repeat surgery or not will be largely dependent on the progress on sequential CT or MRI scans. If the size of the brain abscess remains static, or has shown increase in size, aspiration will be necessary. The possibility of double pathology, double organisms, or abscess formation in addition to an old pathology, e.g. brain tumour has to be considered. It is not uncommon to note a small area of residual enhancement present on neuroimaging even after adequate antimicrobial treatment completed.

Seizures can occur in up to 16-50% of patients. Antiepileptic drug (AED) such as phenytoin or carbamazepine, can be used for prophylaxis or to prevent the recurrence of seizures. The recommended duration of prophylaxis is at least 3 months after surgery. Subsequently, the timing of discontinuation of AED should be individualized based on neurologic examination and findings on EEG.

Whether steroid is useful or not in improving the mortality and morbidity is still a hot debate. There are only a few very small scale studies on this aspect. Hence, corticosteroids are not routinely used except in patients with life-threatening and substantial cerebral oedema or impending herniation from raised intracranial pressure. A short course of dexamethasone (a loading dose 10 mg IV followed by 4 mg Q6H) may be appropriate. Prolonged steroid use is not recommended because it may interfere with capsule formation and reduce the penetration and concentration of antimicrobials within the infected tissue. In cases of further clinical deterioration, endotracheal intubation with urgent measures to control elevated intracranial pressure (e.g. intravenous mannitol or hyperventilation) will be necessary. Hemicraniectomy will be considered in refractory cases of elevated intracranial pressure when medical therapy has been exhausted.

The mortality rates reported in the older series (40-60%) has substantially dropped to <30%. Overall outcome, morbidity, and mortality of brain abscess are related to several factors: 1) time from onset of symptoms to diagnosis, 2) primary source of infection, 3) presence of single or multiple lesions, and 4) patient's neurologic status at the time of diagnosis. For example, patients with lung as the source of infection had highest death rates, and those who presented with depressed level of consciousness (Glasgow Coma Scale score of <9) had high in-hospital mortality in one study. Additionally, immunocompromised individuals have overall worse outcomes and higher mortality rates. Finally, those with intraventricular rupture of brain abscess have mortality rates exceeding 80%. Overall, neurologic sequelae of brain abscess with hemiparesis, seizures, or cognitive decline is present in about 30% to 56% of all patients.

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Table 1. Source of brain abscess and common organisms per site

Source of abscess	**Microbial organism**
Otogenic infection	Streptococcus species
	Enterobacteriaceae
	Bacteroides species (including B. fragilis)
	Pseudomonas aeruginosa
Paranasal sinus infection	Streptococcus milleri group (aerobic streptococci)
	Anaerobic streptococci
	Haemophilus species
	Bacteroides species (non-fragilis)
	Fusobacterium species
Metastatic spread, often multiple lesions, dependent on source	
Lung abscess	Streptococcus species
	Actinomyces species
	Fusobacterium species
Intra-abdominal	Streptococcus species
	Enterobacteriaceae
	Anaerobes
Urinary tract	Enterobacteriaceae
	Pseudomonaceae
Endocarditis	Staphylococcus aureus
	Viridans streptococci
Penetrating trauma, dependent on wound site	Staphylococcus species
	Clostridium species
	Enterobacteriaceae
Post-neurosurgical procedure	Staphylococcus epidermidis
	Staphylococcus aureus
	Enterobacteriaceae
	Pseudomonaceae

Journal review

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Golden MR, Whittington WL, Handsfield HH, et al. Effect of expedited treatment of sex partners on recurrent or persistent gonorrhea or chlamydial infection. N Engl J Med. 2005; 352:676-85.
Erbelding EJ, Zenilman JM. Toward better control of sexually transmitted diseases. N Engl J Med. 2005; 352:720-1.

It is well known that, in treating patients with sexually transmitted diseases (STDs), partner notification, i.e. identifying the sex partners of patients, informing such partners of their infection risk, and providing them with empirical treatment can all help to reduce STD transmission and the subsequent risk of reinfection. However, there has been little research in this area before to determine the most effective strategies for notification. Investigators from King County, Washington, recently conducted such a study. They compared expedited treatment of partners (i.e. patient-delivered partner therapy) with standard referral among women and heterosexual men diagnosed with gonorrhea, chlamydia, or both in their part of the country.

Throughout a period spanning several years, from September 1998 through March 2003, a total of 26,656 such cases were reported; among these patients, 2751 patients were eventually randomised to either “expedited partner treatment” or “standard referral” groups. Participants in the expedited-treatment group were offered partner packets that contained standard antibiotics such as cefixime, azithromycin, or both, along with condoms, medication details, an STD brochure, and contact information for questions. Those in the standard-referral group were advised to have their partners seek free care at an STD clinic according to their own wish. When the patients were reassessed at a second follow-up scheduled 3 to 19 weeks after treatment, it was found that significantly fewer patients had persistent or recurrent infections in the expedited-treatment group, as compared to those in the standard-referral group (10% vs. 13%; relative risk, 0.76; 95% confidence interval, 0.59-0.98). The advantage of expedited treatment over standard referral was greater with gonorrhea (persistent or recurrent infection in 3% vs. 11%; P=0.01) than with chlamydia (11% vs. 13%; P=0.17), and its effect remained stable after adjustment for other predictors of infection. Independent risk factors predicting persistent or recurrent infection included failure to treat all sex partners, as well as sex with an untreated partner.

Discussion

Although this study was fraught with some limitations (such as the exclusion of specific high-risk groups e.g. men who have sex with men), plus potential problems with the approach used (including partners’ use of antibiotics without medical evaluation and attention to drug allergy), these findings seem to suggest that expedited partner treatment is an effective strategy over standard referral. Translating the results into practice will require more work and some compromise in the current standard of care. Nevertheless, the alarming rates of persistent and recurrent gonorrhea and chlamydia in both study groups highlight the need for action, and certainly much more research needs to be done in this area in future.

de Jong MD, Bach VC, Phan TQ, et al. Fatal avian influenza A (H5N1) in a child presenting with diarrhoea followed by coma. N Engl J Med. 2005; 352:686-91.

A total of 45 cases of avian influenza A (H5N1) infection, all characterised by severe respiratory symptoms, were documented in the Southeast Asia region within the year 2004. A case from Thailand presenting with fever and diarrhoea but no respiratory symptoms has since been described. Now, two additional atypical cases, one documented and the other probable, have been reported in this recent issue of the *New England Journal of Medicine*.

A 4-year-old boy from Vietnam presented to the hospital with 2 days' history of severe diarrhoea, vomiting, fever, and headache. Physical examination and chest x-ray were initially normal. Over a time course of 3 days, he showed rapid clinical deterioration, with increasing drowsiness and worsening diarrhoea, for which he was transferred to a pediatric referral hospital. On admission, he was already hypotensive and had cough, but his chest x-ray remained normal. Twelve hours later, the boy had a generalised convulsion and rapidly became comatose. Cerebrospinal fluid (CSF) analysis revealed 1 white cell per mm^3, normal glucose, and elevated protein. Respiratory failure soon ensued, and repeated chest x-ray revealed bilateral infiltrates. The boy eventually succumbed 2 days later. Subsequently, avian influenza A (H5N1) virus was isolated from multiple samples including CSF, serum, and rectal and throat swab specimens. The patient's 9-year-old sister had died 2 weeks earlier from a similar illness, but no virologic studies were performed at that time. Her fatal illness lasted 5 days and shared similar features with her brother's — severe diarrhoea and increasing drowsiness, absence of respiratory symptoms, and normal chest radiography. It was noteworthy that, prior to the onset of her illness, she had swum regularly in a canal frequented by domestic ducks.

Discussion
These reported cases are thought provoking and will arouse much anxiety, as they seem to indicate competent replication of the H5N1 virus in multiple organs, including the central nervous system and gastrointestinal tract. Strikingly, respiratory symptoms were initially absent and did not predominate. Should avian influenza virus acquire the ability to spread efficiently in humans, clinicians must remain alert to the possibility of diarrhoea and coma as the sole presenting manifestations in order to initiate prompt antiviral treatment and infection-control measures.

Michalopoulos AS, Tsiodras S, Rellos K, Mentzelopoulos S, Falagas ME. Colistin treatment in patients with ICU-acquired infections caused by multiresistant Gram-negative bacteria: the renaissance of an old antibiotic. Clin Microbiol Infect. 2005; 11:115-21.

First discovered back in the 1950s, colistin was one of the first broad-spectrum antibiotics effective against Gram-negative organisms including pseudomonas. However, colistin is nephrotoxic, and soon after the availability of better-tolerated ß-lactam agents with a similar spectrum of action in the 1980s, the use of colistin against systemic infections was largely discontinued. With the increasing prevalence of multidrug-resistant Gram-negative bacteria in nosocomial settings, researchers are now reevaluating the antibiotic properties and potential utility of colistin. This is a recent report of a retrospective case series involving patients in Athens, who received intravenous colistin for treatment of documented intensive care unit-acquired multidrug-resistant *Pseudomonas aeruginosa* or *Acinetobacter baumannii* infections.

Among the 43 patients, 31 had pneumonia, while 14 had bacteremia. Clinical cure with

colistin was observed in 30 of the patients, and another 2 showed clinical improvement. Eleven patients, however, did not respond to colistin treatment and subsequently died from their infections. A total of 8 patients (including 5 with preexisting chronic renal insufficiency) developed acute renal failure during treatment, and all of them died. On multivariate analysis, the independent predictors of mortality included age >50 years and development of acute renal failure during colistin treatment.

Discussion

This case series shows that colistin may be a reasonable option to treat infections caused by multidrug-resistant Gram-negative bacteria. However, this agent should be used with caution in patients with advanced age (>50), and in those with pre-existing impaired renal function.

Meetings	
18-21 Aug 2005 05-28 Bali International Convention Center BICC, The Westin Resort Nusa Dua, Bali, Indonesia	The 15th Conference of Asian Pacific Association for the Study of the Liver Contact: The Indonesian Association for the Study of the Liver (Ina ASL) APASL Bali 2005, PO BOX 888 JAT 13000, INDONESIA secretariat@apaslbali2005.com or Jl. Janur indah V Blok LA 15 No.7 Kelapa Gading Permai Jakarta 14240 Indonesia Tel: (62-21) 4532202, 30041026, 315 9610 (62-21) 4535833, 315 9610 Fax: (62-21) 4535833, 30041027, 315 9610 E-mail: secretariat@apaslbali2005.com Web: http://www.apaslbali2005.com/
24-27 Aug 2005 Hobart Australia	17th Annual Conference of the Australasian Society for HIV Medicine Contact: Nicole Robertson Phone: 612-936-820-718 Fax: 61-293-316-537 E-Mail: conferenceinfo@ashm.org.au
1-4 Sept 2005 Warsaw, Poland	The 4th World Congress of the World Society for Paediatric Infectious Diseases Meeting Secretariat: Kenes International / WSPID 2005 17 Rue du Cendrier, PO Box 1726 CH-1211 Geneva 1, Switzerland Tel: +41 22 908 0488 Fax: +41 22 732 2850 E-mail: wspid2005@kenes.com Web: http://www.kenes.com/wspid2005/
20-21 Oct 2005 Paris, France	Managing Infective Therapies Fax: +33 1 40 61 34 05 E-mail: euroconf-ip@pasteur.fr
10-11 Nov 2005 London, United Kingdom	1st International Conference of the Journal of Travel Medicine and Infectious Diseases Organized by Elsevier in association with Travel Medicine and Infectious Disease Contact: Sophie Peters, Travel Medicine Conference Secretariat, Elsevier The Boulevard, Langford Lane, Kidlington Oxford OX5 1GB, UK Tel: +44 (0) 1865 843643 Fax: +44 (0) 1865 843958 Email: s.peters@elsevier.com Web: http://www.travelmedicine.elsevier.com/

7-10 Mar 2006 Waterfront Hotel Lahug, Cebu City	3rd Asian Congress of Pediatric Infectious Diseases and 13th Pediatric Infectious Diseases Society of the Philippines Annual Convention "Pediatric Infections in the 21st Century: Meet the Challenges" Contact: Pediatric Infectious Disease Society of the Philippines (PIDSP) Unit 4 Metro Square Townhomes #35 Scout Tuazon corner Scout de Guia Sts., Quezon City Tel (632) 526-9167; (632) 374-1855 Fax (632) 404-2397; (632) 412-6998 E-mail: aspid@uplink.com.ph Web: http://www.asianpids.org
19-22 Mar 2006 Atlanta Marriott Marquis Atlanta, Georgia	International Conference on Emerging Infectious Diseases Contact: American Society for Microbiology Phone: 202-942-9330 Fax: 202-942-9340 E-mail: iceid@asmusa.org