Vol. 11, no. 2 June 2007

Contents

Nosocomial norovirus infection

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Norovirus (NV) is a common cause of acute viral gastroenteritis worldwide. Many countries have experienced an increase in the number of norovirus outbreaks over the past few years [1,2]. A majority of the infected individuals will present with vomiting in cold seasons and thus it is traditionally known as the “winter vomiting disease”. From 2001 to 2005, the amplitude of NV outbreaks in Hong Kong also gradually increased and the peaks for these outbreaks occurred during winter [3]. However, there was also an unprecedented surge in the number of NV gastroenteritis outbreaks in early summer in 2006 (Table 1). 85 outbreaks were reported from May to mid-July in 2006, but there were only 3 outbreaks during the same period in 2004 and 2005 [4]. Most of these outbreaks occurred in elderly homes but 24% of them emerged from hospitals [5]. Nosocomial outbreaks are distinct from community outbreaks in terms of their transmission patterns, clinical characteristics, outcome and their impact to the health authority. The current review will focus on these areas.

The impact

During the summer outbreaks of NV infection in Hong Kong in 2006, 19 out of 41 hospitals under the Hospital Authority (HA) were involved. It is recommended that the affected ward should be temporarily closed until 72 hours following the identification of last case of an outbreak [6]. An average hospital ward contains about 30 beds. The loss of hospital bed-days was substantial. Additional burden includes sick leave of staff, cleansing, increased demand for isolation ward facilities, increased microbiological testing, etc. Study showed that nosocomial norovirus outbreaks result in significant decline of revenue and increase use of resources [7]. By estimation, the gastroenteritis outbreaks likely cost the British National Health Service US$184 million in 2002-2003 [8]. Therefore prompt identification and control of these nosocomial outbreaks can save a lot of expenses and resources.

Virology

Human NV was previously called Norwalk virus. It was first identified in the stool samples of a group of elementary school students and their family who presented with acute gastroenteritis in Norwalk, Ohio in 1972. It belongs to the family *Caliciviridae* and is a non-enveloped, positive-sense and single-stranded RNA virus. Under electron microscope, a typical calicivirus looks small and round-structured. It consists of a scalloped border with cup-shape indentation on its surface [9]. However, the substructure of NV is less prominent and its outer edge is quite indistinct, therefore it may sometimes be viewed as a non-viral material [10]. Five genogroups have been recognised so far. Genogroups I, II & IV can infect human, while genogroups III and V contain bovine and murine strains respectively. Each genogroup can be further subdivided into genotypes based on phylogenetic analyses and there are more than 20 genotypes identified by now.

New genotypic strain

The unusual outbreaks occurring in summer 2006 in Hong Kong were caused by a new variant of genotype II.4, which was genetically distinct from the predominant variants of 2002 and 2004 but closely related to one of the 1995/6 subset variant which had caused epidemic in Hong Kong in 2001, suggesting that the 1995/6 subset might start to recirculate [4]. Actually new variant of genotype II.4 has been emerging in many other countries, with increased amplitude of infection reported [1,11]. Genotype II infection is associated with higher viral load when compared to that of genotype I. This may translate into higher risk of transmission and increased amplitude of outbreaks [12].

Transmission

The major route for person-to-person transmission is faecal-oral. NV is also an important cause of food-borne infection. Basically any kind of food or fluid contaminated with NV can act as a vehicle for transmission. Shellfishes like oysters and clams are key carriers of NV since they efficiently concentrate the viruses from contaminated water. Swimming pools and public bathrooms are important sites for contraction as the viruses are quite resistant to chlorine inactivation. NV may also be transmitted by airborne route via the aerosolisation of the vomitus from infected individual [13], or by fomites. NV may be introduced into the hospital environment by any of the above routes and then propagated by person-to-person spread. Environmental surfaces including dining room table or even elevator button can also be contaminated [14]. NV may stay on inanimate object for as long as 16 days despite thorough cleansing [15].

As in many other outbreaks in closed settings, nosocomial NV outbreaks are commonly associated with extensive secondary transmission. Although most outbreaks will conclude spontaneously in one to two weeks, they could be more protracted (up to almost 2 months) if the environment is heavily contaminated [16].

Multiple viral and host factors can contribute to the widespread nature of NV infection. Besides having genetic diversity and various routes of transmission, NV infection requires a low infecting dose and remains stable in a number of adverse conditions, including exposure to chlorine, alcohol and heat [17]. NV also confers only brief immunity (up to few months) in human and reinfection with the same strain is possible.

Clinical aspects

Norovirus induced gastroenteritis is usually mild and self-limiting. Kaplan et al had developed criteria including incubation period of 24-48 hours, stool culture negative for bacterial pathogens, vomiting in ≥ 50% of cases and duration of illness lasting for 12-60 hours, to define norovirus outbreaks [18]. Subsequent studies also showed that this set of criteria is highly specific (99%) with moderate sensitivity (68%) [19]. However, a community study in the Netherlands demonstrated that symptoms of norovirus infection can last for a median of 5 days [20]. Clinical symptoms could also be more prolonged in elderly, hospitalised or immunosuppressed patients. A study containing a group of elderly aged 79-94 years old showed that acute symptoms of norovirus infection could be abated after 3-4 days while non-specific symptoms including vertigo, anorexia and lethargy could last up to 19 days [21]. Age greater than 65 years was found to have an odds ratio of 11.6 for diarrhoea lasting for more than 2 days [22]. The virus could continue to shed in stool for as long as 2 weeks even after the infected individual became asymptomatic [20]. This can pose a major difficulty in cohorting patients, especially when isolation facilities are not universally available or become overstretched in time of outbreak. Moreover, a higher mortality rate was noted for hospitalised patients [23,24]. Norovirus infections in patients with underlying conditions such as cardiovascular disease, renal transplant and immunosuppressive therapy may lead to poorer outcome [22].

Diagnosis

Clinical assessment and routine laboratory tests are not helpful in making a specific diagnosis of norovirus infection. Serological tests are not sensitive enough to give an accurate and early diagnosis. Since the virus could not be cultivated, definitive diagnosis relied on electron microscopy in the past. With the advance of molecular technique, reverse-transcriptase polymerase chain reaction (RT-PCR) has become the gold standard for diagnosis. However, extensive genetic diversity may pose difficulties in designing assay

that is sensitive for all variants. Researchers have developed primer selected from junction region between open reading frame 1 and 2. This RT-PCR method can detect norovirus in 99% of stool samples which are identified to be positive by electron microscopy [25]. Clinical correlation of RT-PCR result is necessary since positive result may occur in asymptomatic virus shedder and negative result may not totally exclude norovirus infection in symptomatic cases with strong epidemiologic link. Unfortunately studies relating molecular and clinical findings are lacking.

Treatment and prevention

There is no specific treatment for NV infection. Almost all patients recover completely, but nosocomial outbreaks have been associated with increased morbidity and mortality. Supportive management with meticulous maintenance of fluid and electrolyte balance is essential.

The development of NV vaccine is hampered by genetic diversity of the virus. However, attenuated or inactivated whole virus vaccines have been available for feline calicivirus (FCV), a surrogate virus for NV. Unfortunately problems did arise as vaccine resistant strains were selected after almost 30 years of application [26].

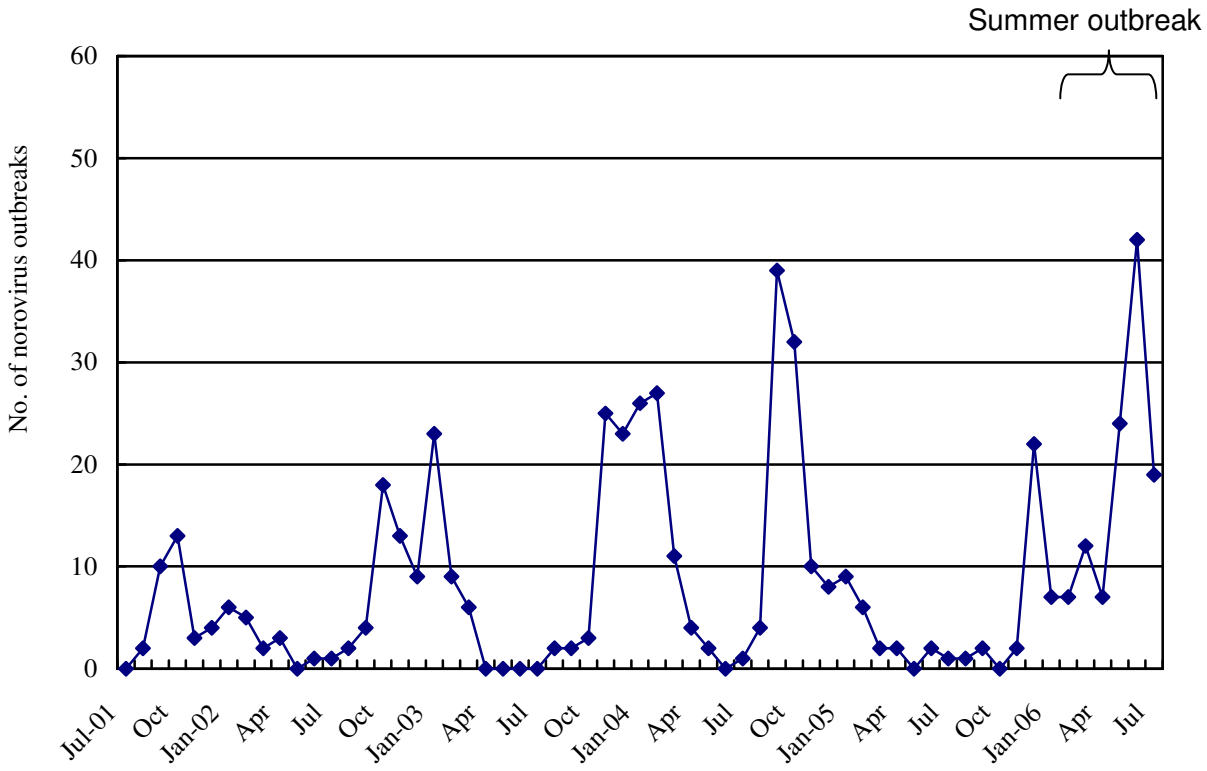
NV outbreaks are difficult to control because of the apparent ease of transmission. By the time an outbreak has been recognised at ward level, most susceptible individuals will have been exposed to the virus. Infection control efforts must prioritise the prevention of transmission by isolation of infected or exposed individuals, hand-hygiene and effective environmental decontamination. Other measures like visitor control, exclusion of affected staff from the wards until 48 hours symptom free, exclusion of non-essential personnel from the wards, and avoidance of unnecessary patient transfer to and from the affected wards should also be implemented simultaneously.

There is no direct evidence supporting the use of particular agents for environmental disinfection. However, complete inactivation of the related FCV requires exposure to 1000 ppm freshly reconstituted hypochlorite, or 5000 ppm pre-reconstituted hypochlorite solution. Glutaraldehyde and iodine-based product can also effectively control FCV while quaternary ammonium product, detergent and ethanol fail to do so [27]. Nevertheless, recent study showed that ethanol of higher concentration ($\geqq$ 80%) might have more superior efficacy against FCV [28].

Conclusion

Norovirus is an emerging infection. It does not only occur in winter. Up till now, there is no effective therapy or vaccine to combat this virus. Despite its mild clinical nature in most patients, it can lead to poor prognosis in hospitalised patients. Diagnosis of norovirus infection relies on RT-PCR. The considerable genetic variability and low infecting dose of the virus can result in epidemics from time to time. Constant vigilance and heightened awareness are imperative. Infection control measures should be strictly enforced once an outbreak is suspected.

Table 1: Monthly distribution of norovirus outbreaks in Hong Kong, July 2001 to 11 July 2006



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Group B streptococci and pregnant women

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Lancefield Group B streptococci (GBS), *Streptococcus agalactiae*, are beta-haemolytic Gram-positive cocci. About 1-2% of GBS are non-haemolytic. Based on the capsular polysaccharides, GBS can be further classified into serotypes I-VIII. Antibody to the capsular polysaccharide confers immunity for an individual person. Presence of sialic acid on the surface of the organism (serotypes Ia, Ib and II) seems to enhance virulence. Sialic acid inhibits activation of the alternative complement cascade and prevents phagocytosis.

GBS colonise the genital and gastrointestinal tracts, as well as the upper respiratory tract in young infants. Published literature suggested that 5-40% of women carry GBS in the genital tract and 10-30% of pregnant women have transient vaginal carriage. However, a previous study done in Hong Kong involving 367 unselected pregnant women between 16 and 24 weeks of gestation showed that the rate of colonisation with GBS was 0.8% only [1]. GBS mainly infect three populations: 1) neonates, 2) pregnant women and post-partum women, 3) elderly and patients with co-morbidities e.g. diabetes mellitus, cancer and alcoholism. In neonates, GBS may lead to sepsis, meningitis, pneumonia, cellulitis, osteomyelitis and septic arthritis. In pregnant women and post-partum women, GBS may cause urinary tract infection, amnionitis, endometritis, wound infection, osteomyelitis, endocarditis and meningitis. In the elderly and patients with co-morbidities, GBS may cause bacteraemia, skin and soft tissue infections, bone and joint infections, pneumonia, urosepsis, endocarditis, peritonitis, meningitis and empyema leading to a higher mortality rate (15-32%).

Neonatal GBS diseases are commonly associated with GBS serotypes Ia, III and V. About 50% of mothers colonised with GBS can transmit GBS to the neonates. Among those neonates colonised with GBS, 2% of them develop early onset GBS diseases which include bacteraemia, sepsis, pneumonia or meningitis. The early onset GBS diseases usually occur within 12 hours and not more than 6 days after delivery. For late onset GBS diseases which occur between 7 days and 3 months, the neonates acquired the GBS from an exogenous source such as the mother and another infant. The manifestations of late onset GBS diseases include bacteraemia without a focus (60%), meningitis (35%) and focal infections. Late onset GBS diseases are less common than the early onset diseases.

The maternal risk factors for early onset GBS diseases in neonates include prior delivery of an infant with GBS disease, GBS bacteriuria, colonisation of GBS at delivery, delivery at less than 37 weeks of gestation, rupture of membranes for > 18 hours before delivery, chorioamnionitis, body temperature greater than 38°C during labour, sustained intrapartum fetal tachycardia, heavy maternal colonisation (vaginal inoculum $>10^5$ cfu/mL), GBS strain with enhanced virulence and deficient maternal GBS type-specific capsular antibody.

Intrapartum antibiotics given to women at risk of transmitting GBS to their newborns are highly effective at preventing early onset neonatal GBS diseases. Intrapartum antibiotics can reduce the vertical transmission of GBS to the neonate and prevent 70-75% of early onset GBS disease.

In 2002, the Centers for Disease Control and Prevention (CDC) published its latest guideline on the prevention of perinatal GBS disease [2]. To identify candidates for intrapartum antimicrobial prophylaxis (IAP), CDC recommends universal prenatal screening at 35-37 weeks of gestation. Swabs (not speculum) from the vagina and rectum are collected. For

further processing, selective broth medium (e.g. LIM broth with colistin and nalidixic acid to suppress the growth of other organisms) should be used to optimise the culture of GBS. The confirmatory tests in the laboratory include a positive CAMP test (positive in GBS and negative in other streptococcus species), a positive hippurate hydrolysis test and demonstration of group-specific carbohydrate by antiserum. Recently, PCR assays of the *cfb* gene (which encodes the CAMP factor) and *scp* B gene (which encodes C5a peptidase) in antenatal vaginorectal specimens were shown to have higher sensitivities of detecting GBS when compared with conventional culture method. The sensitivities are 75.3%, 99.6% and 42.3% respectively [3].

According to CDC guideline, indications for IAP under universal prenatal screening include a) previous infant with invasive GBS disease, b) GBS bacteriuria during current pregnancy, c) positive GBS screening culture during current pregnancy (unless a planned caesarean delivery, in the absence of labour or amniotic membrane rupture), d) unknown GBS status and any of the following intrapartum risk factors: delivery at < 37 weeks of gestation, amniotic membrane rupture > 18 hours or intrapartum temperature > 38°C. IAP is not indicated if a) previous pregnancy with a positive GBS screening culture but the culture was negative during the current pregnancy, b) planned caesarean delivery performed in the absence of labour or membrane rupture, regardless of maternal GBS culture status, c) negative vaginal and rectal GBS screening culture during the current pregnancy, regardless of intrapartum risk factors.

In 2003, the Royal College of Obstetricians and Gynaecologists (RCOG) published her guideline on the prevention of early onset neonatal GBS disease [4]. Contrary to CDC, she does not recommend universal prenatal screening for GBS carrier. The rationale behind include: a) there have been no randomised controlled trials comparing antenatal screening, whether bacteriological or risk factor based, with no antenatal screening, b) in infants exposed to intrapartum antibiotic prophylaxis, it is possible that the confirmation of GBS disease is made more difficult by the presence of antibiotics effective against GBS in the blood, c) no study has yet been able to demonstrate that screening for GBS has any impact on neonatal sepsis as a whole, and d) antibiotic prophylaxis may cause disadvantage to the mother and baby including potential fatal anaphylaxis and infection of resistant organisms. Though universal screening is not recommended by the RCOG, the indications for IAP as stated in the RCOG guideline are similar to that of the CDC guideline. RCOG stated that IAP should be considered if GBS is detected incidentally in the vagina or the urine in the current pregnancy.

Agents for IAP should be administered at least 2 hours before delivery, so that a high protective antibiotic level in the neonate's circulatory system can be achieved at the time of birth. The recommended agent is intravenous penicillin G, 5 million units, followed by 2.5 million units every 4 hours until delivery. Alternative antibiotic is intravenous ampicillin 2 grams, then 1 gram every 4 hours until delivery. For patients having a history of penicillin allergy with low risk for anaphylaxis, the recommended agent is intravenous cefazolin 2 grams, then 1 gram every 8 hours until delivery. For patients having a history of penicillin allergy with high risk for anaphylaxis, intravenous clindamycin 900 mg every 8 hours or erythromycin 500 mg every 6 hours until delivery is recommended. However, intravenous vancomycin 1 gram every 12 hours until delivery should be used if the GBS are resistant to clindamycin and erythromycin. After delivery, blood tests including complete blood picture, blood culture and lumbar puncture should be considered for ill-appearing infants.

Antenatal treatment is only indicated for symptomatic or asymptomatic GBS urinary tract infection. Antenatal treatment with penicillin is not recommended for pregnant women with incidental finding of GBS colonisation in the vagina. Antenatal prophylaxis with oral

penicillin does not reduce the likelihood of GBS colonisation at the time of delivery and so is not indicated in this situation.

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A case of fever and confusion

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Case presentation

A 79 years old female with independent premorbid functional status attended the emergency department with chief complaints of generalised bone and muscle pain, which rendered her unable to walk, as well as dizziness and fever for 4 days. There were no headache, vomiting or photophobia. She had history of injury in her fingers while preparing raw pork at home around 1 week before the onset of symptoms. She had no recent travel, no contact with other ill persons, and no tick or mosquito bite. Upon admission to the ward, she was delirious with a Glasgow coma score (GCS) of E4V1M4 (9/15). She was afebrile. She had no definite meningism and there were no gross neurological deficits or focal signs on examination. As she was markedly confused and uncooperative, fundoscopy could not be performed. Examination of her respiratory, cardiovascular and abdominal systems were unremarkable. Initial investigations included an electrocardiogram (ECG) and a chest radiograph (CXR), which were unremarkable. There was marked peripheral leukocytosis (24.4 x 10^9 /L, 96% neutrophils, 2% lymphocyte). C-reactive protein (CRP) was also increased (388 mg/L, normal range: <8). The haemoglobin, platelet counts, renal and liver functions were all normal.

An urgent computed tomography (CT) scan of the brain was performed, which revealed no feature of structural mass lesion or cerebral oedema. Lumbar puncture yielded blood-stained cerebrospinal fluid (CSF). The opening pressure was grossly elevated at 41 cm. In view of high clinical suspicion of bacterial meningitis, empirical penicillin G 4 MU every 4 hours, cefotaxime 2 g every 4 hours and dexamethasone 4mg every 8 hours were started intravenously. Subsequent analysis of the CSF revealed glucose level of 0.2 mmol/L (concomitant plasma glucose 7 mmol/L), protein level of 5.09 g/L (normal range: 0.15-0.45 g/L), and Gram stain showed Gram-positive cocci in chains. CSF cell count was not performed because of blood-stained CSF. She was intubated and transferred to the Intensive Care Unit (ICU) for close monitoring. Blood and CSF cultures eventually grew *Streptococcus suis*, which was sensitive to clindamycin, erythromycin and penicillin G, with penicillin minimal inhibitory concentration (MIC) of 0.064 mcg/ml. Cefotaxime was stopped, and intravenous Penicillin G was continued. Her conscious level gradually improved and she was extubated on day 5 in ICU. Her condition became more stable and she was transferred back to general ward on day 8 after admission. She became fully alert and orientated in ward and complained of hearing loss of the left ear. She was discharged after given a full course of antibiotic. She was offered an appointment for hearing assessment and would be followed up in the outpatient clinic for progress.

Discussion

We reported a patient of acute community-acquired meningitis presenting with fever and confusion. In the evaluation of any patient with suspected meningitis, detailed history of travel, occupation, contact and clustering (TOCC) should be elicited in order to arrive at the most probable diagnosis. In this scenario, physical examination and CT brain should look for any sign of increased intracranial pressure. A lumbar puncture should be performed if there are no contraindications, namely the presence of haemodynamic instability, cellulitis or abscess at the puncture site, or suspicion of raised intracranial pressure. According to the 2004 guidelines published by the Infectious Disease Society of America (IDSA) [5], a CT brain is recommended before lumbar puncture for the following categories of patients: patients with AIDS/HIV, receiving immunosuppressive therapy or after transplantation; patients with history of CNS disease; patients with new onset seizure within 1 week of presentation; and patients

with papilloedema, abnormal level of consciousness, and/or focal neurological signs on examination (See Figure 1). A routine CT brain is not necessary for patients who do not have any of these risk factors. This practice would certainly allow the LP to be safely performed without delay in patients with suspected meningitis.

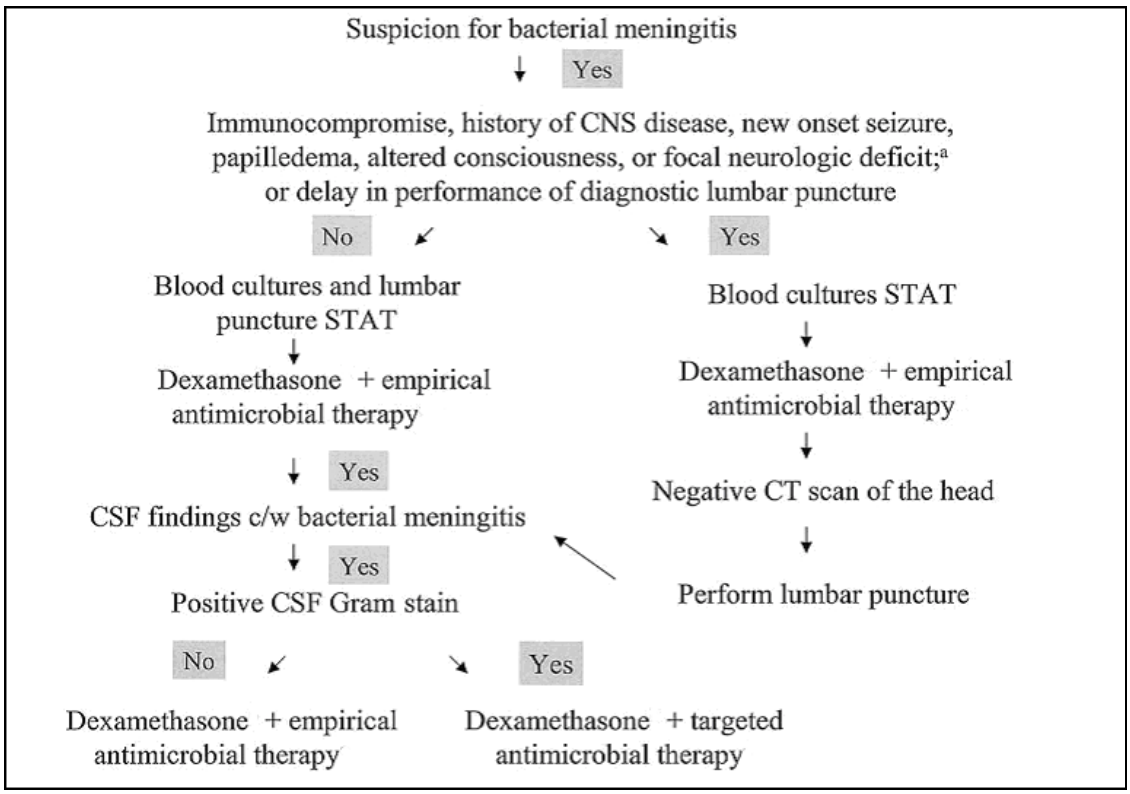

Fig 1. Management algorithm for adults with suspected bacterial meningitis. "STAT" indicates that the intervention should be done emergently. Adapted from [5]

Streptococcus suis is a Gram-positive facultative anaerobe found in many parts of the world where pigs are raised. Based on the capsular polysaccharides, a total of 35 serotypes have been identified so far. Serotype 2 is most commonly associated with diseases in pigs and human [1,9]. Domesticated pig is a major reservoir for the organism. Infection in pigs is usually asymptomatic, but can result in septicaemia, meningitis, pneumonia and arthritis. Young pigs are most at risk of acquiring the infection. Asymptomatic pigs typically carry the bacteria in their palatine tonsils and are probably responsible for the spread of infection between herds. Transmission to human is most likely to occur by direct contact e.g. through wounds on the skin, including minor abrasions [2]. Infection via ingestion or through mucous membrane exposure has been suspected in some cases. The incubation period ranges from a few hours to several days. Classically, infection in human produces fever and signs of meningitis with headache, vomiting, neck stiffness, photophobia and decreased level of consciousness. Infrequently, it can also cause septic shock or toxic shock-like syndrome, with associated high morbidity and mortality. Hearing loss, which is generally permanent and affects around 50% of those infected [4], is due to involvement of the auditory nerve in the basal meningitic process. Early referral for hearing assessment should be considered.

Human infection was first described in the 1960s in Denmark and is increasingly recognised. Most cases have occurred in Southeast Asia, including Thailand, China and Hong Kong. There are now around 400 cases of *S. suis* infection worldwide, most of which occurred in Southeast Asia. Notably, 3 large outbreaks of human infections due to *S. suis* in China had been reported in 1998, 1999 and 2005. The largest outbreak was in 2005 in

Sichuan province, China, which claimed the lives of 38 persons out of a total of 204 cases. Tang and colleagues investigated this outbreak in 2005 [2]. All patients had history of direct contact with ill or dead pigs and most of them had cuts or abrasions on their extremities. There was no evidence of human-to-human transmission. There was concurrent disease outbreak among the pig population, with more than 600 pigs died. Among the 38 fatal cases, 37 had toxic shock-like syndrome, characterised by fever, shock, petechiae over extremities. Some cases developed multi-organ failure syndrome with acute renal failure, disseminated intravascular coagulation (DIC), and acute respiratory distress syndrome. In this cohort, 29% of the patients suffered from toxic shock-like syndrome, while 50.9% had meningitis. In an earlier report from local investigators, Kay et al reported a series of 25 patients infected with *Streptococcus suis* who were admitted to hospital between 1984 and 1993 in Hong Kong [4]. One patient died from septicaemic shock and DIC. Of the 24 survivors, 16 (67%) acquired various degrees of hearing loss as a sequela of their meningitis. Importantly, *S. suis* infection has been included as a statutory notifiable infectious disease in Hong Kong since 2005. There were 13 reported cases in 2005, 8 cases in 2006 and 3 cases reported up to May 2007 [8].

For confirmed *S. suis* infection, patients are commonly treated with penicillin G, accompanied by one or more other antibiotics including ceftriaxone, gentamicin, chloramphenicol, and ampicillin. There is no solid evidence that dexamethasone can help in meningitis caused by *S. suis*, but steroid is now recommended as an adjunct for treatment of meningitis, especially those caused by *Streptococcus pneumoniae* [5]. For less ill patients, intravenous administration of 4 million units of penicillin G every 6 h or 2 g ceftriaxone every 12 h for at least 10 days is effective. For more severe cases, multiple antibiotics are usually given, and the duration of treatment may be extended to 21 days or more [1]. For severely ill patients who develop septic shock, in addition to antibiotics and aggressive supportive measures, considerations could be given to adjunctive therapeutic agents like intravenous immunoglobulins (IVIG), which has been shown to be of benefit in some patients with streptococcal toxic shock syndrome [7]. However, use of IVIG in treating fulminant meningitis due to *S. suis* has not been formally tested in controlled clinical trials, and its benefit remains unknown at this stage.

The most important risk factor in acquiring the infection in human is contact with pigs or uncooked pig products [2,4]. Hence, people at highest occupational risk of contracting the disease are those working as farmers, veterinary personnel, abattoir workers and butchers. To prevent this disease from occurring, education should be given to everyone who handles and cooks pork, especially raw pork. Those with open wounds on the upper extremities should avoid direct contact with raw pork if possible, and should always cover their wounds and wear gloves for protection when contact is unavoidable. All those who prepare pork should wash their hands and clean their utensils thoroughly after contact. Adequate cooking is also essential. WHO recommends that pork should be cooked to reach an internal temperature of 70°C or until the juices are clear rather than pink [6]. Table 1 is a summary of the current local recommendations from Centre for Health Protection (CHP) [8].

Table 1. CHP recommendations for prevention of *S. suis* infection

Observe good personal, food and environmental hygiene
Avoid contact with pigs
When handling pigs or raw pork, wear protective gloves and avoid injury
Wash hands after handling pigs or raw pork
Clean and cover all wounds properly
Raw pork and cooked food should be dealt with and kept separately
Pork should be cooked thoroughly before consumption
Do not bring meat into Hong Kong without a permit

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Journal review

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Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007 May 10; 356:1928-43.
The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007 May 10; 356:1915-27.

Human papillomavirus (HPV) infection in woman is well known to cause both genital warts and cervical cancer. In particular, infection with HPV types 16 and 18 are responsible for approximately 70% of cervical cancers on a global basis. A 3-dose quadrivalent vaccine (covering HPV types 6, 11, 16, and 18) was licensed in the US in June 2006, based upon interim findings from two previously published prospective trials. Investigators have recently reported the longer-term results from these trials in the *New England Journal of Medicine*.

The first trial involved over 5000 women aged 16 to 24, who were recruited from a total 16 countries. The vaccine was found to be 100% efficacious in preventing anogenital intraepithelial lesions, cervical intraepithelial neoplasia grades 1-3 and adenocarcinoma in situ caused by vaccine-type HPV among vaccinated subjects, after a follow-up period of 2.5 years. Efficacy of the vaccine in reducing the incidence of cervical lesions caused by all HPV types was 20%. Vaccine recipients nonetheless had a slightly higher incidence of local and mild febrile reactions than did placebo recipients.

In another similarly designed trial involving over 12,000 women aged 15 to 26 years, the ability of the vaccine to reduce the incidence of HPV-16/18-related high-grade cervical neoplasia was assessed. The primary endpoint was defined as a composite of epithelial neoplasia grade 2 or 3, adenocarcinoma in situ, and invasive carcinoma of the cervix. At 2.5 years after completion of the primary series, the vaccine showed 98% efficacy in preventing the primary endpoint. Intention-to-treat analysis showed a vaccine efficacy of 44% in preventing high-grade HPV-16/18-associated cervical neoplasia and 17% in preventing all high-grade cervical neoplasias. The vaccine did not appear to alter disease course in those women who were already infected with HPV-16/18. Vaccine recipients again had a slightly higher incidence of local reactions than did placebo recipients. There were no adverse pregnancy outcomes for the vaccines.

Points to note: Interim results from these two trials provided reassuring evidence to support vaccine licensure. However, given the relatively short follow-up period, we still do not know the duration of protection or the overall benefit afforded by the vaccine in preventing neoplastic disease in the long term. In addition, the high cost of the vaccine, together with the apparent lack of efficacy in women with previous HPV-16/18 infection, remain issues of concern to healthcare providers. The optimal use of this vaccine could be either among pre-pubertal girls (a group not enrolled in the studies) or through targeted immunisation of older populations who are not likely to be infected with HPV-16/18 yet. Longer-term results of these prospective studies are eagerly awaited.

Grinsztejn B, Nguyen BY, Katlama C, et al. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomised controlled trial. Lancet 2007 Apr 14; 369:1261-9.

Integrase is an enzyme that is essential for the replicative cycle of HIV. Two drugs that inhibit

this enzyme, raltegravir and elvitegravir, are already in advanced stages of clinical development. Now, in a manufacturer-sponsored, phase II trial, researchers have investigated further the safety and efficacy of raltegravir among treatment-experienced patients.

A total of 179 patients infected with HIV strains which were resistant to at least one nucleoside reverse-transcriptase inhibitor, one non-nucleoside reverse-transcriptase inhibitor, and one protease inhibitor were randomised to receive either placebo or one of three doses of raltegravir, together with an optimised combination therapy. The patients were all treatment-experienced with a median duration of therapy of 9.9 years; almost half of them harboured virus strains that were resistant to all other available agents. After 24 weeks of therapy, about 60% of raltegravir recipients achieved undetectable viral loads (<50 copies/mL), whereas only 13% of placebo recipients had attained a similar degree of viral suppression. The mean increase in CD4-cell count from baseline was also significantly greater among raltegravir recipients. Raltegravir was well tolerated and safe.

Points to note: Based on these promising findings, raltegravir was taken forward into phase III trials in treatment-experienced patients (the BENCHMRK studies). Results from these trials (presented in abstract from at the 14th Conference on Retroviruses and Opportunistic Infections earlier this year) confirmed raltegravir's potent activity against multidrug-resistant HIV. The drug is now available through an expanded access programme and will probably undergo FDA review soon in the US. If approved, raltegravir will expand the number of drug options for patients with multidrug-resistant HIV. It might also have a role in management of treatment-naive patients, and this subject is currently under active investigation in clinical trials.

Centers for Disease Control and Prevention (CDC). Update to CDC's sexually transmitted diseases treatment guidelines, 2006: Fluoroquinolones no longer recommended for treatment of gonococcal infections. *MMWR Morb Mortal Wkly Rep* 2007 Apr 13; 56:332-6.

The 2006 Sexually Transmitted Diseases Treatment Guidelines published by the CDC made the recommendation that cephalosporins or fluoroquinolones be used for treatment of all patients with gonococcal infections, except those who acquired the disease in California, Asia, or the Pacific Islands, and among men who have sex with men. During the past few years, it has become apparent that resistance of *Neisseria gonorrhoeae* to fluoroquinolones is becoming more widespread, based on reports from various regions of the world. These changes in gonococcal resistance patterns led the CDC to issue an update to the existing guidelines.

All infections suspected to be due to gonorrhoea must now be treated with cephalosporins (spectinomycin, an agent available in Hong Kong but not the US, is recommended as an alternative). Uncomplicated gonococcal infections of the cervix, urethra, and rectum could be treated with either a single intramuscular dose of 125 mg ceftriaxone (note that a single dose of 250 mg is currently recommended in Hong Kong for uncomplicated gonococcal urethritis; for details please refer to the latest version of the Social Hygiene Manual, available at http://www.chp.gov.hk/files/pdf/pub_phsb_std_sh_manual_20060217.pdf) or a single oral dose of 400 mg cefixime (the local equivalent being a single oral dose of 400 mg ceftibuten or Cedax™). Recommended dosing regimens for treating other gonococcal infections as recommended by the CDC (pharyngitis, epididymitis, disseminated infection, and pelvic inflammatory disease) are available at www.cdc.gov/std/treatment.

Points to note: On-going public health surveillance of sexually transmitted diseases is crucial to allow for modification of recommended management as antibiotic susceptibility patterns of pathogens change with time. The emerging resistance patterns of *N. gonorrhoeae*, as well as those observed in other pathogens, require a constant updating of knowledge by practitioners who are responsible for management of infectious diseases.