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Contents

Occult hepatitis B virus infection

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Several distinct clinical outcomes have been defined after Hepatitis B virus (HBV) infection, including acute hepatitis, chronic active hepatitis, inactive carrier and past infection. These clinical entities are based on the serological profile of the affected individuals. Traditionally, only those with detectable HBV surface antigen (HBsAg) are considered to have clinical implication. However, with the advance and availability of molecular testing, the traditional understanding of HBV infection has been challenged in the past decade.

Occult hepatitis B virus infection can be defined as the persistence of viral genomes in the liver tissue (and in some cases also in the serum) of individuals who are negative for serum HBsAg. This clinical entity has actually been suspected back in the 1970s, when there was report of transmission of HBV infection through blood transfusion from donors with serology suggestive of past HBV infection and clearance of HBsAg. With the widespread use of chemotherapy and potent immunosuppressive agents nowadays, increasing reports of occult HBV reactivation in immunocompromised patients resulting in morbidity and even mortality has been noted. This has urged us to look into this clinical entity and its clinical implication in details.

Virological aspect of persistent infection

Hepatitis B virus belongs to the family of hepadnaviruses. The complete virion consists of an envelope and a core particle which is made up of the nucleocapid protein, the viral genome, and the polymerase protein. The viral genome is a relaxed circular and double-stranded DNA. The key element resulting in persistent viral infection is related to the distinctive feature in the replication cycle of Hepatitis B virus, the formation of covalently closed circular DNA (cccDNA). After attachment to the hepatocyte membrane, the HBV virion is uncoated in the cytoplasm and the viral genome gets into the nucleus, where the cccDNA is formed by conversion from the relaxed circular DNA. Moreover, the core particle formed subsequently in the cytoplasm provides reservoir for formation of the cccDNA in the nucleus. The cccDNA, which would persist in the hepatocyte nucleus at around 30 to 50 copies per cell, acts as a stable replicative template for gene transcription. It has also been shown that the cccDNA is refractory to the effect of antiviral drug despite the significant inhibitive effect on the serum HBV DNA [1]. The stability and persistence of cccDNA, together with long half-life of the hepatocytes, result in long-lasting HBV infection that might persist for life.

HBsAg negativity

The exact reason for HBsAg negativity in individuals with occult HBV infection remains unsolved. Some studies have reported that it could be due to viral genome variability, which resulted in suppressed S protein expression or viral replication [2]. However, in majority of cases, occult HBV carriers were predominantly infected with HBV strains without any mutations in the precore and core promoter regions [3]. Genetic analysis of the viral isolates from occult infection was not different from those with overt infection [4]. The occult status in this clinical entity is likely to be related to the host's immune response and probably the effect of co-infection with other agents.

It is widely accepted that cytotoxic T-cell (CTL) response plays an important role in HBV clearance. Apart from cytotoxic T lymphocytes, the intrahepatic production of T helper cell type 1 (Th-1) cytokines such as interferon-gamma and tumour necrosis factor-alpha also inhibit HBV replication non-cytopathically. The host's CTL response is minimal in individuals with chronic active hepatitis in which the virus has high replicative capacity. It is believed that the relatively potent immune response in occult HBV carriers suppresses the virus below the detectable level of available assays. However, the balance between the virus and CTL response could be disturbed in the presence of events which could compromise the host's immune status, e.g. haematological malignancy or administration of chemotherapy.

The effect of virus interference of HBV by hepatitis C virus (HCV) in co-infected individuals has been well demonstrated in previous studies, which showed that HCV core protein strongly inhibited HBV replication and gene expression. Furthermore, non-viral infective agents may potentially play a role in this aspect. It has been shown that *Schistosoma mansoni* infection can inhibit HBV replication in a transgenic mice model.

Diagnosis of occult HBV infection

The detection of occult HBV infection, as implied by its definition, would be based on the detection of viral genome from the liver tissue. However, it is not always practical that liver tissue could be available in every case for diagnosis. Therefore, detection of serum HBV DNA level has been used most of the time for recognition of the clinical condition. Nonetheless, there is concern about conflicting results due to the variable sensitivity and reproducibility of various HBV DNA serum assays, especially in the clinical context that most occult HBV carriers have low level of viraemia. Currently, internationally standardised assay for detection of occult HBV infection has not been available yet. One of the more widely used methods for testing is the detection of HBV DNA from liver tissue or serum using nested PCR method with the use of oligonucleotide primers specific for different HBV genomic regions. Cases with

detectable HBV DNA using at least two different sets of primers would be considered positive.

Prevalence of occult HBV infection

Studies have shown that occult HBV infection is more prevalent in population co-infected with hepatitis C virus (HCV) or human immunodeficiency virus (HIV). Prevalence of 33% was noted in an Italian study in a group of individuals co-infected with HCV whereas the rates were 70% to 95% in Japanese studies [5]. For people co-infected with HIV, the prevalence rates quoted in various studies ranged from 4% to 40%. In otherwise healthy population, occult HBV infection is a world-wide clinical entity with comparable prevalence rate in Hong Kong as compared with other parts of the world. A recent local study showed that the prevalence of occult HBV infection among haematopoietic stem cell donors was 15.3% [6]. Rates reported in studies from Korea, India and Canada were 16%, 12.2% and 18% respectively.

Overall, prevalence of occult HBV infection is higher in individuals with serological markers suggestive of past HBV exposure. In patients co-infected with HCV and occult HBV, 42% had antibody against HBV core antigen (anti-HBc), 35% had antibody against HBV surface protein (anti-HBs) and 22% had no detectable antibody against both HBV antigens [5]. In locality with high HBV carrier rate such as Hong Kong, the proportion of people with serological markers of past HBV exposure is high. A local study found that there was no correlation with occult HBV infection and the anti-HBc status in a group of otherwise healthy adults. 84% of individuals with occult HBV infection and 74% of the control group had detectable serum anti-HBc [6].

Clinical implication: Who are at risk?

Reactivation of occult HBV infection as a result of shifting of balance between the virus and immune status could lead to disastrous outcome of fulminant hepatic failure and death. Similar to patients with detectable serum HBsAg, use of pre-emptive antiviral therapy could prevent this complication from happening. Certain groups of occult HBV carriers are identified to be at high risk of reactivation of the virus. These include patients with haematological malignancies and HIV infection, as well as patients who underwent chemotherapy, bone marrow or organ transplantation and treatment with anti-TNF (infliximab), anti-CD20 (rituximab), anti-CD52 (alemtuzumab) therapy. The typical clinical course would be acute hepatitis picture weeks to months after completion of the chemotherapy or immunosuppressive agents. The virus replicates substantially during immunosuppressed state. When the immunity returns, the subsequent CTL response mounted results in clinical hepatitis. Therefore, significant rise in HBV DNA serum level would be detected preceding the

clinical event of acute hepatitis when there is acute rise in the transaminase level. Serum HBsAg usually becomes detectable at this stage, but occasionally it may remain undetectable. It has been shown in a study that the median time interval for clinical hepatitis from chemotherapy among a group of patients with lymphoma was 18.5 weeks [7]. Moreover, reactivation of occult HBV infection in these patients was independently associated with much higher risk of fulminant hepatic failure (relative risk: 29.8).

Apart from reactivation, recipients of organ transplantation might also get infected from donors with occult HBV infection. The risk of infection from liver transplantation is much higher than kidney or heart transplant, because liver is the major reservoir of the virus. The transmission rate found in various studies ranged from 17% to 95% in liver transplant. Although the post-transplant outcome of this infection tends to be benign, liver transplantation from donors with occult HBV infection could be associated with decreased 4-year survival [8].

Clinical implication: Occult HBV infection and chronic liver diseases

The impact of occult HBV infection in chronic HCV infection has not been well established. There have been conflicting data on the impact in terms of disease progression to advanced liver fibrosis or development of hepatocellular carcinoma. Occult HBV infection may account for certain unexplained clinical flares of hepatitis in co-infected patients. On the other hand, the evidence on reduced treatment response of HCV infection to interferon has been quite consistent. Various studies have shown that the treatment response could be decreased by around 30% to 50% in co-infected patients irrespective of the HCV genotype.

Occult HBV infection may also play a role in cryptogenic cirrhosis. A local study has shown that although the proportion of subjects having positive serological markers for HBV antigen between a group of patients with cryptogenic cirrhosis and control group was similar at 90%, 32% of those with cryptogenic cirrhosis and none of the control group had detectable HBV viraemia [9].

Recommendation for occult HBV testing

With increasing data on the high prevalence of occult HBV infection and potential fatal clinical outcome of reactivation of the virus in immunocompromised hosts, serum HBsAg should no longer be the only screening test used for detection of HBV infection in these patients. In our locality with high rate of HBV carrier, anti-HBc status is not a reliable marker to guide us for use of pre-emptive antiviral drugs. Sensitive HBV DNA serum assay remains the favourable test for occult HBV infection in this group of patients. A recently published British paper recommended serum HBV DNA testing before chemotherapy only for patients with

haematological malignancies with positive anti-HBc but negative anti-HBs, as well as those with positive results for both anti-HBc and anti-HBs but unexplained elevated transaminase level [10]. Vaccination was suggested for those with negative serological marker for HBV antigen.

There has not been any standard guideline for testing of occult HBV infection and use of pre-emptive antiviral drug in immunocompromised hosts so far. Whether the recently published British recommendation is applicable to our locality might depend on the prevalence of condition, as well as the response rate and efficacy of HBV vaccination which has already been used widely in our locality. We have to be cautious in setting up local guideline for occult HBV testing in immunocompromised host, taking into account of the high prevalence and mortality of this clinical condition which might be well prevented with use of pre-emptive antiviral agents. Overall, the following groups of people should be considered seriously for occult HBV infection testing: (1) patients with risk factors for HBV infection in whom immunosuppression is expected, (2) individuals with detectable anti-HBc in whom presence of occult HBV infection might affect clinical decision e.g. transplant donors, and (3) patients with unexplained liver diseases.

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A 50 year-old patient with diarrhoea and shock

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Case presentation

A 52 year-old gentleman presented with two days' history of fever, abdominal pain and diarrhoea. There was no recent travel or consumption of suspicious food item. His past health includes history of diabetes mellitus on insulin therapy, asthma, iatrogenic Cushing's syndrome on hydrocortisone replacement. He also had history of *Streptococcus bovis* bacteraemia in 2005, during which colonoscopy showed multiple colonic polyps and polypectomy was performed. He also had strongyloidiasis in 2005 and was given a course of mebendazole. He had no drug allergy. He was a farmer 10 years ago in Mainland China. After he came to Hong Kong, he became a factory worker.

On admission, he had normal vital signs and unremarkable physical examination, apart from high fever of 39°C and a mildly distended abdomen with no guarding or rebound tenderness. Initial chest and abdominal X-rays were unrevealing. Blood tests showed normal complete blood picture, renal function tests, but the alanine transaminase was mildly elevated to 66 IU/L.

Five hours after admission, he collapsed in the ward with blood pressure of 90/50 mmHg, pulse of 120/min, and the oxygen saturation was 89% in room air. He deteriorated rapidly and was admitted to the intensive care unit subsequently and required intubation, mechanical ventilation and inotropic support. White cell count was raised to 12.6 x 10^9/L with neutrophil predominance and low lymphocyte count. Monocyte, basophil and eosinophil counts were normal. Liver function tests further deteriorated with total bilirubin 27 umol/L, alkaline phosphatase 150 IU/L and alanine transaminase 252 IU/L whereas renal function tests remained normal. Repeated chest X-ray showed bilateral alveolar infiltrates, compatible with acute respiratory distress syndrome. The patient was put on piperacillin-tazobactam and also albendazole in view of history of strongyloidiasis in the past. Subsequently the stool examination yielded numerous *Strongyloides stercoralis* larvae and blood culture showed growth of *Klebsiella pneumoniae*. Sputum culture was negative. Contrasted computed tomography of the abdomen did not show any liver abscess or intra-abdominal collection. The diagnosis was strongyloides hyperinfection syndrome with *K. pneumoniae* secondary bacteraemia. The patient was given an extended course of amoxicillin-clavulanate according to the sensitivity profile. He clinically improved with resolution of chest X-ray abnormality and normalisation of blood parameters. Repeated stool examination showed persistent excretion of Strongyloides larvae despite 14 days of albendazole. He was then treated with ivermectin for 7 days and stool showed clearance of larvae afterwards. He recovered well and was discharged home.

Discussion and literature review

Strongyloides is a nematode and *S. stercoralis* is the commonest species to cause disease in human. The life cycle of strongyloides is divided into two parts, a free-living cycle in the environment and an infective cycle. After excretion of rhabditiform larvae in the stool they develop into adult male worms in the environment in the free-living cycle. The rhabditiform larvae can also develop into filariform larvae which penetrate the human skin. Inside the human body the larvae are carried to the lungs by the circulation. They then get into the alveolar spaces, travel up the trachea, and go down the gastrointestinal tract as they are being swallowed, where they grow into female adult worms. The adult worms produce eggs which hatch into rhabditiform larvae and are then excreted in stool. The larvae can also cause autoinfection by developing into filariform larvae that penetrate the perianal skin or intestinal

mucosa directly.

Strongyloidiasis is a disease mostly of tropical and subtropical regions with increased prevalence in lower socioeconomic class, in male patients and with alcoholism. Risk is increased in occupations requiring direct contact with damp soil such as farming and coal-mining.

Strongyloides hyperinfection usually presents with development or exacerbation of gastrointestinal or pulmonary symptoms due to accelerated autoinfection with increased larval migration. It only involves organs of the autoinfective cycle, in contrast to disseminated strongyloidiasis, where the larvae penetrate into other organs such as kidneys, liver, central nervous system and produce symptoms. Unlike in chronic strongyloidiasis where patient may be asymptomatic but have a raised eosinophil count, esoinophilia is often absent in hyperinfection and disseminated disease. Translocation of enteric bacteria into the circulation leading to co-existing Gram-negative bacteraemia is common. Organisms isolated included Gram-negative species e.g. *E. coli*, *Klebsiella pneumoniae*, *Proteus mirabalis*, *Pseudomonas species*, and rarely other organisms such as *Enterococcus faecalis*, coagulase-negative Staphylococci, *Streptococcus bovis*, *Streptococcus pneumoniae* [1]. A case series [2] from US including 9 patients with complicated strongyloidiasis revealed that acute respiratory distress syndrome developed in 5 patients (55%), Gram-negative sepsis occurred in 4 patients (44%), and death in 3 patients (33%), all of them had suppressed eosinophil counts of less than 400 /uL, suggesting that low eosinophil count may be associated with poorer prognosis. In another retrospective case series [3] from Hong Kong which included 7 patients with disseminated strongyloidiasis, 6 of the patients were receiving steroid for conditions like chronic obstructive airway disease, systemic lupus erythematosis, and nephrotic syndrome. The outcome was similar with 2 patients developing co-existing Gram-negative infection and the case fatality was 71%.

Risk factors of hyperinfection include immunosuppressive drugs especially glucocorticoids and chemotherapeutic agents, e.g. adriamycin, vincristine, doxorubicin, solid organ and haematopoietic stem cell transplant recipients, malignancies such as lymphoma and carcinoma of the lung. Other conditions implicated included hypogammaglobulinaemia and malnutrition as well [1]. Interestingly, the incidence of hyperinfection in renal transplant recipients was noted to decrease after cyclosporine A was introduced as an immunosuppressive agent. The protective effect was attributed to probable anti-helminthic property of the drug. The association between human T-cell lymphotropic virus type 1 (HTLV-1) infection and strongyloides hyperinfection is well-studied. The presence of HTLV-1 infection is associated with a higher prevalence of strongyloides infection [4], higher risk of hyperinfection [5], and reduced efficacy of treatment of strongyloides infection [6]. One of the postulated mechanisms is that HTLV-1 infection activates the Th1 immune response, leading to increased production of interferon-γ by T cells and inhibition of interleukin-4 and interleukin-5. The final result was decrease in polyclonal and parasite-specific IgE production [7, 8].

Diagnosis of strongyloides infection is often made by stool examination. In chronic strongyloidiasis, excretion of larvae is usually sporadic and in small numbers. Thus, a single stool examination may not be able to detect larvae in up to 70% of the cases [9] and repeated stool examination is essential to increase the yield. Different techniques have been used to identify larvae and increase sensitivity of stool examination, including direct smear in Lugol's iodine stain, Baermann technique, filter paper culture and agar plate culture. Among the listed techniques, the agar plate culture method is found to be the most sensitive of all with a sensitivity of 96% [15], but is time-consuming (requires 2-3 days) and laborious. Other

modalities such as serological tests e.g. ELISA to detect IgG against Strongyloides, skin testing for immediate hypersensitivity towards parasite extracts may be useful but are not available locally. In cases of hyperinfection or disseminated infection, larvae could be easily detected in stool, sputum or other body fluids due to the large number of larvae present in stool.

Strongyloides infection could be treated with azole drugs e.g. thiabendazole and albendazole, and also ivermectin. The azole drugs are broad spectrum agents which act by selectively inhibiting the microtubular function of the helminth. Side effects include gastrointestinal upset, dizziness, headache and rash. Recommended regimes are thiabendazole 1.5 g twice daily for 2 days in acute or chronic strongyloidiasis and extended to 7 to 14 days in complicated infections. Ivermectin is a semisynthetic agent from avermectins. It paralyses worms by opening chloride channels and increasing chloride conductance. It is also frequently used in conditions such as scabies, filariasis, and onchocerciasis. It is better tolerated in comparison to azole drugs but could be associated with skin rash, dizziness, myalgia, and also Mazzotti reaction due to death of the larvae [10]. Apart from oral preparation, parenteral ivermectin has been used with success in cases of hyperinfection or disseminated infection where there were severe gastrointestinal symptoms preventing absorption of oral drug [11,12]. Two trials [13,14] have compared the efficacy of ivermectin against albendazole and ivermectin showed superiority in terms of higher larval clearance rate from stool. Therapy with ivermectin at 200 mcg/Kg once daily for 2 days may be adequate for acute or chronic infections. In hyperinfection or disseminated infection, varying dosing regimes of ivermectin (e.g. 200 mcg/Kg/day for 2 days every 48 hours, 200 mcg/Kg/day for 14 days) have been used and further studies on efficacy of different regimes are needed. Repeated courses of anti-helminthic drug should be given until there is documented clearance of infection by repeated stool examinations over 2 weeks. Furthermore, it is of paramount importance to perform blood cultures and treat co-existing Gram-negative sepsis in hyperinfection or disseminated infections, and so is ICU care in critically ill patients with acute respiratory distress syndrome or shock.

Screening of strongyloidiasis and prophylactic treatment may be necessary in high risk patients e.g. patients living in endemic countries with exposure history, who are planning for immunosuppressive therapy. The decision should be individualised.

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A gentleman with fever, sore throat and a neck mass

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Case presentation

37-year-old Mr. Cheung is known to have alpha thalassaemia trait and otherwise enjoyed good past health. He presented with a 2-day history of fever, chills and sore throat. There was mild productive cough but no shortness of breath or haemoptysis. He passed several times of loose stool which had already subsided upon presentation. There was no recent travel and sick contact. He attended the emergency department because of persistent symptoms despite 2 days of oral cefuroxime and oseltamivir prescribed by general practitioner.

Mr. Cheung had high fever 39.3°C on admission with stable haemodynamics. His throat was congested but the tonsils were not enlarged. There was a 2 cm x 3 cm tender neck mass at the mid-level of left sternocleidomastoid muscle. The mass was soft and had a vague border. No cervical lymph nodes were found. Examination of the respiratory, cardiovascular and abdominal systems was unremarkable. Plain X-ray of the chest showed bilateral lower zone infiltrate. X-ray of the neck was normal. Blood test showed mild leucocytosis (WCC 11.1 Neu 4.7 Mono 1.3) ESR 45 CRP 241. Liver function test was deranged (Alb 27 ALP 187 ALT 50 Bili 21). Renal function test was normal. Nasopharyngeal aspirate for influenza A and B were negative.

Computer tomography (CT) of the neck showed a 4.7 cm thrombus in the lumen of left internal jugular vein (IJV) and a 2.6 cm x 1.6 cm x 3 cm left parapharyngeal abscess with air pockets and mass effect, at the level of oropharynx. CT thorax revealed diffuse nodules measuring 2 mm to 1.5 cm in both lungs, multiple small cavitary lesions up to 1.7 cm, mainly over left lower lobe. CT of the abdomen only showed a hepatic cyst.

He was put on empirical intravenous (IV) amoxicillin-clavulanate after admission which was changed to IV clindamycin 600 mg Q8H and metronidazole 800 mg Q8H after making a presumptive diagnosis of Lemierre's syndrome. Fever came down gradually over the following week and serial chest X-rays (CXR) showed resolution of lower zone infiltrate. Since the clinical response was satisfactory, otorhinolaryngologist suggested continuing medical therapy rather than surgical drainage. Mr. Cheung was finally discharged with oral form of the antibiotics. A total of 4 weeks of clindamycin and metronidazole were completed. Mr. Cheung remained afebrile and free of symptoms. Neck swelling was also resolving. Follow-up CT and ultrasound imaging had been arranged.

Discussion

Lemierre's syndrome is described as a "forgotten disease" in literature. It was common in the pre-antibiotic era but sparsely reported in the 60s-70s. The incidence is 1/1,000,000 person per year [1]. It was first reported by the French clinician André Lemierre in 1936 based on his 20 patients of whom 18 died. "Young and previously healthy adults, presenting with initial pharyngotonsillitis or peritonsillar abscess, followed by septic thrombophebitis of internal jugular vein and subsequently metastatic abscess to lung, bone, joints, skin and soft tissue" is the classical description. *Fusobacterium necrophorum* was later found to be the principle aetiological agent. Some clinicians nowadays also accept Lemierre's syndrome as a diagnosis when the origin of infection is not from the throat e.g. ear, mastoid or tooth infection [7] and when other organisms are isolated e.g. *Streptococci*, *Staphylococcus aureus*, *Peptostreptococci*, *Eikenella*, *Pseudomonas aeruginosa* [4]. It has high mortality in the pre-antibiotic era, approaching 90% in Dr André Lemierre's series. Ligation and excision of the internal jugular vein as an attempt to remove the source of septic emboli was the only available therapy at that time.

Fusobacterium organisms are obligate anaerobic, non-spore-forming, Gram-negative rods. They belong to the family Bacteroidaceae and are normal inhabitants of human mucosal surfaces — oral cavity, female genital tract and gastrointestinal tract. They are known to cause polymicrobial infections in human and a variety of respiratory and abscess-forming disease in the veterinary field. *Fusobacterium necrophorum* is the most virulent member and is able to invade as a primary pathogen due to a variety of toxins e.g. leukotoxin, haemolysin, haemagglutinin, adhesion [6].

The pathophysiology is not entirely understood. It is postulated that the oral mucosal defence was first weakened by a prior bacterial or viral infection (pharyngitis or tonsillitis). Toxins of *F. necrophorum* then cause further tissue destruction, formation of anaerobic environment and finally invasion of lateral pharyngeal space by the bacteria. Direct extension, in the case of otitis media, mastoidtitis and sinusitis, and lymphatic spread were also suggested [5]. Lateral pharyngeal space is bounded by superior pharyngeal constrictor muscle (medially), medial pterygoid (laterally) and styloid process; and its content includes the internal jugular vein (IJV), carotid artery, vagus nerve, the 9th, 11th, 12th cranial nerves and sympathetic chain. Invasion by the bacteria leads to septic thrombotheblitis of the IJV and subsequently metastatic infections. Carotid artery erosion, cranial nerve palsy and Horner's syndrome are rare complications [4].

The degree of initial throat infection is variable, from mild viral pharyngitis to acute exudative tonsillitis with peritonsillar abscess. Painful neck mass begins at the angle of jaw, swelling along sternocleidomastoid muscle with or without trismus follows, signifying the development of IJV thrombosis. Bacteraemia and metastatic infection usually occur within a week. Lungs are the commonest site of metastatic infection, occurring in up to 73% in one study [3]. They are shown as bilateral nodular shadows or even cavities on CXR. Pneumothorax and acute respiratory distress syndrome are rare events.

Large joints such as hip, shoulder, and knee are the next commonest sites of metastatic infection, which occurred in up to 15% in the same study [3]. Pyomyositis and osteomyelitis have been reported. Liver and splenic abscesses are not common but mild hyperbilirubinaemia and slight elevation of liver enzyme occur in around 50% [3]. Hepatosplenomegaly without abscess is also possible. Metastatic infection of the central nervous system is not common; however, cranial nerve palsy as a result of retrograde propagation of IJV thrombosis into cranial sinuses must be watched out for.

Diagnosis is clinical. Blood tests are usually not helpful other than demonstrating the bacteria by culture. Neutrophil leucocytosis raised C reactive protein and abnormal liver function are non-specific. *F. necrophorum* could be cultured in blood in 82% in one study but it may take 48 hours to a week to grow [1]. Culturing pus aspirated from a metastatic site is also helpful. In addition to plain X-ray, CT and magnetic resonance imaging are valuable tools in assessing extent of the disease.

The mainstay of treatment is prolonged antibiotic therapy for at least 4 to 6 weeks, which seems necessary to eradicate the infection, probably because of its endovascular nature and secondly, presence of overt collection of pus which may not be amenable to drainage. *F. Necrophorum* is generally sensitive to penicillin, clindamycin, metronidazole and chloramphenicol [5]. Clindamycin and metronidazole were chosen for our patient because of their superior tissue penetration and they are suggested to be more effective in treating lung abscess [2]. Moreover, beta-lactamase producing strain was isolated in up to 22% in one study [2] whereas in vitro erythromycin resistance has been documented in 22% in another

study. *F. Necrophorum* is intrinsically resistant to gentamicin, while quinolones have relatively poor activity. Besides antibiotics, surgical drainage of pus is another important aspect of management. Anticoagulation is controversial as most patients appear to do well without it. It is now reserved for patients with evidence of retrograde propagation of the jugular thrombosis to carvernous sinus [2]. Resection or ligation of the involved internal jugular vein is only rarely indicated when there is persistent septic embolisation despite adequate antibiotic therapy [2,5].

Recent papers suggested a resurgence of Lemierre's syndrome which is putatively linked to the fact that primary care physicians are now heavily discouraged from prescribing antibiotics for sore throats [2,8]. Early infections which would have previously been aborted by antibiotic now progress to full blown syndrome. Better anaerobic blood culture techniques also lead to improved detection of the organism. More isolates of *F. Necrophorum* being erythromycin resistant is another possible cause.

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Journal Review

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Centers for Disease Control and Prevention (CDC). Norovirus outbreak in an elementary school — District of Columbia, February 2007. MMWR Morb Mortal Wkly Rep. 2008 Jan 4;56(51-52):1340-3.

Norovirus is emerging as an important cause of gastroenteritis both locally and worldwide, and often presents as outbreaks in semi-enclosed populations. Transmission from person-to-person usually occurs by the faecal-oral route, contaminated food or water, or via aerosolised vomitus; fomites are less frequently implicated but could act as important reservoirs in outbreaks.

On February 8, 2007, an outbreak of acute gastroenteritis was reported in an elementary school in Washington, DC. Over a period of 5 days, 27 students and 2 staff members became ill with symptoms of gastroenteritis, including nausea, vomiting, and diarrhoea. Enhanced infection-control measures including increased handwashing and bleach decontamination of shared environmental surfaces were immediately instituted. The DC Department of Health (DCDOH) conducted an outbreak investigation, and questionnaires were sent to all students and staff.

Of the 314 students and 66 school members, 266 (70%) participated in the DCDOH investigation; 103 (39%) met the case definition for gastroenteritis. Vomiting and nausea occurred in more than half the cases, and most experienced only a brief episode of illness (median illness duration = 36 hours). Food-borne source was excluded. Primary risk factors were contact with another sick person and presence in the single first-grade classroom in which students and staff shared computers. Subsequent testing of environmental samples from the keyboard and mouse of one such computer by PCR revealed the presence of norovirus subtype GII. The same viral subtype was identified in stool specimens from ill persons.

Points to note: As we are all familiar by now, norovirus can cause large outbreaks of enteric illnesses in schools and families. This report is the first account of computer-related transmission and highlights the need (particularly during outbreaks) to clean all shared environmental surfaces with diluted household bleach. This information should be useful to public health staff involved in outbreak infection control in the community.

Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008 Jan 10;358(2):111-24.
Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008 Jan 10;358(2):125-39.

Patients with severe sepsis often die despite being treated with broad-spectrum antimicrobials. Recently, researchers have investigated the use of adjunctive therapies in sepsis in two multi-centre, randomised trials, and they have reported their findings in the *New England Journal of Medicine*.

Sprung and colleagues compared hydrocortisone with placebo in a multi-national, double-blind trial involving 499 adults with septic shock. The primary outcome measure was 28-day mortality among patients who did not have positive response to corticotropin tests. Mortality also was evaluated in two other cohorts: patients who had response to the tests and

the overall group. In all three cohorts, no differences in mortality rates were observed.

In an open-label trial, Brunkhorst and colleagues compared insulin therapies (intensive vs. conventional) and resuscitation fluids (colloid [pentastarch] vs. crystalloid [Ringer's lactate]) among 537 adults with severe sepsis or septic shock. Hypoglycaemia was more common in the intensive-insulin group (12.1%) than in the conventional-insulin group (2.1%), and the difference was statistically significant. Moreover, life-threatening hypoglycaemic episodes were more common in the intensive-insulin group (5.3%) than in the conventional-insulin group (2.1%). Intensive insulin therapy was terminated after the first safety analysis. In addition, acute renal failure was significantly more common in the pentastarch group (34.9%) than in the Ringer's lactate group (22.8%), and dialysis was required more often in the former group.

Points to note: Although Sprung and colleagues acknowledged that their study was underpowered due to low enrolment, the likelihood of seeing differences in outcomes between the study groups was deemed to be low. These two trials provide critical new information on the role of adjunctive therapies in patients with severe sepsis or septic shock. Until more information becomes available, the current message is that corticosteroids are probably not effective and that both intensive insulin therapy and pentastarch resuscitation are harmful in patients with severe sepsis or septic shock.

Waters AM, Kerecuk L, Luk D, et al. Haemolytic uraemic syndrome associated with invasive pneumococcal disease: the United kingdom experience. J Pediatr. 2007 Aug;151(2):140-4

Haemolytic uraemic syndrome (HUS) is characterised by the presence of microangiopathic haemolytic anaemia, acute renal failure, and thrombocytopenia. HUS typically occurs after an episode of diarrhoea caused by *Shigella* or enterohaemorrhagic *Escherichia coli*. However, about 5% of cases are associated with *Streptococcus pneumoniae* (atypical HUS). In a recent report, investigators from UK retrospectively reviewed 43 pneumococcal HUS cases (34 proven, 9 suspected) that occurred from 1998 to 2005 at seven children's hospitals. These cases constituted 13.6% of all the HUS cases identified during that period of time.

All cases had known or suspected pneumococcal infections, such as pneumonia, meningitis, and / or bacteraemia. Among the 34 microbiologically confirmed cases, pneumococci were identified by culture in 29 cases, by 16S rRNA sequencing in 3 cases, and by urinary pneumococcal antigen in 2 cases. The median age of the patients was 13 months. 12 isolates were available for serotyping; 6 were serotype 19A, and only 2 were serotypes covered by the 7-valent pneumococcal conjugate vaccine. Over 80% of patients required dialysis and six had plasma exchange. Five patients died, three from complications of meningitis, one from nosocomial sepsis with *Pseudomonas*, and one from a pulmonary embolus. Data on follow-up showed that 10 children had significant renal dysfunction, with 1 remained dialysis-dependent. Only two of the children with meningitis had favourable neurological outcomes.

Points to note: Compared with the current case series, previous case series of atypical HUS were small, and prognosis of patients were varied. The patients in the present study had less residual renal disease than in previous reports. The most serious adverse outcomes were related to the invasive pneumococcal infection itself. Nevertheless, clinicians should be aware of the entity when treating patients with suspected HUS as prompt antibiotic therapy could be life saving.