Concurrent Session 8 – Gastrointestinal Infections

CS8-01 Norovirus Infection: An Emerging Enteric Infection
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CS8-02 Blastocystis-Host Interactions: New Insights on Pathogenesis
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Aims: Blastocystis is an anaerobic, enteric, protistan parasite with zoonotic potential. Its clinical relevance has been debated extensively, as some studies support a pathogenic role for the parasite while others show no correlation between infection and disease. Humans can be infected by a variety of distinct genotypes (subtypes). We hypothesize that subtypes vary in pathogenic potential and we aimed to investigate if such differences can be observed using in vitro cytopathic assays.

Methods & Results: Investigations were carried on Blastocystis subtypes 4 and 7, which are zoonotic genotypes found in rodent and avian hosts respectively. Cysteine protease activity was determined by azocasein assay. The results revealed inter- and intra-subtype variations in protease activity, with subtype 7 isolates harboring higher cysteine protease levels. Apoptosis assays for phosphatidylserine (PS) externalization and nuclear blebbing revealed that subtype 7 induced more cell death in host cells than subtype 4. Similarly, transwell assays for barrier function showed that subtype 7 induced greater barrier disruption than subtype 4. A stress fiber model developed in Caco-2 colonic epithelial cells, revealed that subtype 7 induced reorganization of stress fibers with a possible link to barrier function compromise.

Conclusions: From this study, clear cytopathic differences exist between Blastocystis subtypes, which suggest that variations in pathogenic potential exists among Blastocystis genotypes from different animal hosts.

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CS8-03 A Novel and Dominant Serotype Shigella flexneri Fxb Emerging in China
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CS8-04 Clinical Manifestations and Management of Enterovirus 71 Brain Stem Encephalitis
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Several epidemic outbreaks of Enterovirus 71 (EV71) infection occurred during the past one decade in southern Taiwan. EV71 has the potential to cause a large outbreak worldwide such as that in Taiwan in 1998. The main clinical presentations are herpangina, hand-foot-and-mouth disease (HFMD), and central nervous system (CNS) complications. Brain stem encephalitis (BE) is the cardinal feature of EV71 CNS complications during the outbreak. The predominant neurological presentations are myoclonus jerk, vomiting, and ataxia. BE that progressed abruptly to neurogenic shock and pulmonary edema (PE) was indicative of poor prognosis and high mortality. EV71 BE was categorized into uncomplicated BE, autonomic nervous system (ANS) dysregulation, and PE by disease severity. The PE that occurs in children with EV71 BE is caused by abnormal cytokines activation that produces severe CNS and systemic inflammatory responses. Currently, there is no specific antiviral agent to treat or vaccine to prevent EV71 diseases. Intravenous immunoglobulin (IVIG) has been found to have broad therapeutic applications for the treatment of many infectious diseases. We found a decrease in the plasma concentration of various cytokines following administration of IVIG. Patients with ANS dysregulation is the critical timing to received IVIG infusion. It is possible that a more favorable survival might have been obtained by earlier therapy and larger doses of IVIG. Milrinone, cyclic nucleotide phosphodiesterase inhibitor subtype III, increases cardiac output, and reduces systemic vascular resistance and pulmonary capillary wedge pressure without excessive increases in myocardial oxygen consumption. EV71-associated PE patients treat with milrinone is associated with significantly decreased mortality by attenuated sympathetic activity and cytokine production. Controlled clinical trials are ongoing to confirm these observations. A better understanding of the clinical features and management of EV71 BE may shed light on improving the outcome of severe and complicated EV71 BE.

Concurrent Session 9 – HBV: Treatment Options and Strategies

CS9-01 The Role of Currently Available Antiviral Drugs in Hepatitis B
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The main role of antiviral drug therapy for chronic hepatitis B (CHB) infection is to suppress the hepatitis B virus (HBV) from active replication, thereby preventing hepatitis and the complications. Doctors and patients alike wished for achieving HBV eradication early. This will lower the risk of liver complications and restore health and quality of life of the CHB patients. From the healthcare provider point of view, the transmission of HBV infection can be minimized and the health cost substantially reduced. Eradication of HBV rarely occurs spontaneously; around 0.5 to 2% among CHB individuals lost HBsAg annually. Newer antiviral drugs have higher efficacy and safety. HBsAg loss over and above the estimated spontaneous incidence has been reported after and during therapy. The role of current available antiviral drugs in the full spectrum of CHB disease can be summarized as follows.

There are two main categories of antiviral therapy for HBV infection: (1) interferon-based injections, and (2) oral nucleos(t)ide analogues. Any HBV disease types with viraemia will benefit from antiviral therapy that is efficacious, safe and affordable. Most international and national HBV treatment guidelines focused on individuals with HBV DNA level over 5 log_{10} copies/ml (i.e. around 4 log_{10} IU/L); especially if HBeAg negative; associated with raised serum ALT; and have evidence of significant liver fibrosis. Antiviral therapy is particularly important among males, over middle age, has family history of cirrhosis and hepatocellular carcinoma (HCC). The aim is to halt the existing liver damage, hopefully reverse fibrosis, even cirrhosis, and eliminate the conditions that favour HCC development. Clinical experience and data do support such strategy.
Interferon-based anti-viral drugs have dual actions of viral suppression and immune modulation; thereby have a higher chance of eradicating HBV and the infected hepatocytes. Pegylated interferon alfa-2a therapy for one year resulted in incremental HBsAg loss up to 9% and 11% by year 3 and year 4 respectively after completion of therapy. Higher baseline ALT level, female patients, HBV genotype A have been reported to favour response. The viral kinetics during therapy, the profile of decline in serum HBV DNA, quantitative HBeAg and HBsAg levels, are useful in identifying the patients likely to achieve sustained virologic response, which is relatively low at 30-40%. The defined duration of therapy make pegylated interferon therapy a choice for treating younger patients planning family in the future. These patients need careful counselling and should be warned about immediate and longer term known side-effects. They should be followed and monitored regularly at 4 to 8 weekly intervals. Long term follow-up data showed a significant reduction in serious complications of CHB including reduced incident of hepatocellular carcinoma among those responded to standard interferon therapy. Similar, if not better, results are anticipated after therapy with peyled interferon.

Oral nucleos(t)ide analogues (NAs) act directly and purely by suppressing the HBV DNA polymerase, though there may be some secondary stimulus effect on the host immune system when viral load is suppressed rapidly. NAs have the distinct advantage of low primary non-responder rate. Lamivudine and adefovir have been available for many years. Clinical experience over the years showed high rate of emergence of resistant mutants and moderate antiviral effect. Patients on these NAs require more frequent monitor and add-on therapy should resistance developed. Telbivudine, by comparison, is more potent and has lower resistant profile. The choice is easier when entecavir and tenofovir become available in the market. The consistent and rapid viral suppression, coupled with a much, much lower incident of drug resistant make long term therapy possible. Side-effects are few. The efficacy is not age, gender, ALT, and HBV genotype dependent and can be used in patients with cirrhosis and decompensated disease.

Pivotal clinical trials usually recruit patients of certain age group and specific disease characteristics. The role and safety of the newer NAs in the children and young adults with CHB, patients in immune tolerant phase, and in pregnant women, are still not clear. The role of NA as a prophylactic therapy to prevent relapse or exacerbation of CHB during chemotherapy or steroid treatment has been demonstrated. Another milestone role of NA is the suppression of HBV in liver and other organ/tissue transplantations. The success of transplantation for CHB patients cannot be realized without potent suppression of HBV to stamp out HBV recurrence in the immune compromised state. Current available therapy has created a significant impact in HBV infection and has improved the prognosis of CHB patients. Much more advances are needed to control this disease, to inhibit more profoundly, to eradicate more rapidly. We are at a turning point in the treatment of chronic hepatitis B (CHB). Long-term therapy with nucleoside/nucleotide analogues, both in HBeAg+ and HBeAg- CHB, has most favourable effects on patient outcome, provided that virological and biochemical remission is maintained without development of viral resistance. However, drug resistance become increasingly challenging to clinical management of patients with CHB. Here I would like to focus my presentation on 2 recent studies related with HBV resistance in China.

The first study is an open-label, randomized, controlled study to compare the efficacy and safety of peginterferon alfa-2a versus adefovir dipivoxil (ADV) in treating lamivudine resistant HBeAg positive CHB. Up to 70% of patients treated with lamivudine develop drug resistance after 5 years. Rescue therapies with oral antivirals are limited due to the cross-resistance profiles of nucleos(t)ide analogs. A finite course of peginterferon alfa-2a can offer the possibility of achieving sustained post-treatment response in these difficult-to-treat patients. In order to determine if on-treatment quantification of HBsAg can help identify these patients with lamivudine-resistant HBV most likely to achieve sustained post-treatment response to peginterferon alfa-2a, quantitative HBsAg levels were measured prospectively at baseline and at week 24 and 48 using the Architect QT assay (Abbott Diagnostics) in available sera of 155 patients who received peginterferon alfa-2a 180 μg qw for 48 weeks or 80 patients with adefovir dipivoxil (ADV) 10mg daily for 72 weeks. All patients were HBeAg-positive with documented resistance to lamivudine (YMDD mutation). All patients continued LAM treatment 100mg daily for the first 12 weeks. The primary efficacy endpoint was HBeAg seroconversion at Week 72 (6 months post-treatment in peginterferon alfa-2a arm or at the end of treatment in adefovir arm). HBeAg seroconversion at Week 72 was significantly higher in the peginterferon alfa-2a arm (11.6% vs 3.8%, P=0.045). Three of the 18 patients treated with peginterferon alfa-2a who achieved HBeAg seroconversion also achieved HBsAg seroconversion. No ADV-treated patient cleared HBsAg. HBsAg decline from baseline was more pronounced in the peginterferon alfa-2a-treated patients. At week 24, 31% of the peginterferon alfa-2a-treated patients with available data had HBsAg levels <1500 IU/ml, compared with 14% of those treated with ADV. The rate of HBeAg seroconversion 6 months post-treatment was twice as high in peginterferon alfa-2a-treated patients with HBsAg <1500 IU/ml at W24. There was no association between HBsAg level at week 24 and response to ADV.

Our data show that peginterferon alfa-2a represents a viable treatment strategy for difficult-to-treat patients who bear lamivudine-resistant YMDD mutations and was superior to ADV in achieving HBeAg seroconversion. Quantification of HBsAg level at week 24 may help identify those most likely to benefit from peginterferon alfa-2a.

The second study is about adefovir dipivoxil (ADV) resistance at 5 years in Chinese HBeAg-ve chronic hepatitis B. Long-term ADV provides clinical and histological improvement in CHB, but as with all oral therapies may lead to emergence of ADV resistance-associated mutations. Long term ADV resistance data are best documented in a HBeAg negative population. At 5 years the cumulative probability of resistant mutation with virological resistance was 29%. We report ADV resistance data from a cohort of Chinese HBeAg positive subjects treated for 5 years. Four hundred and eighty HBeAg positive CHB subjects were randomized in an initial 52 weeks controlled ADV study (with a 12 weeks placebo period in two thirds of patients) and then offered open label ADV treatment for a further 208 weeks. Four hundred and eighty subjects were enrolled in the first year study,

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**CS9-02**

The Role of Interferon Therapy in Hepatitis B

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**CS9-03**

Management of Drug Resistance of Hepatitis B: New Data from Chinese Patients

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China is a highly endemic area for hepatitis B virus (HBV) infection with the biggest HbsAg carrier population in the world. The management of chronic hepatitis B (CHB) has improved dramatically over the last decade with the development of new antiviral drugs. In addition to the standard interferon (IFN)-alpha therapy, 4 nucleotide/nucleoside analogues (lamivudine, adefovir dipivoxil, entecavir and telbivudine) and 2 pegylated interferon (pegasys and pegintron) have been approved for the treatment of chronic hepatitis B. Long-term therapy with nucleoside/nucleotide analogues, both in HBeAg+ and HBeAg- CHB, has most favourable effects on patient outcome, provided that virological and biochemical remission is maintained without development of viral resistance. However, drug resistance become increasingly challenging to clinical management of patients with CHB. Here I would like to focus my presentation on 2 recent studies related with HBV resistance in China.