Practical approach to viral hepatitis in New Zealand

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Viral hepatitis contributes significantly to the burden of chronic liver disease. Apart from alcoholic liver disease and haemochromatosis, hepatitis B virus (HBV) and hepatitis C virus (HCV) constitute the major causes of liver cirrhosis, liver cancer and death from liver failure. Furthermore, in an environment of limited organ donation, viral hepatitis accounts for a large number of patients assessed for orthotopic liver transplantation.

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Hepatitis B infection (HBV)

Worldwide HBV infects more than 300 million people. The natural history of infection differs according to the time of acquisition. If infected perinatally, acute hepatitis-like clinical picture is rare, but chronic carrier state ensues invariably (>95%) with substantial risk of cirrhosis and hepatocellular cancer (HCC) over a lifetime. Adult infections are aquired parenterally, usually by sexual exposure or percutaneously from intravenous drug use or infected blood products, however, since routine screening of all blood products in 1993, no transfusion-associated HBV infection has been documented. This is typically associated with an acute hepatitic illness and results in chronic infection infrequently. It has become self-evident that New Zealand has an endemic proportion of HBV infection and resultant morbidity and mortality.

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In 1998 the Ministry of Health finally approved funding for a New Zealand Hepatitis B screening programme. Target populations are Maori, Pacific Island people and Asian people over 15 years of age, living in the North Island. A major difference in the demographics of the Auckland region compared with the Southern region is that the northern region comprised >90% urban residents (41% Maori, 31% Pacific Island and 28% Asian), while the southern region was mostly rural (almost 80% Maori).

When assessing HBV infection there are several issues to be addressed:

- Is the patient a carrier?
- Is there ongoing viral replication?
- Are there clinical signs suggestive of chronic liver disease or cirrhosis?
- When does the patient warrant specialist opinion?

Chronic carrier state is indicated by HBsAg+ve state (HBsAb-ve or anti-HBsAg-ve). If the patient has received HBV vaccine or cleared natural infection the HBsAb will be positive (with positive HBcore IgG in the past infection). Infectivity is reflected by viral replication as evidenced by HBeAg+ve and HBV DNA positive for wild-type infection. New Zealand has about 50% HBeAg-ve and HBV DNA positive hepatitis, presumed to be due to mutation in pre-core region (unable to express eAg) but yet still highly infectious. In the present screening programme HBsAg+ve status was seen in up to 6.2% Maori, 8.3% Pacific Island, 6.9% Asian and 5.6% other target populations. Fortunately, a sizeable proportion of screened individuals show evidence of cleared past infection with HBeAb+ve (40–50% depending on

area). Even though New Zealand has established infant vaccination and school vaccine programmes, 30–40% of screened individuals show no signs of immunity (HBsAb-ve and HBcAb-ve). These people, particularly in high risk areas, should be vaccinated.

Suggested follow-up of carriers is dictated by ALT. When the ALT is normal, annual repeat ALT is indicated with repeat HBeAg in previously positive patients. If the ALT >60, this should be repeated in six months and referral made to a specialist clinic if persistently elevated. In Pacific Islanders co-infection with Hepatitis D virus (HDV) should be excluded and co-infection with HCV, HIV will be assessed by the secondary care centre in adult acquired infections.

Patients may be aware that assessment has previously included a liver biopsy. Currently patients with HBeAg+ve hepatitis under the age of 30 years should not require a biopsy as long as there are no clinical signs suggestive of chronic liver disease. However, in patients over 30 years, those who have clinical signs of liver disease or those who have HBeAg-ve hepatitis may require a liver biopsy to establish histological stage of disease with respect to the stage of fibrosis.

Treatment options for patients with chronic HBV infection with raised ALT have improved over the last five years. These include interferon-based therapy or nucleoside analogue-based therapy. The treatment schedule should be individualised according to HBeAg status, level of ALT, severity of histological liver injury and hepatic synthetic function (absence of hepatic decompensation). Currently the government funds both standard interferon and lamivudine. Sustained viral response can be achieved in many patients and treating chronic infection will reduce long-term risks of chronic liver disease associated with decompensation, hepatocellular cancer and need for transplantation.

HBV infection is a DNA virus and the integrated virus causes HCC in the absence of cirrhosis and following the establishment of cirrhosis. Thus screening for HCC should take into account the absolute risk of developing this. It is not cost-effective to screen all patients. There is no clear consensus regarding an optimal screening interval but those at highest risk should be screened with six-monthly alpha-foeto protein (AFP) and yearly ultrasound. Individuals at highest risk will be those with raised ALT, family history of hepatocellular cancer and those with established cirrhosis. An AFP >20 should be repeated in one month (remember to exclude pregnancy in female patients or testicular lesions in men) and if it remains elevated this should be referred immediately as should those patients with an initial AFP >100. If an hepatocellular cancer is detected early (<5cm), this may be curable and immediate assessment by secondary referral clinic is essential.

Hepatitis C infection (HCV)

This RNA virus has become a leading cause for chronic liver disease in countries with effective HBV vaccine-based programmes. The virus is usually acquired parenterally and results in chronic infection in over 80% of patients. There is a small (15%) chance of initial clearance but once established yearly clearance rates are negligible. Perinatal (<5%) or sexual (<3%) acquisition is rare, while transfusion associated infection has not been documented since effective screening of blood products in 1993. Therefore, the major risk factor of infection is intravenous drug use (78%) and to a lesser extent tattooing (12%). Once chronic infection is established, approximately 20% of carriers progress to chronic liver disease and associated cirrhosis. Cirrhosis is also associated with the development of hepatocellular cancer of 3–5% per annum.

Key Points

- Apart from alcoholic liver disease and haemochromatosis, hepatitis B virus (HBV) and hepatitis C virus (HCV) constitute the major causes of liver cirrhosis, liver cancer and death from liver failure.
- Treatment options for patients with chronic HBV infection with raised ALT have improved over the last five years.
- HBV infected patients at highest risk for hepatocellular cancer should be screened with six monthly alpha-foeto protein (AFP) and yearly ultrasound.
- The major risk factors for hepatitis C infection are intravenous drug use (78%) and to a lesser extent tattooing (12%).
- Alcohol causes chronic liver injury on its own but also upregulates viral replication and decreases response to treatment in patients with HCV infection.
- Treatment for hepatitis C has seen quantum leaps in the last five years.
- Clearly, there is good cost-benefit in preventing the burden of chronic liver disease that is facing New Zealand.

The risk of progressive disease is known to be related to several factors. There is a correlation with the following four factors and fibrosis on liver histology. The factors are:

- male gender (RR 2);
- length of infection;
- age at infection (especially >40 years old); and
- alcohol consumption.

Our own study has shown an almost linear correlation between length of

infection and the degree of fibrosis on liver biopsy. Alcohol causes chronic liver injury on its own but also upregulates viral replication and decreases response to treatment in patients with HCV infection. We have shown a RR 5.76, when comparing those with no alcohol history to those who drink any alcohol. Other studies confirm that there is no safe level of alcohol ingestion. However, higher alcohol consumption (more than 40g/day) exacerbates the problem.

Treatment for hepatitis C has seen quantum leaps in the last five years. All current regimens still use interferon-based combination therapy and with the use of genotyping we have been able to individualise treatment. Excluded from therapy are patients with psychiatric history particularly major depressive illness and schizophrenia. With careful selection, patients with remote or mild depression can be treated successfully. Patients on stable methadone replacement therapy can also be assessed for suitability. We have used the Hospital Anxiety and Depression (HAD) score as a useful clinical adjunct to assessing patients and have a good relationship with our psychiatry liaison team.

Patients with persistently normal ALT, who have no signs of chronic liver disease, which may indicate established cirrhosis, will generally not respond to treatment. More importantly though, is that although these patients have a chronic infection, they have a very low rate of progression. If all co-factors are avoided, the risk of cirrhosis in these patients is as low as 2% over their lifetime.

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The patients targeted for treatment are those with persistently elevated ALT >60. Interferon alone has resulted in low rates of sustained viral response (SVR) of 20%. In combination with ribavirin there is a significantly greater SVR of 40%. Once we stratify patients into genotypes, the differences in SVR become more pronounced. Genotype 1 patients require 12 months combination therapy with interferon and ribavirin. Gentotype 3 (or 2) need six months of combination treatment and will not benefit from prolongation or dose escalation. Recent studies with pegylated-interferon have shown that >50% of all patients can achieve SVR. Genotype 3 patients can expect an almost 80% SVR. The major benefit of the longer acting Peg-interferon is for those individuals with genotype 1 and/or evidence of significant fibrosis (even cirrhosis) on biopsy. This treatment, however, is not readily available except on special access programmes, while the Ministry of Health contemplates funding. Clearly, there is good cost-benefit in preventing the burden of chronic liver disease that is facing New Zealand.

Viral hepatitis is a leading cause of morbidity and mortality in affected communities and effective primary preventive strategies need to be established and maintained. However, while these will take several generations to show benefit we are still faced with a need to assess patients and offer effective treatment where appropriate. Significant advances have been made in our understanding of risk factors for progressive disease and development of hepatocellular cancer. Screening the at risk population and referring for specialist opinion will ensure those who will benefit most from treatment are seen.

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