

Hepatitis: The management of chronic hepatitis B virus infection in Aboriginal and Torres Strait Islanders

Authors: Dale Fisher; Sarah Huffam

Topic Reviewers: Ivor Alexander (RAN, Nhulunbuy CDC), Steven Skov, Dan Ewald

This background paper quite deliberately focuses on hepatitis B. While the authors acknowledge that most observed abnormal liver enzyme tests are related to fatty deposits in the liver secondary to diabetes or dyslipidaemia, it is clear that most controversy for health care providers in remote Aboriginal communities comes from the management of patients with hepatitis B. Abnormal liver function tests are also recognised frequently in a setting of kava or alcohol abuse. The management of such abnormal liver function relates to management of these underlying problems and as such we will not expand on these issues here. Other causes of chronic liver disease – such as hemochromatosis, Wilson’s disease, auto immune hepatitis and (thankfully still) hepatitis C – are rare at best.

Summary

Over the last five to 10 years, treatment options for patients with chronic hepatitis B have evolved considerably. The mainstay of management of this common worldwide problem remains primary prevention. As universal vaccination in the NT was introduced initially in the late 1980s, concerns over ensuring optimal management of chronic hepatitis B infection will remain for decades yet. Those with chronic infection require an emphasis on avoidance of exacerbating hepatic insults, particularly alcohol. As well as this there is increasing utilisation of more sophisticated therapy including antiviral drugs for those with progressive inflammation and fibrosis. Furthermore, medical and surgical developments have increased the options for those with stable cirrhosis as well as decompensated disease and hepatocellular carcinoma.¹ The literature provides some guidelines to assist primary health providers in the broader community deliver best care to patients with hepatitis B.^{2,3} They do not, however, commit to guidelines for screening of hepatocellular carcinoma and this is because of a lack of evidence as to its value. Such guidelines designed for general practitioners for the general population assist with testing and indications for specialist referral, but do not offer specific information for the remote Aboriginal and Torres Strait population known to have Australia’s greatest hepatitis B burden.

The summary of hepatitis B, published by the Gastroenterological Society of Australia in 2000, is an excellent resource for those wishing further reading.³ The core issues to be addressed by this chapter are the role of

testing and follow-up in the primary care setting of remote Aboriginal communities. The issue of referral for consideration of the newer specialised treatments is also addressed. Finally, even in the absence of satisfactory evidence, we must define a guideline for screening for hepatocellular carcinoma, which does not exist in the broader community but is a constant (and appropriate) question emanating from primary health care providers in this endemic setting.

Natural history of endemic chronic hepatitis B virus infection

The need for any intervention is a function of the natural history of the disease to be treated. Of those infected with hepatitis B virus (HBV) at birth or early childhood, 95% will become chronically infected. Each year 5-10% will lose their envelope antigen (e Ag) status and 10% will remain HBe Ag positive for life. Hepatitis B surface antigen (HBs Ag) will be lost in 1-2%/yr of those chronically infected.

Of those remaining HBs Ag positive around 25% will progress to end-stage liver disease.⁴ There is a 200-fold increased risk of hepatocellular carcinoma (HCC) in chronically infected patients. Patients without cirrhosis, and with negative HBe Ag and negative DNA, have a low risk of HCC. However, most patients who develop HCC are HBe Ag negative.

The risk of a patient developing sequelae of HBV associated cirrhosis is related to male gender, young age of acquisition, concurrent hepatitis C or HIV and alcohol misuse. Patients with chronic HBV that are HBV DNA negative and have normal ALT levels have little liver-related mortality. A longitudinal study of 92 such patients over 15 years showed no liver related deaths.⁵ Survival in patients with hepB cirrhosis is 71% at five years, with death being due to bleeding, sepsis or HCC.⁶

Early diagnosis of HCC allows for a variety of treatment options aimed at cure as well as prolonging length and improving quality of life. Treatment modalities range from transplantation to radio and microwave frequency ablation, resection and hemihepatectomy, intra-arterial chemotherapy and embolisation and percutaneous intralesional ethanol injections, each requiring extensive work-up and attendance at tertiary referral hospitals.¹ The natural history of HCC is dismal, with survival beyond two years rare.

Screening for hepatitis B and vaccination

Opportunistic screening for hepatitis B infection in the context of sexually transmitted infection, prenatal care or biohazard injury should be followed with vaccination if the individual is not immune. Universal vaccination of newborns for hepatitis B commenced in the NT in 1988 for Aboriginal children, and vaccination of non-Aboriginal children was commenced in 1990 and actively promoted in 1993. A 'catch-up' program was conducted in 1998 to vaccinate children age 6-16 years. The efficacy of vaccination is related to development of HBs Ab and will occur in >95% of infants undergoing recommended protocols.⁷ For the purposes of this chapter we will assume the reader has a good understanding of the essential role of primary prevention via vaccination (including immunoglobulin administration), contact and family screening and the overall importance of counselling and education.

The role of antiviral therapy

Alpha-interferon was the first drug to become available for treatment to prevent progression of liver disease. Success is defined as loss of viraemia and normalisation of liver function tests and occurs in 40% of those treated with a six-month subcutaneous course. The side effect profile is high.

More recently, lamivudine became available as an alternative antiviral agent for patients with active chronic HBV infection. The seroconversion rate in those treated is up to 73% at four years.⁸ Those most likely to respond will have a high ALT and low-level viraemia together with a high degree of activity on biopsy. Patients, to receive treatment, need serial blood tests demonstrating an elevated serum ALT and HBV viraemia. They must consume little alcohol over six months and then undergo a liver biopsy. Treatment is a daily tablet, for possibly years. The drug is very well tolerated with few side effects reported. Success is defined as loss of viraemia and normalisation of ALT at which time treatment may stop.

Survival of patients treated successfully with loss of HBe Ag, viraemia and possibly sAg is significantly better than those not treated and those treated without seroconversion.⁹

It is unlikely that there is any role for interferon in the Aboriginal and Torres Strait Islander population at this stage. Lamivudine is less toxic and taken orally. It also has cumulative benefit although there is concern over the selection of resistant strains.⁸

Future treatment options likely to become available include other nucleoside analogues and more acceptable preparations of interferon plus combination approaches. Currently, both interferon and lamivudine require initiation and monitoring via a hospital based liver clinic. They are funded via the S100 scheme.

Studies in hepatitis B patients being immune suppressed for other reasons, notably renal transplant or chemotherapy, have a decreased risk of hepatitis flare when given lamivudine.¹⁰

Transplantation for end-stage and decompensated HBV cirrhosis is now widely accepted since the recognition of improved graft survival with lamivudine. This involves extensive assessment of a variety of patient factors. Once accepted, the patient must live within ready access of a major centre and be available to respond immediately to a page. Waiting times are generally in the order of three to nine months and dependent largely on blood group status. For a period post operatively the patient is required to remain close to the major centre. Regular specialist follow-up is lifelong and immunosuppressive drugs are taken daily. The side effect profile including the risk of sepsis is significant. Management is complicated where co-morbidities in the form of renal disease, hypertension and diabetes exist.

Relevance in the remote Aboriginal and Torres Strait Islander population

In Australia, 90 000 Aboriginal people live in remote communities, many of which are accessible only by aircraft especially in the wet season. Most have much worse social and economic circumstances, education, living conditions and health status than other Australians.^{11,12,13}

Aboriginal and Torres Strait Island people have death rates over three times higher than the Australian population overall with life expectancy approximately 20 years less than other Australians.^{11,12,13,14} The major causes

of death in Aboriginal people include cardiovascular and respiratory disease, injuries and poisoning. Furthermore, there are increasing trends in cancer, diabetes, chronic liver disease and suicide. In the Northern Territory in 1991-95, chronic liver disease (all causes) and cirrhosis death rates were four times higher for Aboriginal males and 5.5 for Aboriginal females, compared to the non-Aboriginal population. There were a total of 62 deaths from chronic liver disease in the NT during this period¹⁴ (figures 1 and 2 below).

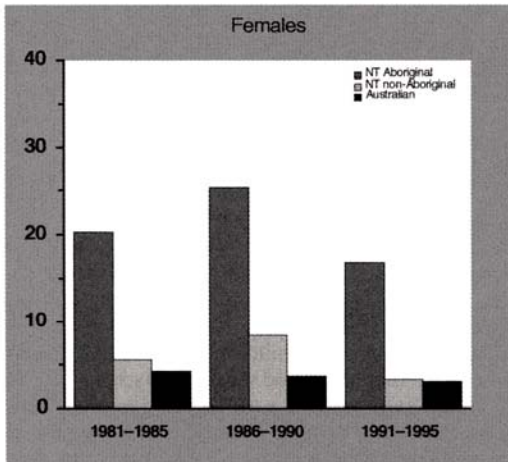


Figure 1: Age adjusted death rates per 100 000 for chronic liver disease (females)

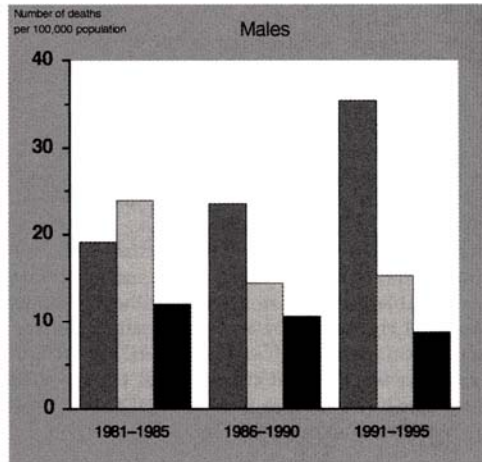


Figure 2: Age adjusted death rates per 100 000 for chronic liver disease (males)

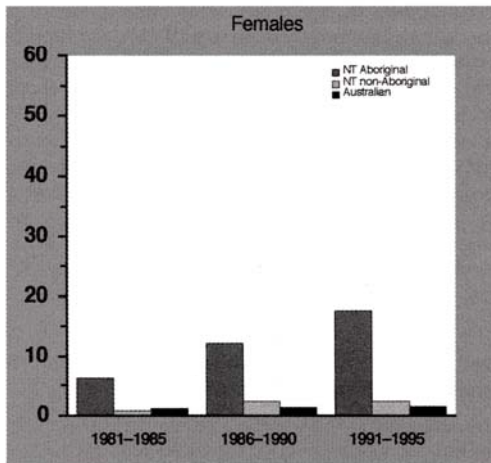


Figure 3: Age adjusted death rates per 100 000 for liver cancer (females)

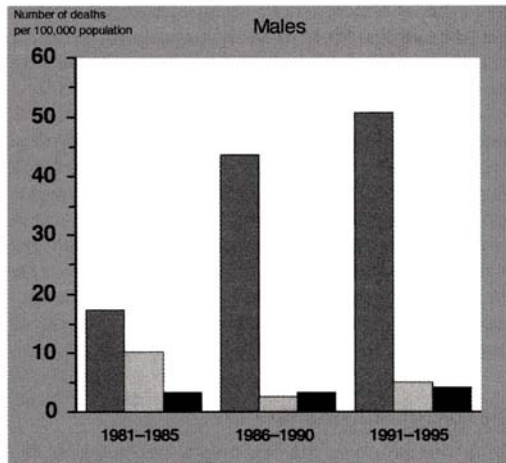


Figure 4: Age adjusted death rates per 100 000 for liver cancer (males)

Incidence and prevalence of hepatitis B

Studies from 1989-93 in 24 Northern Territory urban and rural schools of children aged nine to 17 years, and teachers, demonstrated serological markers of HBV infection in 18.7% of school children. This included 46.9% of 439 Aboriginal children, 13.7% of 556 children from 'low prevalence' (e.g. Caucasian) groups and 32.1% of 109 'other' ethnic groups. 12.8% of school staff from low prevalence backgrounds and 37.9% from 'other' including Aboriginal and Asian backgrounds had HBV markers.¹⁵

Other studies have shown HBs Ag detected in 8-26% of rural Aboriginal populations.^{16,17,18}

Liver cancer death rates have almost tripled in the period from early 1980s to the early 1990s (figures 3 and 4). Where serology was undertaken in patients with HCC one study demonstrated HBs Ag was positive in 7/11 Aboriginal cases (63.6%) and 2/4 non-Aboriginal cases. The median and mean age was 59 years.¹⁹ Aboriginal people are 12 times more likely to die from liver cancer than Australians generally.¹⁴

There were 28 deaths from HCC diagnosed in the Northern Territory between 1991 and 1995. During the period 1987-97 primary liver cancer was the third most common cancer and the second highest cause of cancer death in Aboriginal males.¹¹

However, as a health priority, many issues are more significant than hepatitis B to this population. Furthermore, interventions for higher priority conditions may be less consumptive of resources and more culturally appropriate. Preventing vascular disease (for example) will have a much greater impact on community mortality than efforts on hepatitis B such as antiviral therapy or screening for HCC. This is not to say, however, that an individual should be refused 'best care' if it is deemed by the patient and clinician to be in that individual's interest. This is still the case when co-morbidities (and therefore life expectancy), plus other issues e.g. preparedness to have a liver biopsy, or treatment in a larger city or even interstate, are considered.

The role of new therapies and of HCC screening in ATSI populations

Investigation and treatment of asymptomatic individuals needs to be justified in any health care setting. In remote Aboriginal communities where the general burden of disease is high, and resources are scarce, this is particularly important. Local health care workers are generally overburdened and need to prioritise their efforts for maximal gain to their patients in terms of length and quality of life. The financial cost for an investigation in a patient living remotely may be significantly greater especially if it involves travel. The cost benefit of any screening, investigation and treatment in an asymptomatic individual may not be considered worthwhile, if cultural factors, co-morbidity, life expectancy and personal priorities are taken into account.

For so many reasons the decision to screen, investigate and treat needs to be justified in Aboriginal and Torres Strait Islanders living in remote communities. The corollary is that not screening, investigating or treating equally needs justification, especially when mortality is documented to be so high and increasing.

By defining a guideline we necessarily generalise about a population's characteristics and needs with respect to a particular disease. Aboriginal and Torres Strait Islanders living in remote communities live with endemic chronic HBV infection, and guidelines are needed for primary health care providers despite the fact that such guidelines are not laid down for the broader community.

While defining guidelines, however, it is acknowledged that it is always essential that clinicians adapt them to suit an individual patient's needs. The need for guidelines is well discussed in the setting of CARPA protocols.²⁰

Screening/surveillance for HCC

In the case of screening/surveillance for HCC, where there is a dearth of evidence, experts disagree on protocols and thus we can be comfortable that no sensible management plan can be deemed 'wrong'. Surveillance for HCC is practised widely by hepatologists but there is no published and accepted protocol. There is no randomised controlled trial showing benefits from surveillance, however, many believe that patients identified early have a greater opportunity to access curative therapy. One group has attempted guidelines in this field but undertaken screening only in those with clinical or biopsy-proven cirrhosis.²¹

A 16-year longitudinal study screening for hepatocellular carcinoma in hepatitis B sAg positive Alaskan Indigenous people showed benefit in screening by AFP alone.²² While screening with AFP is a reasonable compromise, the highest yield comes from a combination of AFP and ultrasound.²³ Whether early diagnosis and intervention benefits the individual remains controversial. Furthermore, the appropriateness of dedicating resources required for such programmes is also debatable.

Patients being screened and monitored will require a good understanding of the reasons to investigate and consider treatment, particularly as they are likely to be asymptomatic at the appropriate time to intervene.

Antiviral therapy

Regarding antiviral therapy, clearly selected individuals can benefit. Patients being considered for treatment will require a good understanding of the reasons surrounding investigation and follow-up. They will need to understand the possibility of treatment failure. It should be seen that in the context of that individual's care that treatment is being considered, because it is likely, that the sequelae of hepatitis B will possibly have an impact on that individual's prognosis.

Recommendations

After negotiation and discussion with a person with chronic HBV infection, they should have a monitoring/ surveillance plan. This should fall into one of three streams based on their serology and LFTs (see flow chart at end of article).

Before committing to follow-up, education should emphasise its purpose, which is to decrease the risk of decompensated liver disease and hepatocellular carcinoma. Compliance with attendance and modification of other lifestyle factors, particularly alcohol, has a greater priority than biochemical testing. It should be remembered that other causes might result in abnormal liver function tests and in particular include diabetes, obesity, dyslipidaemia, medications, alcohol and kava consumption.

A person may move between categories. We also recommend some flexibility for primary health providers in determining the follow-up category. For instance, the intensity of follow-up can be downgraded or even removed for a number of reasons as listed below.

- Patient choice if appropriate decision-making opportunities ensured
- Unacceptable patient compliance with regards follow-up and life-style issues including alcohol consumption
- Existence of significant co-morbidities, thus altering the patient's prognosis for other reasons, including age

- A belief after discussion with the patient and relevant others that treatment options are culturally/socially inappropriate even if screening does demonstrate significant early and asymptomatic disease.

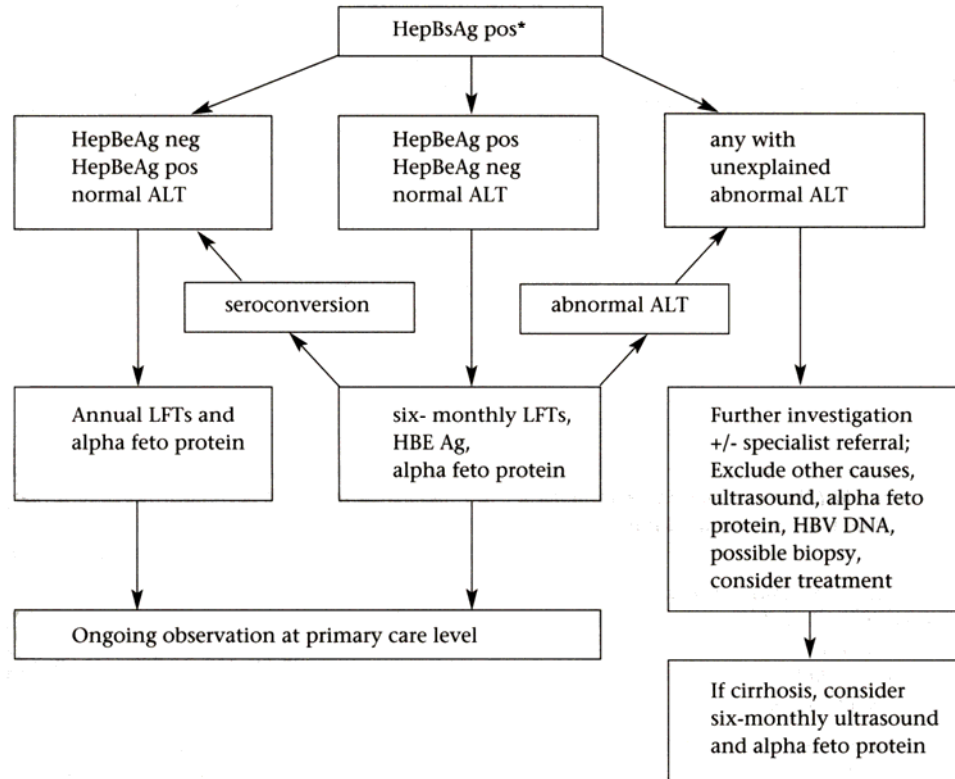
The management of chronic HBV infection is complex, and made more so by factors in this population including remoteness, co-morbidities, patient desires and resources. These guidelines outline many of the issues necessary to consider and provide a simple guide to facilitate follow-up and appropriate and timely referral for further investigation and consideration of treatment.

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Follow-up of hepatitis Bs Ag positive patients*

Follow up of hepatitis Bs Ag positive patients*



* This management is for patients who are deemed (after appropriate patient/health care provider interaction) to be amenable to treatment should investigation/surveillance result in such recommendation.