Hepatitis B and liver cancer

Implications for practice nurses

MONICA ROBOTIN

Cancer Council NSW
Why Do We Care About Chronic Hepatitis B?

- Without adequate management, 25% of people with chronic hepatitis B will develop liver cirrhosis and/or liver cancer.
- 60-80% of primary liver cancer worldwide is caused by chronic hepatitis B.\(^1\)

Bridging the Gap between Viral Hepatitis and Liver Cancer
Policy Recommendations of the European Expert Group for Better Control of Liver Cancer by Optimally Managing Viral Hepatitis

Chaired by
Dr. Thomas Ulmer MEP and Mr. Stephen Hughes MEP
Hepatitis B facts

- Hepatitis B is the most common cause of cancer after tobacco.\textsuperscript{xi}

- Hepatitis B can cause chronic liver disease and puts people at high risk of death from cirrhosis of the liver and liver cancer.\textsuperscript{xii}

- Individuals chronically infected with hepatitis B virus are 200 times more likely to develop HCC than uninfected people.\textsuperscript{xiii}

- Hepatitis B is 50 – 100 times more infectious than HIV.\textsuperscript{xiv}; worldwide, it is estimated that 350 million people are chronically infected with hepatitis B.\textsuperscript{xv}

- 1 out of 4 adults who become chronically infected with hepatitis B during childhood, later die from liver cancer or cirrhosis caused by the chronic infection.\textsuperscript{xvi}

- Globally, hepatitis B virus accounts for an estimated 600,000 deaths each year, mainly due to the consequences of chronic hepatitis, such as cirrhosis and liver cancer.\textsuperscript{xvii}

- Hepatitis B is preventable with a generally safe and effective vaccine.\textsuperscript{xviii}

- Hepatitis B is largely asymptomatic.


Bridging the gap between viral hepatitis and liver cancer
Policy recommendations of the European Expert Group for better control of liver cancer by optimally managing viral hepatitis, April 2012
Liver cancer facts

- Liver cancer is the third most common cause of death from cancer worldwide.\textsuperscript{xxvi}
- Hepatocellular carcinoma (HCC) is the most frequent cancer of the liver.\textsuperscript{xxvii}
- HCC accounts for 70\% to 85\% of cases of liver cancer worldwide.\textsuperscript{xxviii}
- In 2008 alone, liver cancer caused around 694 000 deaths worldwide.\textsuperscript{xxix}
- The lack of appropriate treatment of liver cancer leads to deaths within months of diagnosis.\textsuperscript{xxx}

\begin{itemize}
\end{itemize}
Recommendations

- A vast majority of liver cancer cases could be prevented with appropriate management of viral hepatitis B and C

- Specific policy measures are required to ensure earlier detection of viral hepatitis, cirrhosis and liver cancer and increase the chances for better health outcomes

- Education and awareness-raising, especially among policy makers, the general public and healthcare professionals, is pivotal to improve the prevention and management of viral hepatitis, cirrhosis and liver cancer

- Prevention measures must be offered, such as regular screening to high-risk groups, so as to detect viral hepatitis, cirrhosis and liver cancer.

- The EU and Member States should support the setting up of specific patients’ registries for viral hepatitis and liver cancer as to allow the collection of data that could facilitate surveillance, research and the overall management of these conditions

- The EU and Member States should develop and implement an action plan to tackle viral hepatitis and cirrhosis and liver cancer, as recommended in the World Health Organization (WHO) Resolution on Viral Hepatitis
Hepatitis B - global impact

Worldwide 2 billion people have been infected with the hepatitis B virus.

350–400 million people in the world have with chronic (lifelong) hepatitis B.

60–160 million people with chronic hepatitis B infection die of cirrhosis or liver cancer.

World population 6 billion

WHO Fact Sheet 204, available at www.who.int
HBsAg Prevalence

- ≥8% - High
- 2-7% - Intermediate
- <2% - Low

Geographic distribution of chronic hepatitis B infection

Estimated prevalence of BBV infection, 2007

<table>
<thead>
<tr>
<th></th>
<th>Australia</th>
<th>NSW</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV:</td>
<td>16,692</td>
<td>9,013</td>
</tr>
<tr>
<td>HCV:</td>
<td>207,600</td>
<td>79,000</td>
</tr>
<tr>
<td>HBV:</td>
<td>≈ 160,000*</td>
<td>≈ 55,000</td>
</tr>
</tbody>
</table>

NB: *Revised estimate of CHB prevalence (Butler et al, 2009)
~190,000 people

Proportion of all people DIAGNOSED with chronic viral hepatitis

- HCV: ≈ 80%
- HBV: ≈ 65%

NCHECR Annual Surveillance Report 2008
HCV Projections Working Group, MACASH 2006
Butler et al, ACERH 2009
Routes of hepatitis B transmission in Australia

- Perinatal
- Household contacts
- Sexual contacts
- Reuse of injecting or tattooing equipment
- Occupational exposure
Hepatitis B distribution in Australia

90,000 – 160,000 people estimated to be chronically infected in Australia
13,500 – 64,000 people likely to develop cirrhosis, liver failure or HCC

ACT HBV. Hepatitis B in Australia: Responding to a diverse epidemic. 2006
Hepatitis B infections by State and population group in Australia

Thousands of Hepatitis B infections

- Indigenous: 60.0
  - NSW: 32.9
  - QLD: 19.3
  - SA: 7.7

- China-, HK-, or Vietnam-born: 22.2
  - NSW: 13.5
  - QLD: 4.4
  - SA: 3.5

- Australia-born (non-indigenous) and other migrants: 10.7
  - NSW: 25.2
  - QLD: 7.7
  - SA: 3.0
  - TAS: 2.2
  - VIC: 2.1
  - WA: 10.4

Source: ABS 2006 census; Nguyen et. al. 2007; O'Sullivan et. al.; G. Dore; team analysis
Natural history of HBV, HCV infections

**Hepatitis B**
- Normal liver
- Acute infection
- Chronic infection (>90% children; <5% adults)
- Chronic hepatitis
- ≥30% cirrhosis
  - Liver failure
  - Transplantation
    - Death
    - Re-infection (low)
- HCC 5-10% a year
- Death

**Hepatitis C**
- Normal liver
- Acute infection
- 80% Chronic infection
- Chronic hepatitis
- ≥30% cirrhosis
  - Liver failure
  - Transplantation
    - Death
    - 100% re-infection
    - Death

Schiff 2006: Lancet 368; 896-7
Natural history of CHB infection

- ~25% of people with chronic HBV infection will die from decompensated cirrhosis and/or HCC
  - c.f. HCV, HCC can occur without cirrhosis in HBV

- 5-year rates of progression:
  - Chronic hepatitis to cirrhosis – 12-20%
  - Compensated to decompensated cirrhosis – 20%
  - Cirrhosis to HCC – 5-15%

- Four phases of chronic infection
  - Immune tolerance
  - Immune clearance
  - Immune control
  - Immune escape
Natural History of Chronic HBV
The 4 Phases and Relevance to Treatment Decisions

<table>
<thead>
<tr>
<th>Immune Tolerance</th>
<th>Immune Clearance</th>
<th>Immune Control</th>
<th>Immune Escape</th>
</tr>
</thead>
<tbody>
<tr>
<td>High HBV DNA, Normal LFTs, HBeAg positive</td>
<td>High HBV DNA, Abnormal LFTs, HBeAg positive</td>
<td>Low HBV DNA, Normal LFTs, HBeAg neg; anti-HBe pos</td>
<td>High HBV DNA, Abnormal LFTs, HBeAg neg; anti-HBe pos</td>
</tr>
</tbody>
</table>

At risk of progression to cirrhosis and HCC therefore should be referred for consideration of treatment.
Winning the battle against hepatitis B - related liver cancer

1. Reduce/ eliminate HBV transmission
   - Safe blood supply
   - Vaccination against HBV
   - Harm minimisation

2. Reduce the impact of HBV infection
   - Timely diagnosis of chronic hepatitis and institute treatment
   - Education, increased public awareness, practitioner up skilling

3. Diagnose and treat liver cancer early
How well are we faring in the primary prevention of HBV?

- Preventing neonatal transmission
- Routine neonatal HBV immunisation
- “Catch-up vaccination” through age 18
- Vaccination of adults in high-risk groups
  1. People at occupational risk (HCW)
  2. Indigenous populations
  3. STD clinic clients
  4. Inmates in correctional settings
  5. MSM
  6. Migrants from high-risk countries
  7. IDUs?

Why don’t we call people “carriers” any more?

Chronic Hepatitis B – is there such a thing as a “healthy carrier”?

No patient with chronic hepatitis B should be considered to be a “healthy carrier” and these patients should never be dismissed from regular follow-up. There is no such thing as a “healthy carrier” of hepatitis B.

Dr Sam Galhenage, Fremantle Hospital, Western Australia
Professor Darrell Crawford, Greenslopes Private Hospital, Queensland
Professor Geoff McLaughlan, Royal Prince Alfred Hospital, NSW
Professor John Olynik, Fremantle Hospital, Western Australia
Associate Professor Simone Strasser, Royal Prince Alfred Hospital, NSW

May 2008
HEPATITIS B AND LIVER CANCER
Liver cancer is commonly diagnosed in countries where hepatitis B infection is common.
CHB and HCC

- In NSW, HCC incidence is increasing faster than any other internal malignancy
- Nationally, it has the second fastest increasing cancer mortality rate

- Prognosis for patients diagnosed with HCC in Australia is amongst the poorest of all cancers: median survival 15mo.
- Late diagnosis a big problem – in NSW 1990-2002, ¼ of all deaths following HBV notification occurred within 6 months

Cancer in New South Wales
Incidence and Mortality Report 2008

Figure 4
Percentage change in mortality rates in males and females, NSW, 1999-2008

Lung -16.2%
Colon -15.2%
Prostate -20.3%
Brain -19.2%
NHL -19.5%
Leukaemia -23.7%
Bladder -20.3%
Kidney -32.5%
Pancreas -16.3%
Testis -56.4%
Lip -66.1%

Liver 47.9%
95.4%

Figure 5
Relative survival in NSW 2002 to 2006 followed to the end of 2007

Testis 96%
Thyroid 96%
Lip 91%
Melanoma 90%
Prostate 90%
Breast 88%
Hodgkin’s lymphoma 85%
Uterus 80%
Cervix 73%
Kidney 66%
Rectum 65%
Bowel 65%
Colon 65%
Non-Hodgkin’s lymphoma 65%
All Cancers 64%
Head and Neck 60%
Bladder 55%
Leukaemia 48%
Myelodysplasia 48%
Multiple myeloma 44%
Ovary 44%
Stomach 31%
Brain 22%
Cancer unknown primary 19%
Oesophagus 17%
Liver 16%
Lung 10%
Mesothelioma 10%
Pancreas 6%
### HCC attributable fractions in different world regions (%)

<table>
<thead>
<tr>
<th>Attributable fractions (AF)</th>
<th>Europe &amp; US</th>
<th>Asia</th>
<th>Africa &amp; Asia</th>
<th>Australian estimates&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B virus</td>
<td>22</td>
<td>20</td>
<td>60</td>
<td>~ 33%</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>60</td>
<td>63</td>
<td>20</td>
<td>~ 33%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>45</td>
<td>20</td>
<td>-</td>
<td>All other risk factors cumulatively~33%</td>
</tr>
<tr>
<td>Tobacco</td>
<td>12</td>
<td>40</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>-</td>
<td>-</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Aflatoxin</td>
<td>Limited exposure</td>
<td>Limited exposure</td>
<td>Important exposure</td>
<td>Limited exposure</td>
</tr>
<tr>
<td>Other risk factors</td>
<td>&lt;5</td>
<td>-</td>
<td>&lt;5</td>
<td>N/A</td>
</tr>
</tbody>
</table>

1 Australian estimates courtesy Prof Jacob George and the liver cancer STREP grant team

Modified from Bosch et al: Gastroenterology 2004, 127( S 5-16)
CCNSW Country of Birth Report

- 24.5% of all cancers in NSW occurred in migrants
- 46% of primary liver cancers occurred in migrants

SIRs for liver cancer diagnosed in NSW migrants by place of birth
“Missing” bars: incidence not calculated due to insufficient number of cases
MEDICAL MANAGEMENT OF CHB INFECTION

Preventing CHB-related liver cancer
# Medical management of CHB

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Interferon</th>
<th>Nucleoside/tide Analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune modulation and antiviral effect</td>
<td>Block viral replication</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Available agents</th>
<th>Pegylated interferon alfa-2a</th>
<th>Lamivudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telbivudine</td>
<td>Adefovir (2nd line)</td>
<td></td>
</tr>
<tr>
<td>Entecavir</td>
<td>Entecavir</td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Tenofovir (S100 pending)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of therapy</th>
<th>12 months</th>
<th>&gt;12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance, particularly with LMV/ADV monotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indefinite duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety in pregnancy?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Limitations</th>
<th>Significant toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing replication in many</td>
<td></td>
</tr>
</tbody>
</table>
Following a diagnosis of CHB

Counselling of patient (+ ideally partner / family)

- Natural history
- Modes of transmission and risk reduction
  - including discussion of vertical transmission if appropriate
- Availability of treatment
- Need for ongoing, potentially lifelong monitoring
- Alcohol minimisation, weight loss, smoking cessation, IDU harm reduction as appropriate
- Adequate time to answer questions
- Appropriate use of interpreters and translated resources
- Expect to have to go through it all again
CHB management - other considerations

- Notification
  - Any newly diagnosed viral hepatitis must be notified by both laboratory AND treating doctor

- Contact notification and testing
  - Sexual, IDU, household (HBV)

- Immunisation
  - Of patient, and of contacts in setting of HBV

- Post-exposure testing
  - Serological follow-up for those exposed to either HBV or HCV should extend to 6 months post exposure (usually at 1, 3 and 6 months)
Barriers to diagnosis and treatment

- Language
- Low income/poverty
- Education
- Immigration
- Health workforce

"racial concordance is associated with greater patient participation, higher patient satisfaction, and greater adherence." IOM
Maslow’s hierarchy of needs

1. The need for self-actualisation
   Experience purpose, meaning and realising all inner potentials.

2. Esteem Need
   The need to be a unique individual with self-respect and to enjoy general esteem from others.

3. Love and belonging needs
   The need for belonging, to receive and give love, appreciation, friendship.

4. Security Need
   The basic need for social security in a family and a society that protects against hunger and violence.

5. The physiological needs
   The need for food, water, shelter and clothing
Primary liver cancer incidence in NSW males by LGA (1998-2002)
Fairfield city - demographic indicators

Country of birth (top 10), Fairfield City and Sydney Statistical Division, 2006 (Enumerated data)

Source: Australian Bureau of Statistics, 2006 Census of Population and Housing

Proficiency in English, Fairfield City and Sydney Statistical Division, 2006 (Enumerated data)

Source: Australian Bureau of Statistics, 2006 Census of Population and Housing (Enumerated)
The Index of Relative Socio-Economic Disadvantage has "...been constructed so that relatively disadvantaged areas (e.g. areas with many low income earners) have low index values.

The Index of Relative Socio-Economic Disadvantage is derived from attributes such as low income, low educational attainment, high unemployment, jobs in relatively unskilled occupations and variables that reflect disadvantage rather than measure specific aspects of disadvantage (e.g., Indigenous and Separated/Divorced).

<table>
<thead>
<tr>
<th>Local Government Area</th>
<th>2006 SEIFA index of disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fairfield (C)</td>
<td>876.1</td>
</tr>
<tr>
<td>Auburn (A)</td>
<td>922.1</td>
</tr>
<tr>
<td>Canterbury (C)</td>
<td>927.1</td>
</tr>
<tr>
<td>Bankstown (C)</td>
<td>944.7</td>
</tr>
<tr>
<td>Campbelltown (C)</td>
<td>954.5</td>
</tr>
<tr>
<td>Botany Bay (C)</td>
<td>962.3</td>
</tr>
<tr>
<td>Liverpool (C)</td>
<td>966.4</td>
</tr>
<tr>
<td>Wyong (A)</td>
<td>966.8</td>
</tr>
<tr>
<td>Holroyd (C)</td>
<td>972.4</td>
</tr>
<tr>
<td>Blacktown (C)</td>
<td>972.8</td>
</tr>
</tbody>
</table>
Cancer Risks and Prevention Practices Among Vietnamese Refugees


**Risk factor knowledge**
- 13% never heard of cancer
- 27% did not know smoking causes cancer
- 28% believed cancer is contagious
- 48% had never heard of hepatitis B
- 35% men reported binge drinking

**Preventive health behaviours**
- Young people reported more fat and less fibre in their diet
- 32% women never had a Pap test
- 28% never had a breast examination
- 83% never had a mammogram
Tackling Hepatitis B and liver cancer in South-West Sydney

The B Positive project
'B Positive' Project
Screening and Surveillance Protocol

- Initial Enrollment
- Doctor visit every six months

**HBsAg POSITIVE**

- Tests via GP: HBsAg, HBeAg, HBV DNA, LFT’s (ALT)

  **HBV DNA LOW**

  - Routine Hepatitis Care:
    - GP-led six-monthly testing: HBsAg, HBeAg, ALT
    - Annual HBV DNA

  **ALT NORMAL**

  - Enhanced HCC Surveillance:
    - GP-led routine hepatitis care (as above):
      - Six-monthly AFP and liver ultrasound

  **ALT HIGH**

  - Special Referral (HCC Prevention):
    - Enhanced HCC surveillance (as above) AND specialist-led disease staging and treatment
    - Six-monthly AFP + liver ultrasound
    - Consider liver biopsy

**HBsAg NEGATIVE**

- Vaccine Immunisation

**HIGH ALT: ≥ 1.5 UPPER LIMIT OF NORMAL**
### B Positive program: Optimising population-level CHB management to prevent HCC

<table>
<thead>
<tr>
<th>Some issues/ questions</th>
<th>Some solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is a population-level intervention affordable – what are its costs &amp; benefits?</td>
<td>Carry out economic modelling</td>
</tr>
<tr>
<td>What are the workforce implications of such a program?</td>
<td></td>
</tr>
<tr>
<td>Facilitating follow up and recall of CHB patients</td>
<td>CHB disease Registry</td>
</tr>
<tr>
<td>Increasing CHB awareness in target population</td>
<td>Identify and address community barriers to screening and follow up</td>
</tr>
<tr>
<td>How well is CHB surveillance implemented at primary care level</td>
<td>Provide appropriate GPs support to carry out screening, follow up &amp; referral</td>
</tr>
</tbody>
</table>
Antiviral therapy for hepatitis B-related liver cancer prevention is more cost-effective than cancer screening

Monica C. Robotin¹,²,* Melrose Kansil³, Kirsten Howard², Jacob George⁴,⁵, Steven Tipper¹, Gregory J. Dore⁶, Miriam Levy⁷, Andrew G. Penman⁸

Table 3
Average costs and outcomes per patient with chronic hepatitis B treated under current practice, HCC surveillance or HCC prevention algorithms.

<table>
<thead>
<tr>
<th>Program</th>
<th>% Patients with each clinical outcome</th>
<th>Total cost per patient</th>
<th>Total QALYs per patient</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AUS (present value)</td>
<td>Present value</td>
<td>AUS per QALY gained</td>
</tr>
<tr>
<td>Current practice</td>
<td></td>
<td>2,632</td>
<td>12,527</td>
<td>–</td>
</tr>
<tr>
<td>HCC Surveillance</td>
<td></td>
<td>8,479</td>
<td>12,541</td>
<td>401,516 (vs. current practice)</td>
</tr>
<tr>
<td>HCC Prevention</td>
<td></td>
<td>14,600</td>
<td>13,450</td>
<td>12,956 (vs current practice)</td>
</tr>
</tbody>
</table>

Abbreviations: CHB, chronic hepatitis B; HCC, hepatocellular cancer; QALY, quality-adjusted life years.
Antiviral therapy for hepatitis B-related liver cancer prevention is more cost-effective than cancer screening

Monica C. Robotin\textsuperscript{1,2,*}, Melanie Kansil\textsuperscript{3}, Kirsten Howard\textsuperscript{2}, Jacob George\textsuperscript{4,5}, Steven Tipper\textsuperscript{1}, Gregory J. Dore\textsuperscript{6}, Miriam Levy\textsuperscript{7}, Andrew G. Penman\textsuperscript{8}
Relative proportion of costs attributable to elements of the B Positive program
Program costs supported mostly by the Federal government

Total discounted costs for program by payer
$ Million, discounted

- Medicare: $11.9
- PBS: $38.1
- Program: $2.9
- State: $0.3
- Patient: $1.7

Note: Discounted at 5%
Source: Economic model
B Positive challenges

- Low levels of information about hepatitis B and HCC among GPs
- Low levels of information about hepatitis B and HCC in target communities
- Hepatitis B not a priority among new migrants
- Limited support for a CHB Registry
For further details contact
Mamta Porwal
B Positive Project Coordinator
mamtap@nswcc.org.au
Ph 9334 1431

Or

Monica Robotin
Medical Director CCNSW
monicar@nswcc.org.au
9334 1727
Thank you