Community/GP based screening & management of HBV & HCV

Catherine Stedman
Department of Gastroenterology, Christchurch Hospital and University of Otago, Christchurch
Disclosures

I have the following financial relationships to disclose within the past 12 months:

- Advisory board committees or speaking for Gilead Sciences, Janssen, MSD
Case: Mr W

- 55 Maori man
- Developed pneumonia when on holiday
- During hospital admission noted to have slightly abnormal LFT
  - ALT 60; AST 58, other LFTs normal
- Hep C AB positive
- Fibroscan 20 KPa = cirrhosis
- AFP 80
Mr W

- USS normal
- AFP monthly: 80/100/120
- MRI liver: 2cm hepatocellular carcinoma
- HCC resected May 2014
Risk factors for Hepatitis C

- Injecting drug use (even once!)
- Tattoos
- Blood transfusion pre 1992
- Overseas healthcare
- Time in prison
- Sexual partner with HCV
- Mother with HCV

Especially baby boomers
Risk factors for Hepatitis C

- Injecting drug use (even once!)
- Tattoos
- You cannot tell by looking at the patient
  Check the HCV Antibody
- Sexual partner with HCV
- Mother with HCV

Especially baby boomers
Hepatitis Foundation Public awareness / targeted testing campaign

Can you say yes?

I've injected drugs
I got a tattoo or body piercing using unsterile equipment
I had medical attention when I was overseas
I had a blood transfusion prior to 1992
I've been in prison

If you can say yes to any of these, get tested for hepatitis C. It can be treated.

Talk to your doctor or get a free test from The Hepatitis Foundation of New Zealand. Call 0800 33 20 10 or visit www.hepatitisfoundation.org.nz. Hepatitis C. Know it. Test it. Treat it.
What advice should I give my patient with Hepatitis C?

- **Reduce alcohol**
  - NO alcohol if advanced liver fibrosis

- **Reduce cannabis**
  - Cannabis increases liver fibrosis

- **Encourage coffee**
  - Protective effect on liver

- **Healthy weight**
  - - avoid additive effect of fatty liver

- **Women with HCV - test their children**
What advice should I give my patient with Hepatitis C?

- “Get your liver assessed”
- Liver biopsy seldom required now
What advice should I give my patient with Hepatitis C?

- “Get your liver assessed”
- Fibroscan now allows non-invasive assessment of liver fibrosis for patients with hepatitis C
Fibroscan for HCV: non invasive assessment of liver fibrosis

Excellent at separating:

- Normal liver (F0/F1)
  - No rush to treat HCV
  - No need for USS surveillance

From:

- Advanced fibrosis (F3/F4)
  - HCV Treatment more urgent and difficult
  - Requirement for HCC surveillance (USS)
Disease progression in hepatitis C:

- Normal liver
- Acute infection
- Chronic infection (80%)
- Chronic hepatitis
- Cirrhosis (20%)
- HCC (1–4% per year)
- Slowly progressive (~75%)
- Decompensation (~20%)

Female sex, young age

≥30 years after infection

- Infection resolves spontaneously (20%)

Fast

- Slowly progressive (~75%)

20 years after infection

Alcohol use, co-infection with HIV or hepatitis B virus, fat

HCC = hepatocellular carcinoma

HCV Epidemiology and Trends
Effect of an Aging Cohort

Prevalence of Chronic HCV

Proportion with Cirrhosis

Davis G, et al Gastroenterology; 2010: 331-8
HCV Epidemiology and Trends

Increasing Liver Cancer in NZ

NZLTU 1991-2010 (n=895)
Hepatocellular Carcinoma

Early HCC
- Asymptomatic
- Detected on surveillance USS
- Curative therapies:
  - RFA
  - Surgery
  - Transplant

Advanced HCC
- Symptomatic
- Incurable
- Months to live
- Palliative chemotherapy expensive not funded
HCV: who is at risk of hepatocellular carcinoma?

- Patients with advanced liver fibrosis
- Stage 3 or 4 fibrosis (cirrhosis)
- Fibroscan >9.5KPa
- Should be offered 6 monthly USS surveillance & AFP

“Get your liver assessed”
The Hepatitis Pilot
Facilitated by The Hepatitis Foundation of New Zealand, for Ministry of Health

- Bay of Plenty DHB; Wellington sub-region (Capital & Coast, Hutt Valley, and Wairarapa DHBs)
- 2012 to 2014

Objectives:

1. To increase awareness and understanding of hepatitis C in the community.
2. To improve access to, and uptake of, HCV testing, assessment, and treatment.
3. To improve health outcomes for people living with hepatitis C.
4. To improve data quality, to enable the programme to address disease burden.
Targeted testing

Phase One (on-going)

Identify existing patients living with hepatitis C

- Use Medtech query builder to identify patients
- Refer patients to the CAS Programme for information, support, and assessments (including FibroScan®)

Phase Two (From 1 April 2013)

Identify those patients who have not yet been diagnosed

- Public awareness media campaign
- Risk factor based testing approach (GPs; CADS; NEX; Prisons; Sexual Health)
A key information resource for both health professionals and people living with hepatitis C

In New Zealand, an estimated 50,000 people are currently infected with chronic hepatitis C. However, less than 25 per cent of those infected have been diagnosed.

With timely diagnosis and appropriate course of treatment, in many cases, hepatitis C can be successfully treated and cured.

Support is available in a range of modes and formats; this website provides access to many of these.

Hep Central offers a portal to information and support for people living with hepatitis C, people who may be at risk, and professionals.

Heptatitis C. Know it. Test it. Treat it.
Communication with the patient - education and support

- Welcome pack
- Information brochures
- Sent copies of clinical letters
- Website
- Helpline services
- Quarterly magazine
Hepatitis C Treatment

Is HCV worth treating?
What are the treatment options?
Hepatitis C is potentially curable: Sustained virological response (SVR) = viral cure

- Nearly 100% of patients who achieve SVR remain undetectable during long-term follow-up\(^{1-4}\)

![Graph showing patients with SVR and duration of follow-up]

Benefits of cure in HCV advanced fibrosis

If SVR achieved:

- ↓ Risk of hepatic decompensation within 12 months
  Morgan et al Hepatology 2010; 52(3):833
- Prevent/delay de novo onset of oesophageal varices
  Bruno et al Hepatology 2010; 51:2069-76
- Over 7 years followup marked reduction in liver related mortality/morbidity and death/liver transplantation compared to non-responders
- Transplantation outcomes improve
- Ongoing risk of HCC though reduced

Morgan et al Hepatology 2010; 52(3):833
Hepatitis C Sustained Virological Response

% SVR

Genotype 1  Genotype 2/3

IFN 6mths  IFN 12mths  IFN/RBV 6-12 mths  PEG/RBV 6-12 mths

5% 11% 9% 18% 27% 65% 75% 45% 75%


Hepatitis C Sustained Virological Response
Peginterferonα/ ribavirin treatment for HCV

Poor tolerability  Peg/RBV
- Flu-like syndrome
- Anorexia, weight loss
- Insomnia
- Bone marrow suppression
- Depression

Contraindicated in some patients
Refused by many patients
Can we do better than interferon-based therapy?

“I want you to find a bold and innovative way to do everything exactly the same way it's been done for 25 years.”
Direct acting antivirals

- Inhibit HCV virus replication
Ledipasvir/Sofosbuvir in HCV Genotype 1

Efficacy: Phase 3: ION-1, ION-2, ION-3

- **ION-1**: GT 1 treatment-naïve including cirrhotics
- **ION-2**: GT 1 treatment-experienced including cirrhotics and PI failures
- **ION-3**: GT 1 treatment-naïve non-cirrhotic

<table>
<thead>
<tr>
<th></th>
<th>12 Weeks</th>
<th>24 Weeks</th>
<th>8 Weeks</th>
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<td><strong>ION-1</strong></td>
<td>99/214</td>
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97% (1886/1952) overall SVR rate

Error bars represent 95% confidence intervals.
Hepatitis C is now curable in 12-week all-oral interferon-free regimens that are relatively free of side effects.
Hepatitis C: Treatment

- Currently the only funded therapy for chronic HCV is interferon-based therapy.
- Interferon-based treatment still has a role in many patients, particularly those who can’t afford to wait.
- Clinical Trials provide access to new direct-acting antiviral drugs.
HCV: key messages

- **HCV epidemic:**
  - Increasing pool of patients at risk from HCV complications—especially “Baby Boomers”

- **Refer for assessment:**
  - Fibroscan allows non-invasive assessment of liver fibrosis

- **Treatment is changing…**
Hepatitis B

- Acute Hepatitis B
- Chronic Hepatitis B
- Cases
- Benefits of surveillance
Hepatitis B - A Global Problem

- 350 million long-term carriers worldwide\(^1\)
- Up to 25% will die due to hepatitis B or related complications\(^2\)
- ~1 million die each year from HBV infection\(^3\) (9th leading cause of death worldwide\(^4\))

75% of long-term carriers live in Asia Pacific\(^5\)

\(^1\) WHO 1998; \(^2\) Mast 1993; \(^3\) Lee 1997; \(^4\) Boag 1991; \(^5\) Gust 1996
Estimated >90,000 HBsAg+ living in New Zealand
Majority are Maori, Pacific or Asian ethnicity
Impact of Endemic HBV Infection in New Zealand

LIVER MORTALITY

- HBV: 63%
- Alcohol: 31%
- Other: 4%
- HCV: 8%

200 cases per annum

HEPATOMA CLINIC

- HBV: 60%
- Alcohol: 9%
- NASH: 7%
- HCV: 21%
- Other: 4%

120 cases per annum


Hepatitis B:

Acute Hepatitis B

vs

Chronic Hepatitis B
How is Acute Hepatitis B Acquired?
(Western Countries)

- Transfusion and transplant recipients
- Individuals with multiple sexual partners
- Newborns of long-term carriers
- Intravenous drug users
- Prisoners and other institutionalised people
- Healthcare workers
Acute Hepatitis B

- **Incubation**
  - Few weeks - 6 months (mean 60-90 days)

- **Prodrome:**
  - Serum-sickness like illness
    - (fever, arthralgia, rash 20%)

- **Acute hepatitis:**
  - 30% Jaundice
  - ALT typically 1000-2000 U/L
  - Fulminant hepatitis <1%
Acute Hepatitis B: Which serology tests?

- **HBsAg** = HBV infection compatible with acute or chronic HBV

- **Anti-HBc IgM** = acute HBV
  
  1\textsuperscript{st} to be positive
Acute Hepatitis B: Management

1. Monitor LFTs, INR, creatinine, albumin weekly until improving
   - Refer if INR/creatinine ↑ or albumin ↓

2. Screen/vaccinate contacts

3. Follow up: HBsAg, anti-HBs
   - HBsAg negative by 12 weeks in 80% of cases
   - Refer if HBsAg remains positive

Most Acute Hep B is self-limited
How is Chronic Hepatitis B Acquired?

- Transfusion and transplant recipients
- Early childhood/Newborns of long-term carriers
- Individuals with multiple sexual partners
- Healthcare workers
- Intravenous drug users
- Prisoners and other institutionalised people
1984: NZ Kawerau Community Study

- Township built in 1953 around paper mill
- Population 10,000, predominantly Maori
- 98% of population screened

Mode of HBV transmission is early horizontal **not just vertical**

HBV Vaccination: Reduces HCC Incidence and Mortality*

*Nationwide vaccination in Taiwan, implemented July 1984.
Hepatitis B: Prevention

An Ounce of Prevention is Worth a Pound of Cure
Questions to identify people at risk of Chronic Hepatitis B

- Where were you born?
- Ethnic background?
- Is there hepatitis B in your family?
NZ National HBV Screening Programme

Prevalence according to Ethnicity

- Maori: 5.8%
- Cook Is: 7.4%
- Niuean: 9.1%
- Tongan: 13.3%
- Indian (50,000): 0.6%
- SE Asian (20,000): 9.3%
- Chinese (72,500): 9.4%

Consequences of chronic HBV infection

- **Normal**: 60% of the population
  - Liver stays normal for many years

- **Chronic HBV infection**: 40%
  - Liver damage = the result of unsuccessful attempts to clear infected hepatocytes in the immunoclearance stage of disease

- **60%**

**CIRRHOSIS**

**CIRRHOSIS/ESLD**

**HCC**
Hepatitis B: Initial Investigations

1. HBV serology
2. LFTs
3. CBC, INR, albumin
4. USS /AFP
   - screen for cirrhosis, portal hypertension and HCC
5. HBV DNA (viral load)?
Hepatitis B serology

Envelope containing HBsAg
Defines infected state (acute or chronic)

Chronic infection if present > 6 months

Anti-HBs:
• Marker of resolved infection or vaccination
• Occasionally seen in chronic carriers
HBV: other Serology and Viral Loads

Anti-HBc total (HBcAb)
- **Exposure** to HBV (present or past infection)
- Can differentiate whether anti-HBs from vaccination or prior infection

Viral Load (HBV DNA)
- Correlates with infectivity and risks of cirrhosis and hepatocellular carcinoma
- **Used in decisions re treatment**

Hepatitis B serology

HBeAg +ve (HBcAg)
High viral load = Infectivity

May be absent in some mutations

Anti-HBe
? consistent with lower-level viral replication

But: Present in HBeAg negative hepatitis
Hepatitis B serology

HBeAg +ve (HBcAg)
High viral load = Infectivity

May be absent in some mutations

HBeAg status helps determine phase of Hep B infection

replication

But: Present in HBeAg negative hepatitis
# 4 Phases of Chronic HBV Infection

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<th>Inactive Carrier State</th>
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**Optimal treatment times**
Case 1: Miss AC

- 21 year old woman (student), born in Hong Kong
- Hepatitis B diagnosed at age 15 years
- Investigations:
  - HBsAg +
  - HBeAg +, anti-HBe –
  - HBV-DNA > 1.1 x 10^8 IU/mL
  - ALT 19 u/L (repeatedly)

Chronic Hepatitis B: Immuno-tolerant phase

Lots of VIRUS
NO liver inflammation
4 Phases of Chronic HBV Infection

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Optimal treatment times
Management of Immuno-tolerant Phase

- Safe to monitor mid-teens to twenties if ALT normal

- FOLLOW UP crucial:
  - Check LFTs (x3 initially)
  - Then 6 monthly LFT and Hep B serology (Hepatitis Foundation)

- Screen and vaccinate close contacts

While LFTs normal WAIT but WATCH CAREFULLY
Case 2: Ms VN

- 36 year old woman, migrated from Vietnam
- HBV infection diagnosed incidentally (HBsAg+)
- Investigations:
  - HBeAg+, anti-HBe–
  - HBV-DNA $1.2 \times 10^7$ IU/mL
  - ALT 165 u/L, AST 120 u/L
  - Liver biopsy - hepatic fibrosis + inflammation

HBeAg +ve hepatitis (immune clearance phase)
4 Phases of Chronic HBV Infection

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Optimal treatment times
Hepatitis B Antivirals

- Lamivudine 100mg/day or Entecavir 0.5mg/day
- Adefovir 10mg/day or Tenofovir 300mg/day

Pros:

- Oral agents
- Minimal side effects
- Suppress virus well (initially)
- Only option in decompensated patient - may recover liver function

Cons:

- Indefinite therapy
- Drug resistance (& cross-resistance)
- Pregnancy issues
Practical aspects of Hep B treatment

**Goal:** good immune control or *undetectable* HBV DNA on drugs

**Interferon:**
- specialist hepatitis nurses monitor patients

**Direct acting antivirals**
1. Detectable virus = risk of resistant mutations
   - Avoid interrupted dosing (mutations/ resistance)
2. Never stop abruptly (risk of fatal flares)
3. Watch creatinine (adefovir/tenofovir)
4. Pregnancy: discuss with specialist (switch to tenofovir)

Maintain continuous drug supply
Hepatitis B: Initial Investigations

- If ALT abnormal: refer to secondary care
  - e.g. ALT >60 x2 results- or single higher value
Case 3: Mr. AT

- 35 year old man born in China
- Hepatitis B sAg+ve on “check-up”
- No abnormal physical findings
- Investigations:
  - HBeAg –, anti-HBe +
  - HBV-DNA not detected
  - ALT: 3 x over 3 months all normal

Hepatitis B: Inactive Carrier
4 Phases of Chronic HBV Infection

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Hepatitis B: Inactive Carrier

- If initial LFTs, INR, platelets, AFP normal, then refer to Hepatitis Foundation for enrollment in Hep B Screening Programme
  [www.hepatitisfoundation.org.nz](http://www.hepatitisfoundation.org.nz)
- Screen/vaccinate contacts
- ALL Hepatitis B patients need monitoring
- Risks:
  - Active Hepatitis
  - Hepatocellular Carcinoma

Beware immunosuppression: risk of flare!
HBV investigations: “alarm” signs

- Thrombocytopenia (<150)
  - suggests cirrhosis, hypersplenism and portal hypertension
- Prolonged INR
- Low albumin
- ALT/AST ratio: if inverted (AST>ALT) - suggests cirrhosis (or alcohol)
- Raised AFP

Refer urgently to secondary care
What are the long-term benefits from the national HBV screening programme?

~20000 enrolled from initial screening programme and primary care referrals
National HBV Screening Follow-up Programme: Surveillance for Hepatocellular carcinoma

- **ALL HBsAg+**
  - Inactive HBsAg → LOW RISK → 6 mthly AFP & LFT
  - **Male CHB >40**
  - **Female CHB>50**
  - **Stage F3/F4** or **Family Hx HCC** → HIGH RISK → 6 mthly AFP and U/S

**National HBV Screening Follow-up Programme:**

Surveillance for Hepatocellular carcinoma
### Characteristics of NZ Hepatoma 2000-2009

#### Comparison between Screened and Non-screened Tumours

<table>
<thead>
<tr>
<th>Feature</th>
<th>Screened (n=284)</th>
<th>Non-screened (n=374)</th>
<th>p-value</th>
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<tr>
<td>Larger than 5cm</td>
<td>26%</td>
<td>28%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Multinodular Tumour</td>
<td>83%</td>
<td>64%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Bilobar Tumour</td>
<td>16%</td>
<td>46%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>PV Thrombosis</td>
<td>6%</td>
<td>38%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Metastasis</td>
<td>3%</td>
<td>29%</td>
<td>p&lt;0.001</td>
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Median tumour size: 3cm vs 8cm (p<0.001)

Treatment of NZ Hepatoma
Screened vs Non-screened tumours

**Survival: Hepatocellular Carcinoma**

Screened vs non-screened HBV tumours

- **Screened group**
  - Median survival = 2931 days
  - n = 284
  - Log-rank: P<0.0001
  - Cumulative Survival: 81% at 730 days, 56% at 1460 days, 50% at 2190 days

- **Non-screened group**
  - Median survival = 130 days
  - n = 374
  - Cumulative Survival: 27% at 730 days, 5% at 1460 days, 2% at 2190 days

Hepatitis B: Key Points

1. Hepatitis B major cause of morbidity and mortality
2. Vaccinate!
3. Screen NZ Maori, people from Asia-Pacific and known contacts for HBsAg
4. All Hepatitis B carriers require lifelong monitoring
   - 6 monthly LFT and AFP
   - IF HBeAg positive then HBeAg and anti-HBe should also be monitored
   - Hepatitis Foundation NZ can assist
Chronic Hepatitis B: Key Points

5. Who to refer to secondary care?
   **Refer** - if ALT raised or AFP elevated
   - HBeAg positive patients greater than 30
   - Anyone with alarm features ↓ platelets,
     ↓ albumin, ↑ INR

6. HCC screening: refer to Hepatitis Foundation

7. Patients on antiviral treatment: patient *adherence* to continuous therapy is crucial

8. Treatment guidelines can change