HEPATITIS DIAGNOSTIC DILEMMAS

Dr Mike Catton

VIDRL

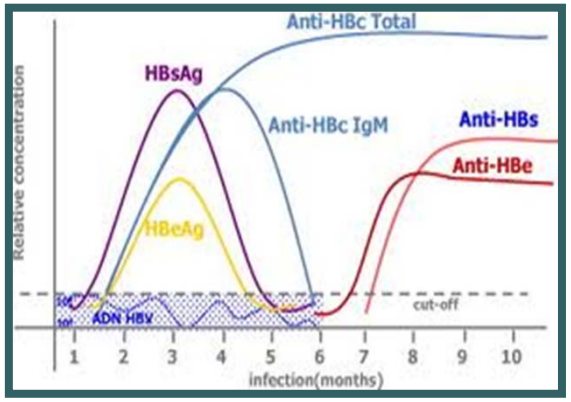
VIDRL
Victorian Infectious Diseases Reference Laboratory

Interpretation of Hepatitis B Serologic Test Results

HBsAg anti-HBc anti-HBs	negative negative negative	Susceptible
HBsAg anti-HBc anti-HBs	negative positive positive	Immune due to natural infection
HBsAg anti-HBc anti-HBs	negative negative positive	Immune due to hepatitis B vaccination
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	positive positive positive negative	Acutely infected
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	positive positive negative negative	Chronically infected

Adapted from: A Comprehensive Immunisation Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunisation Practices. Part 1: Immunisation of infants, Children, and Adolescents. MMWR 2005:54 (No.RR-16)

1. Isolated Hepatitis B core Antibody



- Anti-HBc is directed against HBV capsid peptides
- Earliest antibody marker of acute hepatitis B:
  - Predominantly IgM-anti-HBc ~ 6-8 weeks
- Typically persists for life
  - Predominantly IgG-Anti-HBc ~ 6 months
- IgM-anti-HBc detectable at very low levels often years into chronic HBV infection
- Isolated anti-HBc = anti-HBc without either HBSAg or HBsAb
- Generally anti-HBc laboratory tests measure total (IgM + IgG) anti-HBc unless IgM requested.

Potential Causes of Isolated Hepatitis B core Antibody

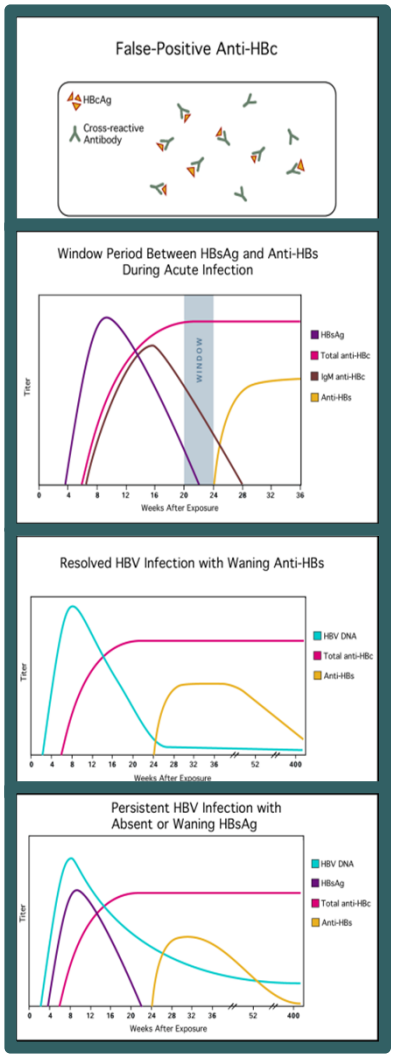
Frequency:

- Relates directly to HBV prevalence in test population
- Blood donors in low prevalence areas: 0.4 – 1.7%
- Endemic areas; 10-20-%
- May be high frequency sub-populations: IVDU, HIV infected, chronic HCV

Potential Causes:

- False positive test
- IgM-anti-HBc during acute HBV window period
- Resolved HBV without anti-HBs development
- Chronic occult HBV infection

Potential Causes of isolated anti-HBc



- **False positive anti-HBc**
  - Non-specific binding
  - Likelihood inversely related to HBV prevalence
- **Window period**
  - Anti-HBc appears as IgM $\geq$ 12 weeks
  - Between resolution of HBsAg and appearance of anti-HBs, anti-HBc may be sole marker
  - Usually other evidence of acute hepatitis: transamintis etc.
- **Resolved HBV infection**
  - Generally the most common scenario
  - Particularly common in high prevalence populations
  - Waning anti-HBs
  - Challenging to prove: HBV DNA will (generally)be negative, detection of anti-HBe helpful.
- **Occult Chronic HBV**
  - Actively replicating HBV at low levels
  - No HBsAg production
  - Biological basis poorly understood
  - Even anti-HBc not detectable in some cases
  - Typically HBeAg and anti-HBe tests negative
  - Diagnosis requires sensitive detection of HBV DNA

Management of Isolated anti-HBc

- **Patients with no risk factor history**
  - Consider the test likely false positive
  - Repeat test, test a second specimen etc.

- **Patients with risk factors**
  - Variety of options
  - Repeat anti-HBc test then vaccinate x 3 if negative, or vaccinate x 1 and check for anti-HBs anamnestic response

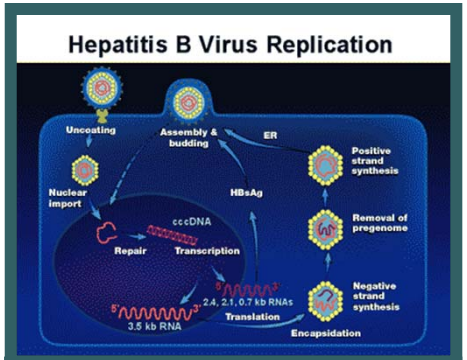
- **Patients with biochemical evidence of hepatitis & risk factors**
  - HBV DNA test ± IgM anti-HBc
  - Anti-HBs test in several weeks.

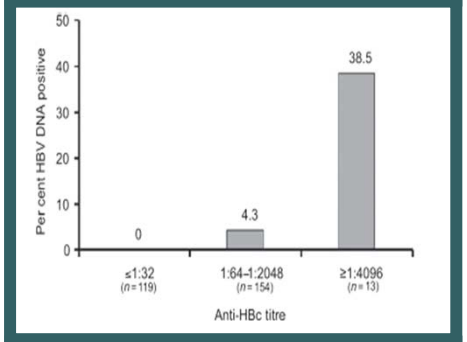
- **Unexplained persistent transaminitis**
  - HBV DNA test

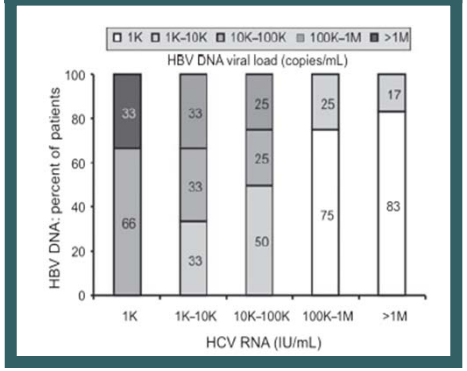
Transmissibility of HBV from isolated anti-HBc positive patient

- Infectiousness of such patients not precisely defined
- HBV DNA detectable in up to 14%, but generally low levels.
- Isolated reports of HBV transmission by blood or transplant
- Contradicted by relatively large studies showing no transmission
- Conclude risk is generally low, except where large exposing blood volumes: transfusion or liver transplant
- No studies have estimated sexual transmission risk.

2. Occult Hepatitis B Infection







- Two main characteristics: absence of HBSAg and low viral replication
- First reported 30 years ago as post transfusion infection case report
- Only extensively studied since 2000
- Prompts re-examination of understandings regarding HBV clearance/immunity

Definition

- Persistence of HBV genomes in liver tissue ± serum
- Associated with negative HBSAg serology
  - 'seropositive': anti-HBc (50%) and/or anti-HBs (35%)
  - 'seronegative': no anti-HBc or anti-HBs (20%)

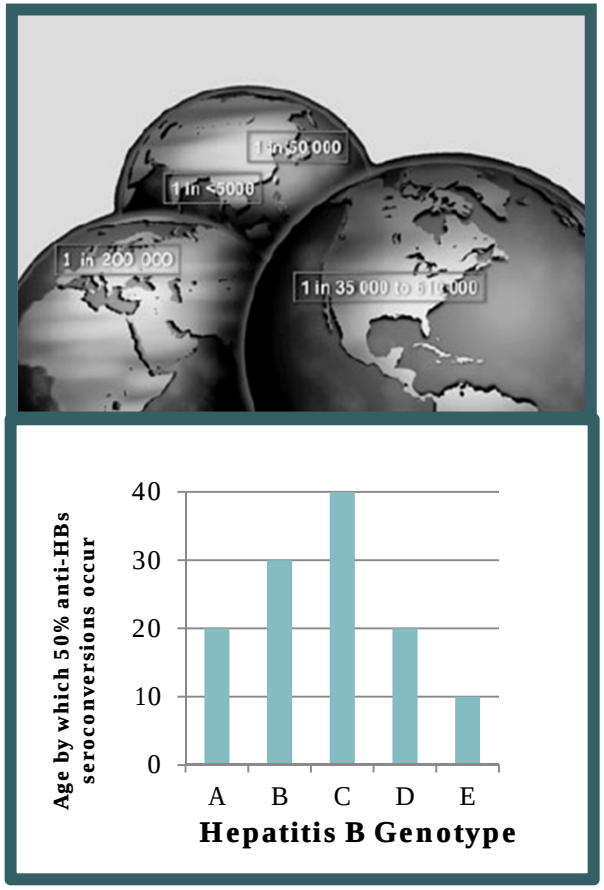
Molecular Basis

- Persisting episomal ccc DNA in cell nuclei

Mechanisms

- Recovery from acute infection with viral persistence in sanctuaries (liver)
- Undetectable HBSAg at the tail of chronic carriage (non-replicative phase)
- Escape mutants interfering with HBSAg synthesis/detectability
- Interference by coinfecting viruses (HCV)

Epidemiology



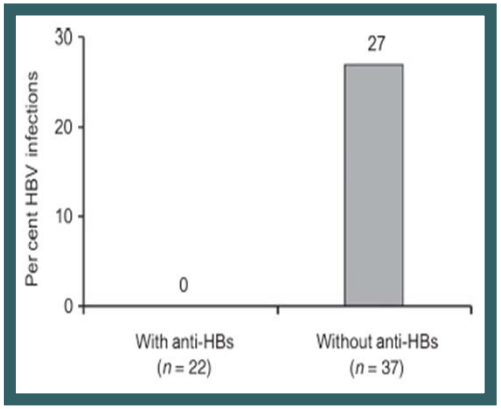
- Prevalence varies greatly globally (methodology varies between studies)
- Detected prevalence will vary with sensitivity of HBV NAT (↑) & HBsAg test (↓)
- Prevalence varies with HBV endemnicity:
  - Low endemnicity, (5% HBV prevalence) 0.1-2.4% OHB
  - Sexual transmission/IDU → resolved infection → late loss anti HBs → OHB
  - High endemnicity, (70-90% HBV prevalence) ≤6% OHB
  - Vertical/horizontal transmission → chronic infection → late loss HBsAg → OHB
- Prevalence varies with genotype
  - Based on how early anti-HBe conversion occurs in each genotype
  - More frequent where genotypes A, D, E prevalent
  - Less frequent where genotypes B & C prevalent

Epidemiology

Prevalence also varies with the population studied. Well established that high risk groups exist.

▪ Chronic HCV infection	15-33%
▪ HIV infection	10-45%
▪ IDU	45%
▪ Haemodialysis patients	4-27%
▪ HCC patients	62%
▪ Cryptogenic liver cirrhosis	32%
▪ Liver transplant patients	64%

Clinical Significance

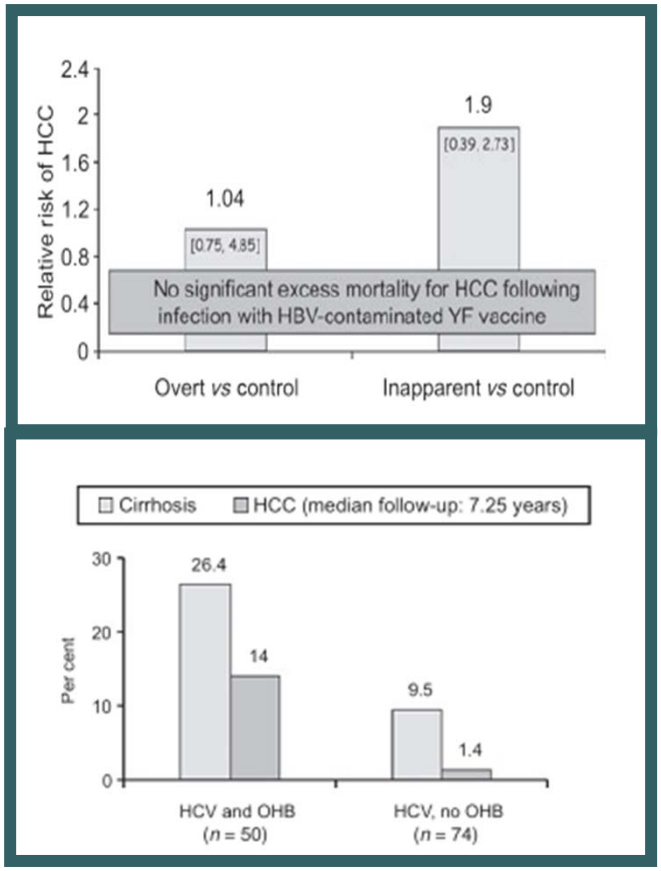


- Greatest significance is difficulty of detection via conventional screening
- Hence possible threat of transfusion/transplant transmissibility
- Clinical significance for individual affected patient is controversial

Transmission

- Risks variable: 0.4-90%
  - greatest when livers from anti-HBc pos donors given to seronegative recipients.
- Transfusion recipients
  - donor anti-HBS seems protective for chimpanzees and human recipients
  - immunosuppresed recipients at risk
  - DNA + anti-HBc represents transmission risk
  - Viral load correlates poorly with infectivity
- Transplantation
  - low transmission risk in kidney and heart and no morbidity
  - liver transplantation transmits to susceptibles at 17-94% but severity varies
  - Anti-HBc pos livers for HBsAg pos or anti HBc/anti HBs pos recipients
  - Lamivudine prophylaxis for naïve recipients

Clinical Significance



Clinical Disease:

Immunocompetent

- Immunocompetent individuals recovered from HBV, but with OHB have no clinical liver disease.
- Small early series suggested ≤ 35% of fulminant HB due to OHB, but not supported by larger more recent studies.
- Cryptogenic chronic hepatitis patients ≅ 30% OHB, but not prospective data.

Immunosuppressed

- Immunosuppresed OHB patients reactivate HBV 4-10%
- Reactivation unlikely where anti HBs> 100ml iu/l
- Highest risk in antiHBc pos/antiHBS neg bone marrow transplant patients
- Immunosuppresed OHB with cirrhosis at risk of fatal hepatitis reactivation 5-40%

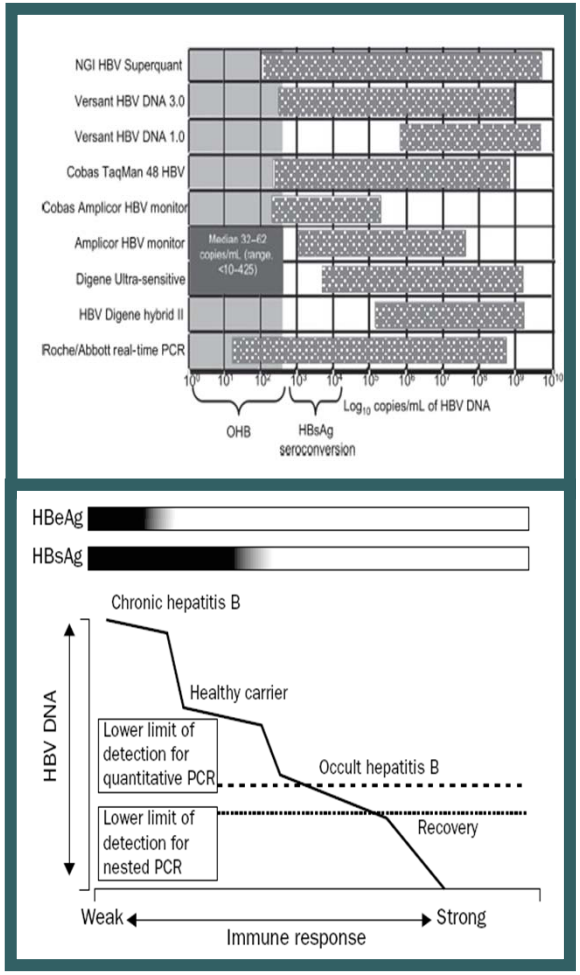
Liver Cancer

- HCC - mechanisms and probable risk of progression comparable to that in overt low grade HBV.

Co-Infected

- Common in chronic HCV infection (≤65%)
- Acute ALT flares in early HCV Rx or persistently elevated ALT in Rx non-responders
- Acceleration of progression to cirrhosis, decompensation, HCC.

Diagnosis



Assays

- Sensitive HBsAg assays consistently detecting < 0.1 ng/ml and detecting 'a' determinant mutants – excludes false negative HBsAg.
- Sensitive HBV NAT capable of detecting ≤ 10 IU/ml HBV DNA

Approach

- Testing for multiple HBV genome targets recommended (S,X, core)
- Testing of liver biopsy when available
- Periodic sampling in high risk groups for intermittent viraemia:
- Chronic HCV patients that are anti-HBc pos
- Chronic HCV infected with acute ALT flare on therapy/therapy non-responders with persistently elevated ALT.

3. HBSAg Without Detectable Anti-HBc

- **Rare**: -Hard to estimate prevalence

  -39/2169 (1.79%) chronic HBV in one study

- **Mechanisms**: -HBV core gene variants (with minor wild-type population 'helper')

  -T-Cell tolerance to HBcAg and HBeAg in children from transplacental maternal HBeAg (often transient)

  -Lack of responsiveness to HBcAg in immune compromise (HIV, chemotherapy, leukaemias etc)

  - False negative anti-HBc due to assay insensitivity

Assessment: -Verify anti-HBc and HBsAg results

- HBV DNA

- Investigate cause as required

Summary: Some More Hepatitis B Test Results

Isolated anti HBc:		
HBsAg	neg	▪ False positive anti HBc
anti HBc	pos	▪ Resolved HBV with waning anti HBs
anti HBs	neg	▪ Window period in acute infection
		▪ Occult HBV
Occult HBV:		
HBsAg	neg	▪ Resolved acute HBV with waning anti HBs
anti HBc	pos/neg	▪ Late chronic carriage with HBsAg loss
anti HBs	pos/neg	▪ Interference by coinfecting virus (HCV)
HBV DNA	Low level (neg)	▪ Escape mutant interfering with HBsAg
Isolated HBsAg:		
HBsAg	pos	▪ Lack of anti-HBc response in immune compromise
anti HBc	neg	▪ Transient T-cell tolerance to HBcAg in children
anti HBs	neg	▪ False negative anti-HBc
		▪ HBV core gene variant