



## Diagnosis of Occult Hepatitis B

Modified by: S.A. Rahim Rezaee (PhD in Immunovirology), Mashhad University of Medical Sciences, Mashhad, Iran.

The hepatitis B virus (HBV) a worldwide public health problem;

About 1/3 of the world's populations have serological evidence of past or present HBV infection.

In 2008 defined occult hepatitis B virus infection (OBI) as “the presence of HBV DNA in the liver tissue of individuals who test negative for HBsAg, by currently available assays, regardless of the detection of HBV DNA in the serum.

When detectable, the level of HBV DNA in the serum is usually very low (<200 IU/mL)”

## Phases of natural history of HBV infection

EASL guidelines on management of patients with chronic hepatitis B infection

phases	HBeAg	HBV DNA level	Aminotransferases levels	liv.necroinflammation	Fibrosis progression
Immunotolerant	+	High	normal	No or mild	No
Immunoreactive	+	High	Increased or fluctuating	Moderate to severe	Rapid
Inactive carrier st.	-	Low	Normal		Very low
HBeAg - CHB	-	High	High		Yes
HBsAg – phase (Occult BI)		Very low or undetectable		??	??

recovered (immune) subjects following self limited acute HB

**Table 2. Clinical groups at risk for occult hepatitis B**

Clinical group	Occult hepatitis B prevalence*
Chronic HCV with hepatocellular carcinoma	High <sup>16</sup>
Liver transplant recipients from core antibody positive donors	High <sup>17</sup>
Chronic hepatitis C, positive for hepatitis B core antibody	Moderate <sup>18</sup>
Cryptogenic cirrhosis/advanced fibrosis	Moderate <sup>19</sup>
Intravenous drug users	Moderate†
Routine blood donors	Low <sup>20</sup>

A representative study is referenced for each clinical group.

\*While better estimates of prevalence are needed, prevalences have been provisionally categorised as high if >50%, moderate if 10–49%, and low if less than 10%.

†Authors' unpublished observations.

## TARGET POPULATIONS FOR INVESTIGATING THE PRESENCE OF OBI

**Table 2: Categories of occult HBV carriers known to be prone to viral reactivation**

### Patients with

- Haematological malignancies
- HIV infection

### Patients who have undergone

- Bone marrow transplantation
- Liver transplantation
- Renal transplantation
- Chemotherapy
- Treatment with anti-CD20 (Rituximab)
- Treatment with anti-CD52 (Alemtuzumab)
- Treatment with anti-TNF- $\alpha$  (Infliximab)

- chronic hepatitis C especially those with flare in liver enzymes
- solid organ, hematopoietic stem cell transplantation, and blood transfusion.

17

## Definition of OBI

The presence of HBV DNA without HBsAg, with or without the presence of HBV antibodies outside the acute phase window

Adami JP. Occult hepatitis B virus infection. *Transfus Clin Biol* 2004; 11: 18-25

Presence of HBV DNA in the liver (with detectable or undetectable HBV DNA in the serum) of individuals testing HBsAg-negative with currently available assays. (and introduced a cutoff value for serum HBV DNA (< 200 IU/mL)).

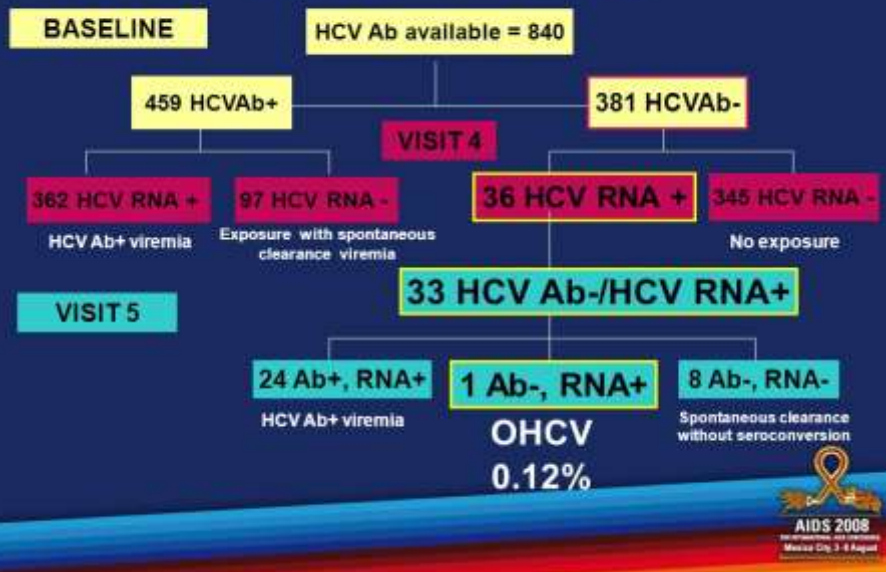
Raimondo G, et al. *J Hepatol* 2008; 49: 652-65

## Occult Chronic Hepatitis B

- HBs Ag -ve
- HBs Ab -ve
- HBe Ag -ve
- PCR <200 IU/ml
- Normal ALT
- HBc IgG Ab +ve

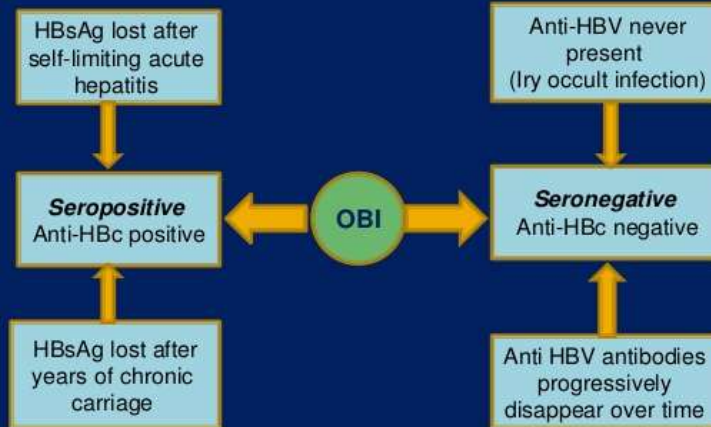
Serum hs-HBsAg could assist differentiation of occult HBV patients from individuals with only past HBV exposure.

## Prevalence OHCV

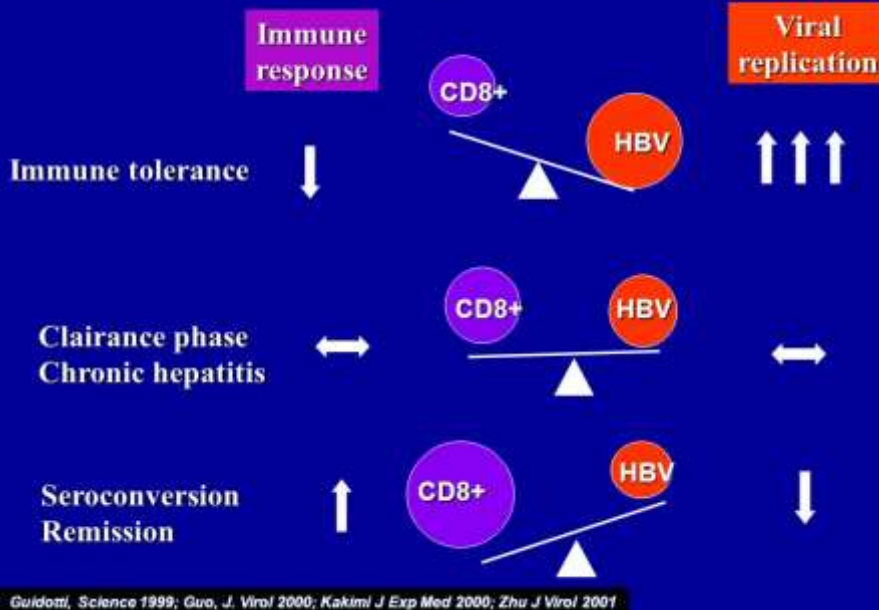


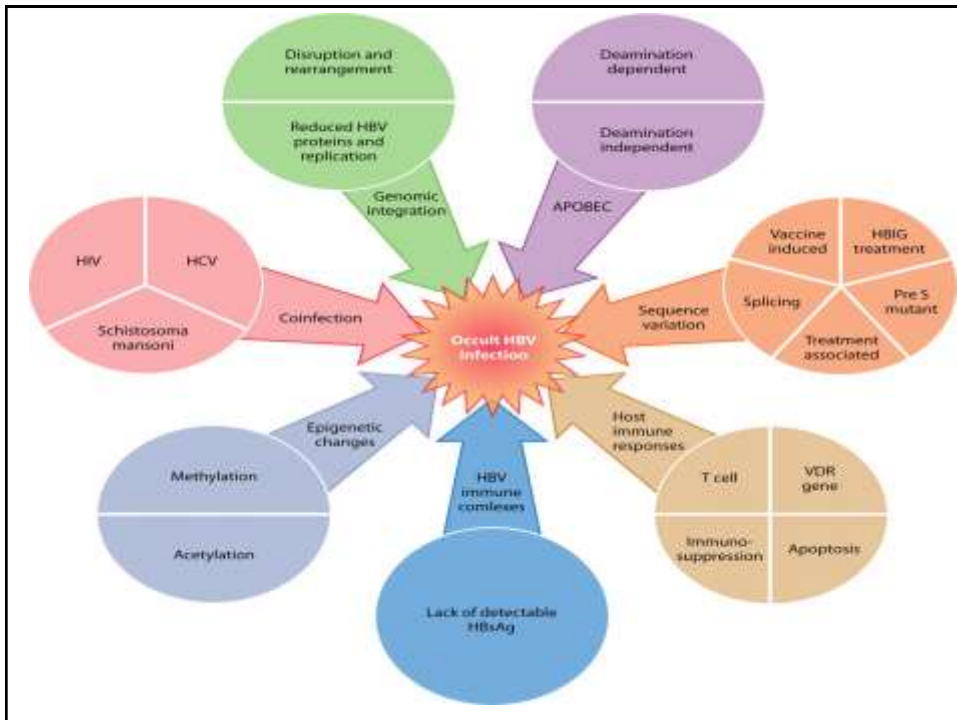
## Schematic representation of the various conditions leading to different OBI seropatterns

Science Immunopathol (2013) 35:36-52



## Immunopathology of HBV Infection

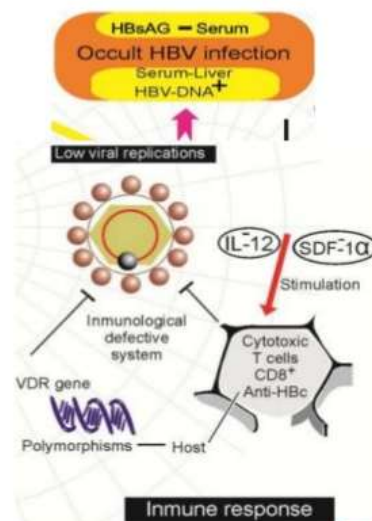




### Host Immune Responses and Occult HBV Infection:

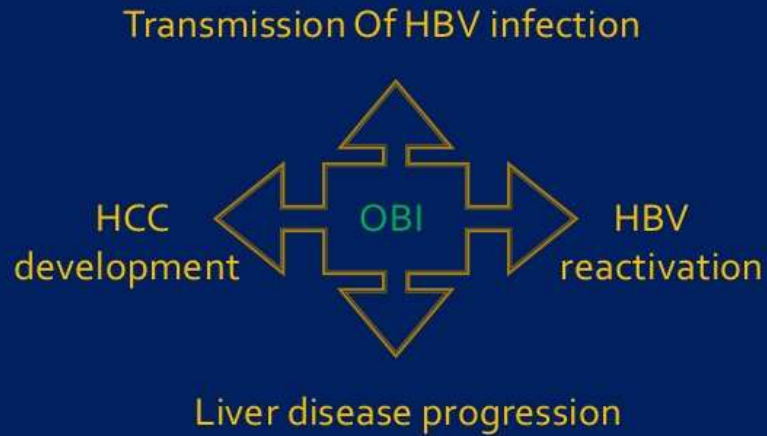
Host immune responses are involved in-

- ✚ viral clearance,
- ✚ viral persistence, and
- ✚ immunopathogenesis of HBV infection.



## Schematic representation of possible clinical impacts of occult HB infection

Giovanni Squadrito, *Ann Gastroenterol* 2014; 27(2): 15-19



**Indicative  
OBI  
Markers**

**Definitive  
OBI  
Markers**

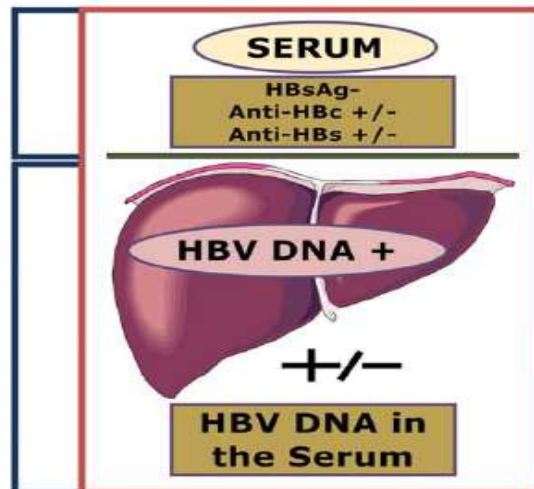


Fig. 1. Classification of OBI as suspected or confirmed OBI.

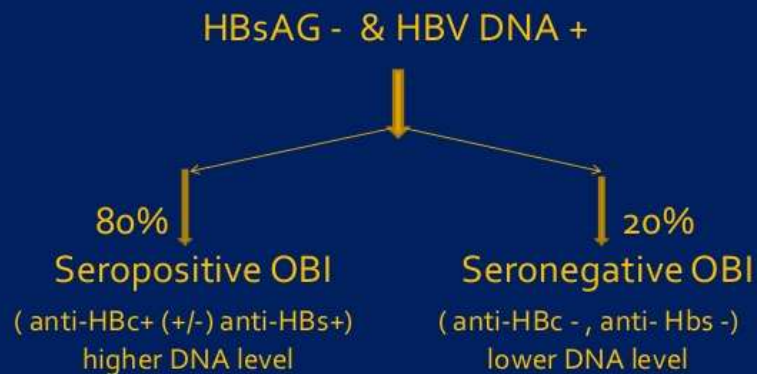
## Diagnosis of OBI

- Gold Standard : Analysis of liver tissue and blood for HBV DNA
- HBV DNA in blood by nested-PCR, real-time PCR, and transcription based mediated amplification (TMA)
- Anti-Hbc is a less than ideal surrogate marker when HBV DNA measurement is not feasible.

Raimondo G, et al. *J Hepatol* 2008; 49: 652-65

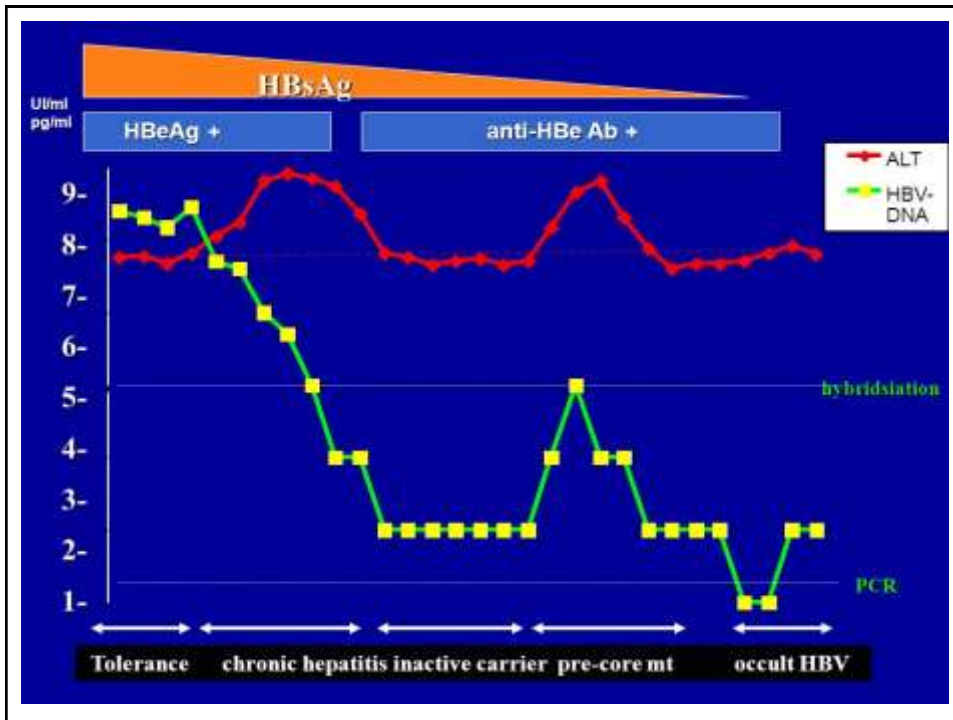
## Serological pattern of OBI

Torbenson M, Thomas DL. *Lancet Infect Dis* 2002; 2: 479-486



recovered (immune) subjects following self limited acute HB





## Definition of "False" OBI

### "False" OBI

**HBsAg negative & positive serum DNA levels comparable to levels in overt HBV infection.**

**Infection with HBV mutations in S gene (escape mutants), producing a modified HBsAg that is not recognized by some or all commercially available detection assays**

Raimondo G, et al., J Hepatol 2008; 49: 652-65

the use of multivalent anti-HBs antibodies in the HBsAg assays is strongly recommended for optimal detection of these variants

## Conclusion

### EVALUATION OF DIFFERENT OBI DIAGNOSTIC TECHNIQUES

**Liver biopsy:** Detection of HBV DNA Best way for diagnosis.

**HBsAg, Anti-HBc testing:** anti-HBc alone might reflect an occult HBV infection. **The absence of antibody does not exclude OBI (seronegative).**

**HBV DNA testing:** The gold standard test for detection of OBI is the amplification of HBV DNA(from liver or blood).

**Anti-surface antibody:** **the last antibody to appear (about three months after acute phase), and it is able to neutralize the virus.**

Anti HBs and anti-HBc to study the serological status of patients with a probable OBI.

## SEROLOGICAL PATTERN OF OCCULT HEPATITIS B INFECTION

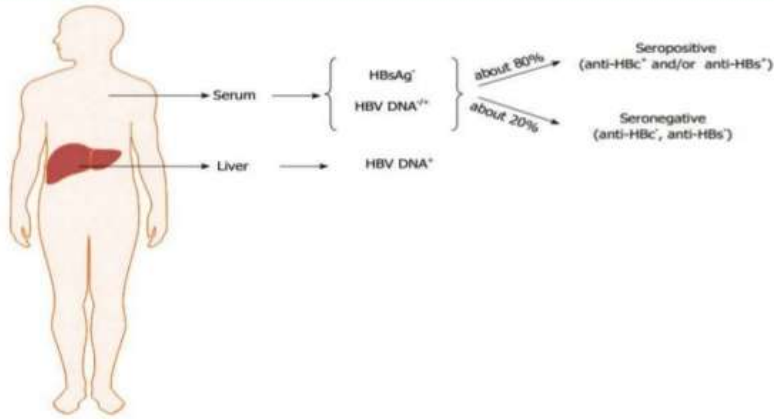
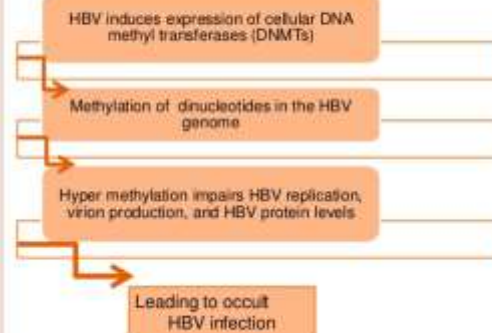


Figure 1 Schematic representation of hepatitis B virus profiles in occult hepatitis B virus infection. HBV: Hepatitis B virus.

7

## Epigenetic Mechanisms

### Methylation



11