Hepatitis B Project ECHO

March 25th, 2021
12pm Eastern Time
Reoccurring every 4th Thursday

Agenda

Introductions (10 minutes)

Project ECHO Defined and Session Format (2 minutes) *Catherine Freeland*

Didactic Presentation: HBcAb (15 minutes) *Robert Gish, MD,*

Case Presentation (5-10 minutes)

Case Feedback and Recommendations (15 minutes)

Introductions

Name, Affiliation

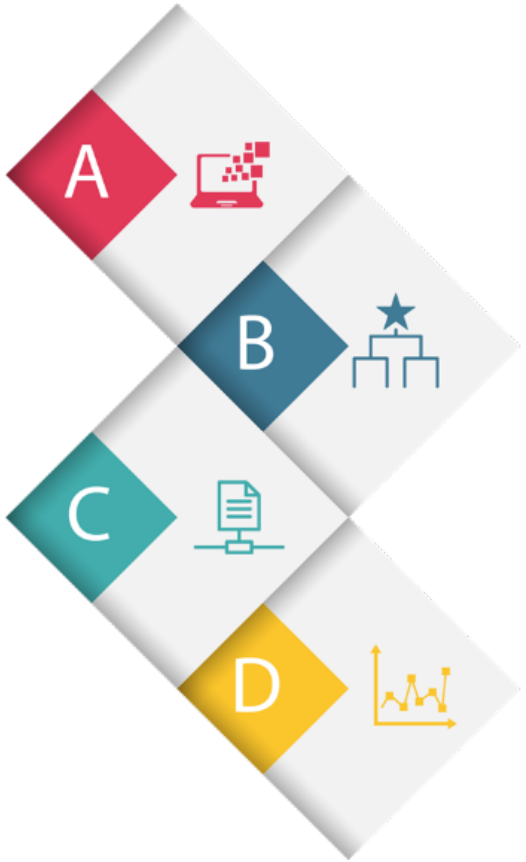
The ECHO Model

Amplification – Use **Technology** to leverage scarce resources

Share **B**est **Practices** to reduce disparity

Case Based Learning to master complexity

Web-based **D**atabase to **Monitor Outcomes**



Anti-HBc: State of the Art
What is the CORE of the Issues?

Robert Gish MD, FAASLD, AGAF, FAST
Robert G Gish Consultants LLC – Principal
Professor of Medicine – Loma Linda University
Hepatitis B Foundation - Medical Director
Adjunct Professor of Medicine:
University of Nevada Las Vegas
University of Nevada Reno
UCSD Skaggs School of Pharmacy and Pharmaceutical Sciences

Epidemiology - Worldwide

- 2 Billion People have HBV disease defined as anti-HBc(+) and who have HBV DNA/cccDNA in their liver

  have serologic evidence of exposure, and “past” or present HBV infection,
  Defined by anti-HBc +

- 292 Million HBsAg(+) Carriers WW and up to 2.4 M in the US

  are chronically infected with HBV

- 1 Million People or more WW die each year from HBV-related Chronic Liver Diseases

HBV Tests Part I:

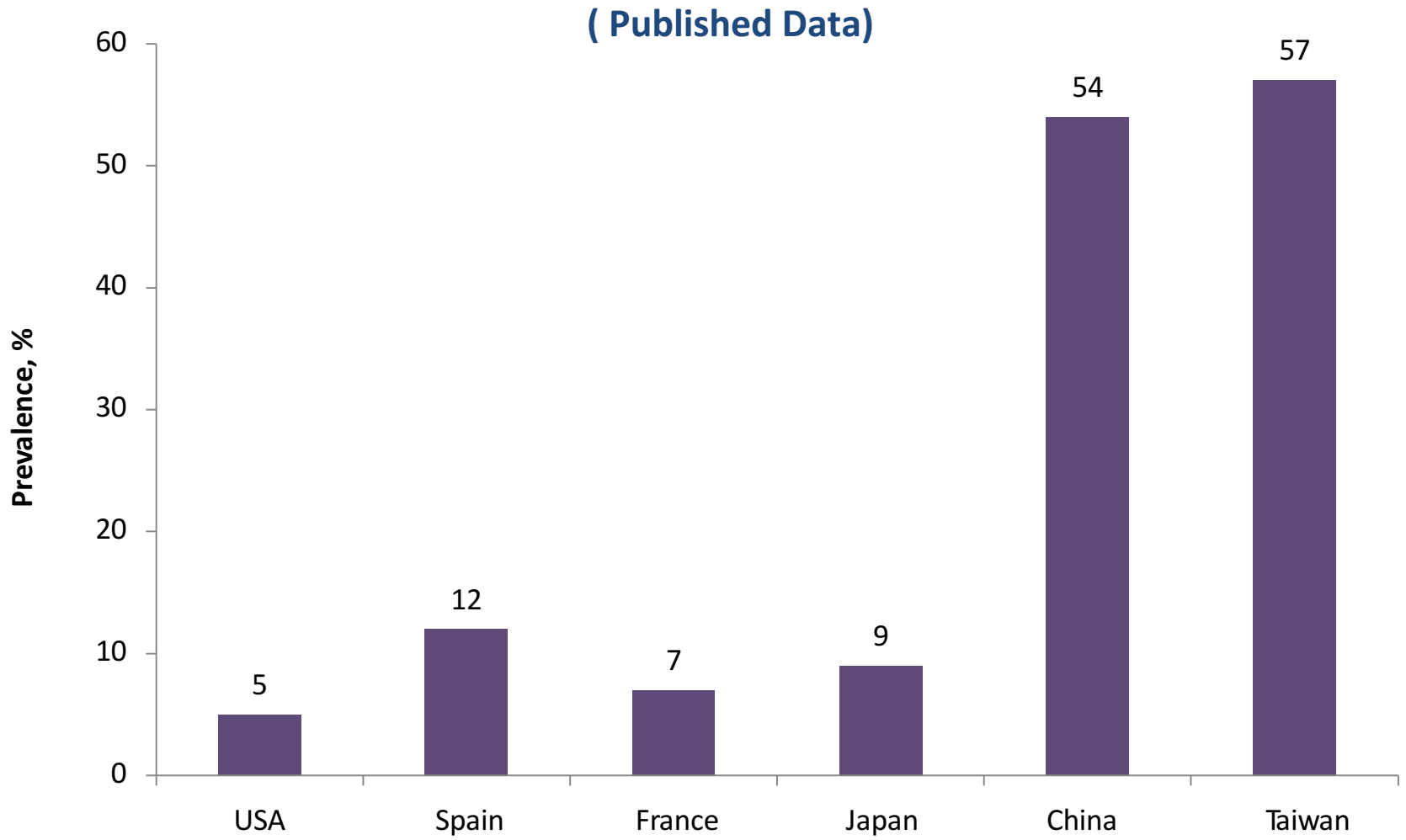
All patients need this "triple panel" when evaluating for HBV

- +HBsAg = infection (Test all patients for HDV)
- +Anti-HBc = exposure = cccDNA = persistence
  - Eval for Occult HBV if HBsAg (-) and anti-HBs(-)
  - Educate about HBV reactivation risk with HCV DAA and immunomodulating agents/treatments
  - Advise: No HBV vaccine boosting
- +Anti-HBs = immunity, ***only*** if anti-HBc is negative
- Note:
  - HBV is incurable
  - There is no "natural immunity" to HBV

What are the basic concepts?

- HBV is a DNA virus like EBV CMV HSV VSZ and is incurable, all patients have a remnant of HBV DNA in their liver in the form of cccDNA
- HBV has no natural immunity
- Anti-HBc is the test for HBV exposure = HBV infection = remnant HBV in the liver due to the life-long persistence of cccDNA
- Anti-HBc + has a false (+) rate at 0.2% even in low risk or very low risk patients
- Anti-HBc(+) indicates a gradient of risk for reactivation based on the type of immune suppression or HCV DAA treatment
  - Anti-HBs + and titers are not protective against reactivation
    - High titers of anti-HBs has a slightly lower risk of reactivation, but the risk remains substantial, a declining titer indicates a higher risk of reactivation, there is no data that “boosting” anti-HBs with a HBV vaccine dose in a patient with anti-HBc has any value
- Any HBV Vaccine dose for patients with anti-HBc(+) has no role in the peer review literature, there is no role for boosting anti-HBs

Global Prevalence of Anti-HBc Positivity among Liver Donors



- Multiple Studies
- Cholongitas E, et al. *J Hepatol* 2010;52:272-279.

Is development of anti-HBs "protective" ? In patients who are anti-HBc (only){+}?

- Historically; patients who are anti-HBs and anti-HBc(+) were considered to be "naturally" immune
- This terminology is an oxymoron
- HBV is a chronic disease and once infected patients retain HBV in nucleus the form of cccDNA in liver or portions of the virus as integrated DNA.
- HBV is similar to other DNA viruses: CMV, EBV, herpes family: there is no cure for any of these infections

The Answer Is:

- Anti-HBs (+) in the setting of Anti-HBc (+) and HBsAg (-)
- Anti-HBs provides: Some protection from reactivation if (+) after natural infection
- Higher natural titers: more protection from reactivation
- Decreasing titers: higher risk of reactivation
- This is no relevant data to support vaccine “boosting”

Summary: if anti-HBc+: use prophylaxis according to guidance document and risk

Perrillo Gastro 2015

Rituximab-Associated HBV Reactivation in Lymphoproliferative Disorders

Meta-analysis and review of FDA safety profiles

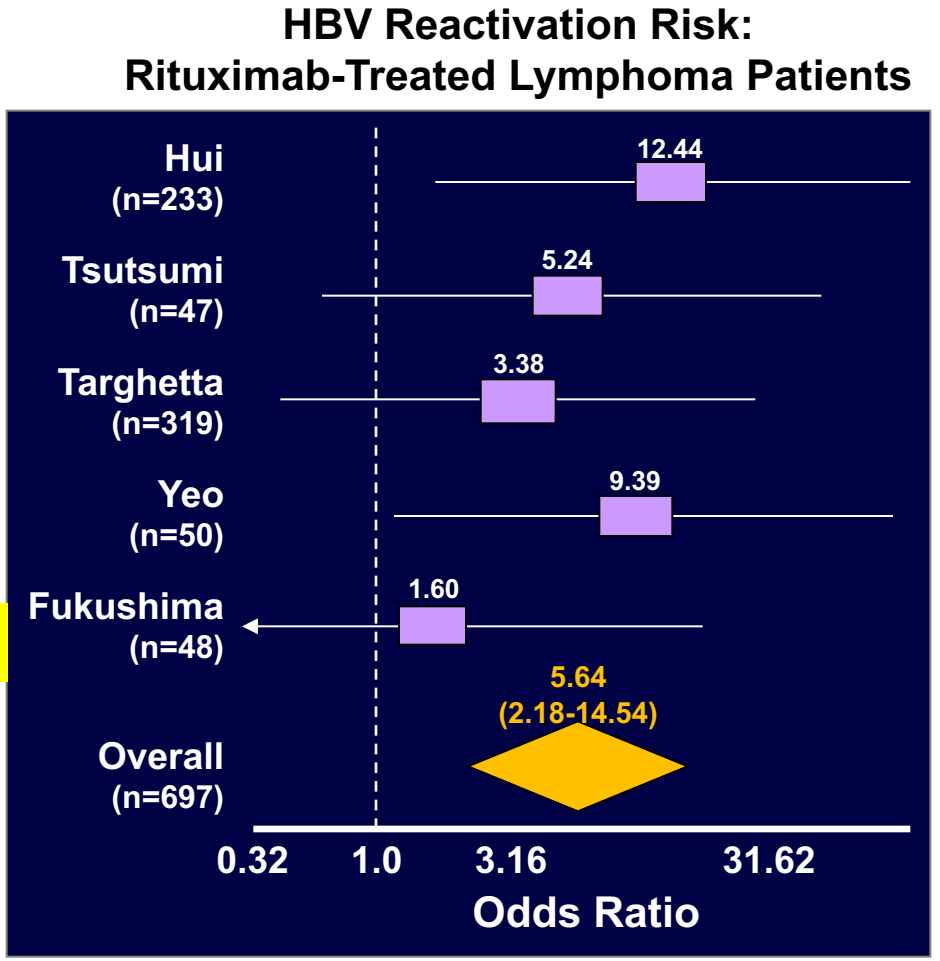
- Case reports (n=27)
- Case series reports (n=156)

Onset post last rituximab dose

- Median: 3 months (range: 0-12 months)
- >6 months: 29%

Reactivation in anti-HBc positive patients receiving rituximab versus no rituximab

- Odds ratio: 5.73 (*P*=0.0009)



Evens AM, et al. *Ann Oncol.* 2011;22:1170-1180.

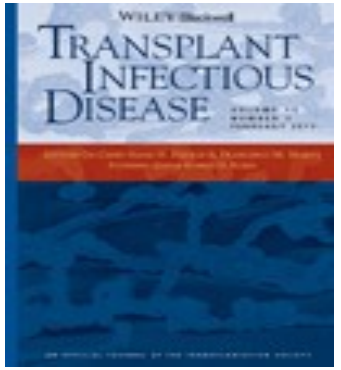
Is anti-HBs protective against reactivation: ?

Outcomes and risk factors for hepatitis B virus (HBV) reactivation after kidney transplantation in occult HBV carriers

Table 3. Logistic multivariate analysis of risk factors for hepatitis B virus reactivation

	OR value	95% CI	*P*-value
Age >60 years	11.69	2.844–48.12	0.001
Anti-T-cell antibodies	4.87	1.184–20.03	0.028
HBsAb (+)	0.046	0.009–0.241	<0.001
Lamivudine prophylaxis	0.038	0.004–0.348	0.004

OR, odds ratio; CI, confidence interval; HBsAb, hepatitis B surface antibody.



Chen GD *et. al*, **Transplant Infectious Disease**
8 MAR 2013 DOI: 10.1111/tid.12065

Antibody testing to HBc: what are the current details?

Interpretation of Results

Initial ARCHITECT Anti-HBc II Results

Initial Result (S/CO)	Instrument Flag	Interpretation	Retest Procedure
< 1.00	NONREACTIVE	Nonreactive	No retest required.
≥ 1.00	REACTIVE	Reactive	Retest in duplicate.

Final ARCHITECT Anti-HBc II Interpretation

Initial Interpretation	Results with Retest	Final Interpretation
Nonreactive	No retest required.	**Nonreactive**
Reactive	If two of the three results are < 1.00 S/CO	**Nonreactive**
Reactive	If two of the three results are ≥ 1.00 S/CO	**Reactive**

Table 1: ARCHITECT Anti-HBc II Precision

Panel member	n	Mean (S/CO)	Within Run		Total**	
			SD	%CV	SD	%CV
Negative Control	432	0.22	0.01	6.52	0.02	7.57
Positive Control	431	2.97	0.08	2.63	0.09	2.87
Human Plasma Panel 1	144	0.81	0.02	2.73	0.03	3.24
Human Plasma Panel 2	144	1.18	0.03	2.52	0.03	2.87

* Representative data; results in individual laboratories may vary from these data.

** Total is an accumulation of within run, between run and between day.

Specificity

The ARCHITECT Anti-HBc II assay is designed to have an overall specificity of ≥ 99.5% on a blood donor population and ≥ 98.0% on a hospitalized/diagnostic population. A study was performed at one internal and two external evaluation sites. A total of 5141 serum and plasma specimens collected from five blood-donation centers and 260 hospitalized/diagnostic specimens were evaluated to assess specificity.

Table 2: ARCHITECT Anti-HBc II Specificity

Category	N	IR [%]	RR [%]	Clinical Specificity	95% Confidence Interval
Overall Blood Donors	5141	44 [0.86]	41 [0.80]	99.71% (5098/5113)	99.52 - 99.84%
Blood Donor Serum	3584	25 [0.70]	22 [0.61]	99.75% (3561/3570)	99.52 - 99.88%
Blood Donor Plasma	1557	19 [1.22]	19 [1.22]	99.61% (1537/1543)	99.16 - 99.86%
Hospitalized/ Diagnostic Specimens	260	28 [10.77]	28 [10.77]	100% (231/231)	98.42 - 100%

* Representative data; results in individual laboratories may vary from these data.

Sensitivity

A total of 406 anti-HBc positive specimens from patients with acute, chronic and recovered HBV infection and signs and symptoms of HBV infection were tested, resulting in a sensitivity of 100% (406/406), 95% confidence interval: 99.10% - 100%. (Representative data; results in individual laboratories may vary from these data).

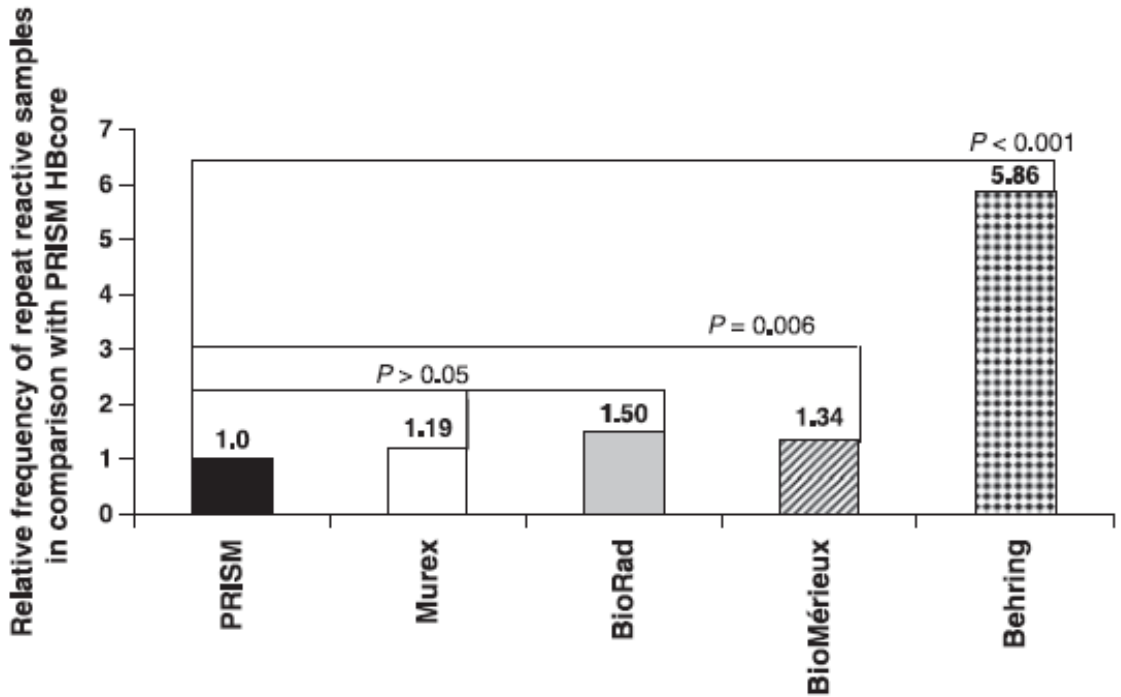


Figure 2. Relative frequencies of repeat reactive samples in different anti-HBc assays. Since samples positive by PRISM® HBcore were also positive in all other assays, the assays were normalized with respect to the relative frequency of repeat reactive samples with the PRISM® HBcore, which was set to 1.0. Diagnostic specificity was comparable for PRISM® HBcore, Murex® Anti-HBc total and Bio-Rad Monolisa® Anti-HBc PLUS, slightly reduced for bioMérieux Hepanostika® Anti-HBc Uniform and markedly reduced for Dade Behring Enzygnost® Anti-HBc monoclonal.

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Vox Sanguinis (2006) **91**, 237–243

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DOI: 10.1111/j.1423-0410.2006.00818.x

ORIGINAL PAPER

Anti-HBc screening of blood donors: a comparison of nine anti-HBc tests

M. Schmidt,[1,*] C. M. Nübling,[2,*] H. Scheiblauer,[2] M. Chudy,[2] L. A. Walch,[1] E. Seifried,[1] W. K. Roth[1] & M. K. Hourfar[1]

[1] *Institute of Transfusion Medicine and Immunohematology, German Red Cross, Johann Wolfgang Goethe University, Frankfurt, Germany*
[2] *Paul Ehrlich Institute, Langen, Germany*

All 112 anti-HBe-reactive samples were also concordantly reactive in the nine anti-HBc assays, providing strong evidence for anti-HBe as the most specific marker for a past HBV infection. Figure 2 shows S/Co values for each group according to the different anti-HBc assays. One might also consider the S/Co ratio of anti-HBc results as an indication of distinguished true and false-positive anti-HBc results: significantly lower anti-HBc signals were obtained with the anti-HBs- and/or anti-HBe-negative samples compared with anti-HBs- and/or anti-HBe-reactive samples (Fig. 2, $P < 0{\cdot}01$).

Summary of the improvements of anti-HBc test performance

1) Use a recombinant HBcAg that has a broadly prevalent serotype such as ayw

2) Use well characterized serum specimens of patients with known past HBV infection

3) Choose appropriate S/CO levels

4) Consider confirming with anti-HBe when developing new antibody testing to prove specificity

5) WHO now has the first international standard for anti-HBc which is derived from the PEI (Paul Erlich Institute) standard

When does anti-HBc appear after acute infection?

Acute hepatitis B virus infection with delayed appearance of hepatitis B core antibody in an immunocompromised patient: a case report

Abstract

Background

Despite the introduction of universal hepatitis B immunization programs worldwide, outbreaks of acute infection still occur in unimmunized individuals. A timely diagnosis of hepatitis B is necessary to ensure adequate clinical care and public health interventions that will reduce transmission. Yet, interpretation of hepatitis
B serological markers can be complex. We present a case of hepatitis B with atypical markers, including delayed appearance of hepatitis B core antibody.

Case presentation

A 62-year-old white woman was identified as a sexual contact of a male individual with acute hepatitis B virus infection. She had a history of recurrent low-grade non-Hodgkin lymphoma and had recently received immunosuppressive therapy. At baseline she had a negative serology and received three double do
ses (40 μg) of Engerix-B vaccine (hepatitis B vaccine) with a 0-month, 1-month, and 6-month schedule. One month following the last dose, hepatitis B surface antigen was positive in the absence of hepatitis B core antibody. The only sign of infection was a slight elevation of alanine aminotransferase enzymes a few m
onths after first sexual contacts with the male individual. Hepatitis B virus infection was later confirmed despite the absence of hepatitis B core antibody. The development of hepatitis B core antibody was finally noted more than 6 months after the first positive hepatitis B surface antigen and more than 12 months after elev
ation of alanine aminotransferase enzymes. Immunosuppression including rituximab treatment was the most likely explanation for this serological profile. On her last medical assessment, she had not developed HBeAg seroconversion despite lower hepatitis B virus deoxyribonucleic acid levels with tenofovir treatment.

Conclusions

When confronted with positive hepatitis B surface antigen in the absence of hepatitis B core antibody, consideration should be given to the possibility of both acute and persistent infection particularly in the setting of immunosuppression so that appropriate clinical management and public health interventions can take place. Given the increasing use of biologicals such as anti-tumor necrosis factor therapies either alone or with other immunosuppressive agents, this phenomenon may be encountered more frequently.

J Med Case Rep. 2017; 11: 111.
Published online 2017 Apr 17. doi: 10.1186/s13256-017-1264-9
PMCID: PMC5393022

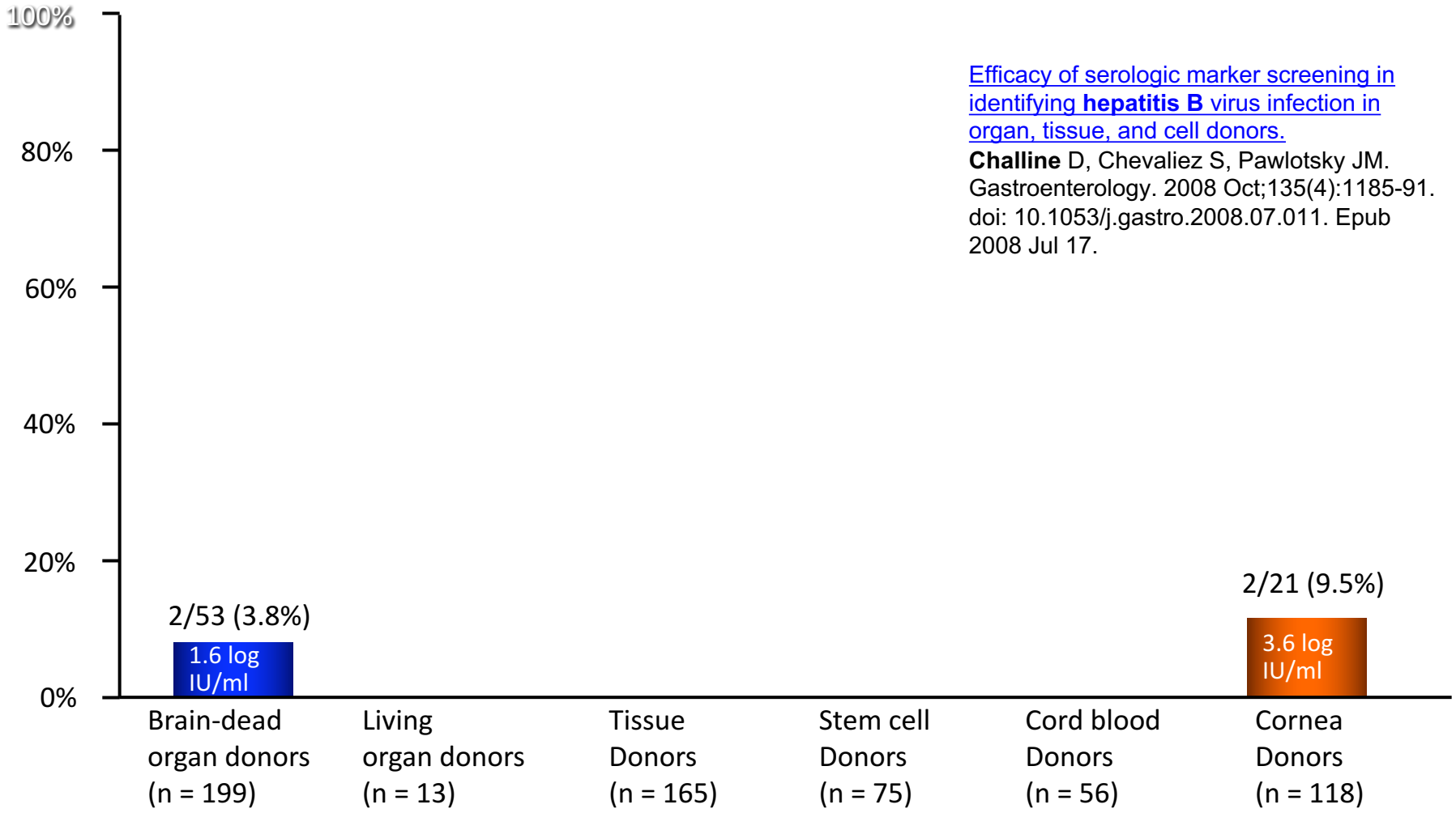
What is rate of anti-HBs(+) if anti-HBc(+) ?

- Anti-HBs(+) in 93.7% in blood donors who are anti-HBc(+)
- Inverse: Anti-HBc(+) “only” is 6% of patients tested

Sensitivity and specificity of Anti-HBc screening assays – which assay is best for blood donor screening?

M. K. HOURFAR*, L. A. WALCH*, G. GEUSENDAM†, T. DENGLER‡, K. JANETZKO‡, K. GUBBE§, K. FRANK§, A. KARL§, M. LÖHR¶, W. SIREIS*, E. SEIFRIED*, M. SCHMIDT*

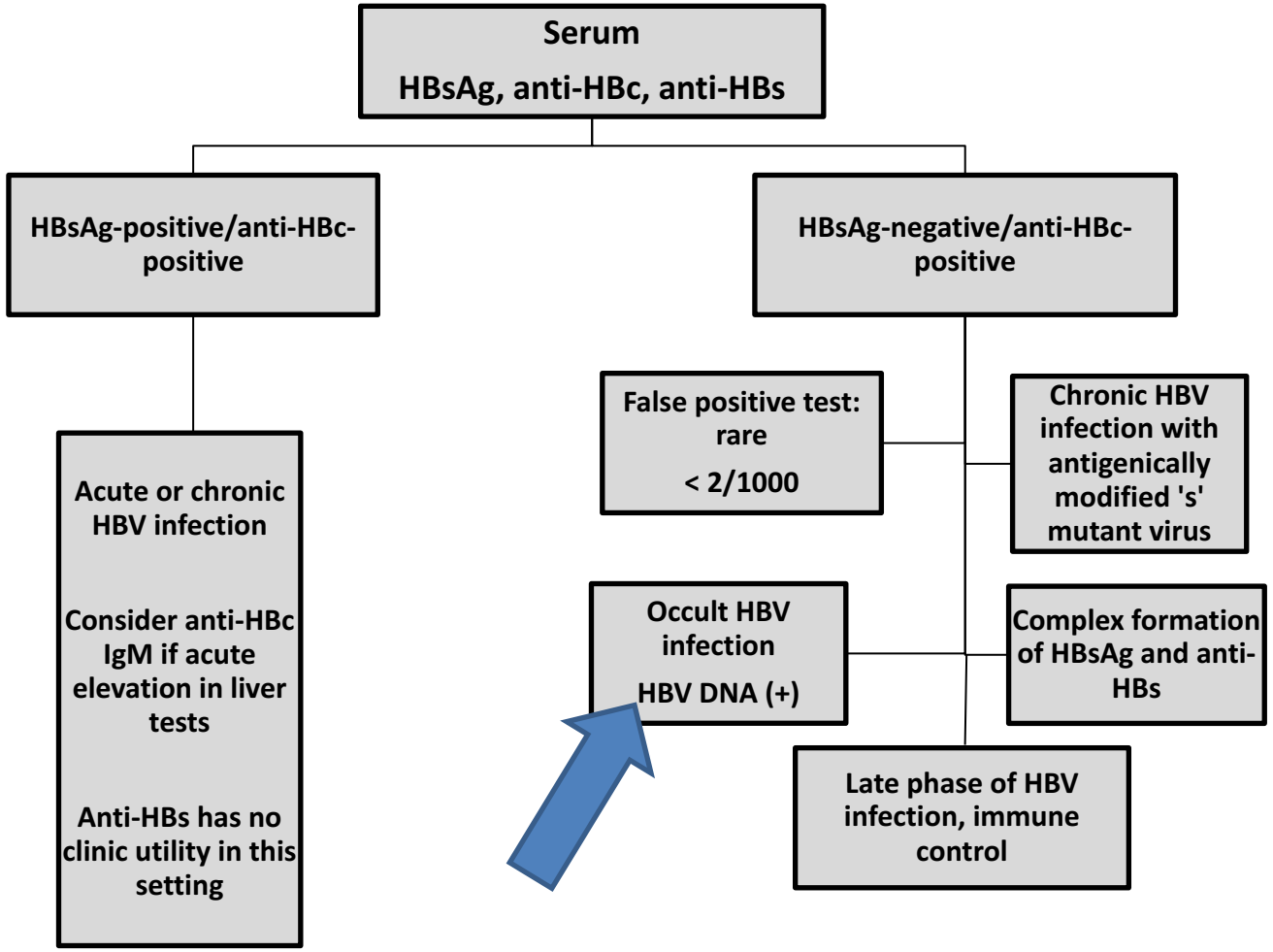
HBV DNA in Donors with Isolated Anti-HBc Ab



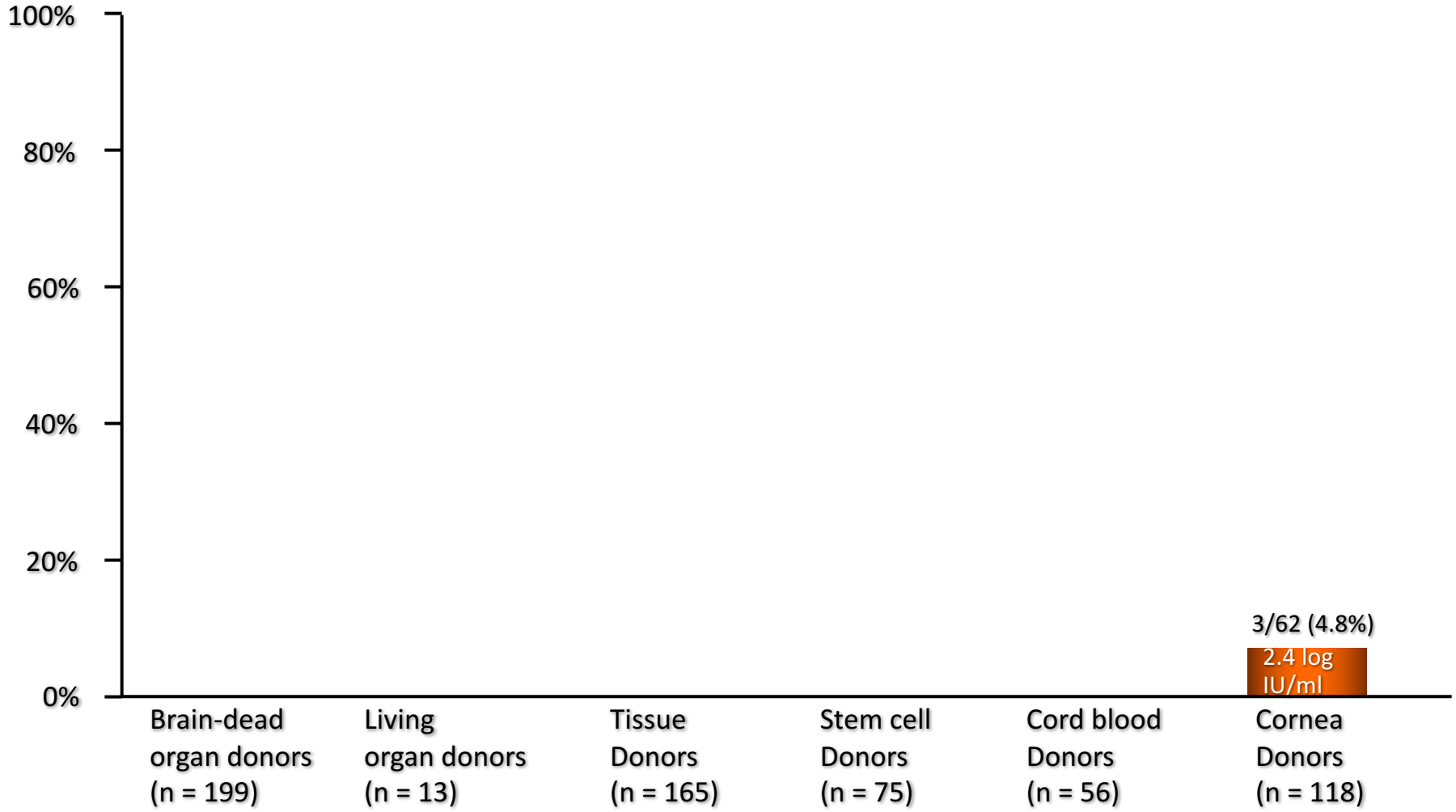
Efficacy of serologic marker screening in identifying **hepatitis B** virus infection in organ, tissue, and cell donors.
Challine D, Chevaliez S, Pawlotsky JM. Gastroenterology. 2008 Oct;135(4):1185-91. doi: 10.1053/j.gastro.2008.07.011. Epub 2008 Jul 17.

Also see Transfusion 2003;43:696-704.

A Focus on OBI



HBV DNA in Donors with Both Anti-HBc and Anti-HBs Ab



CHALLINE et al

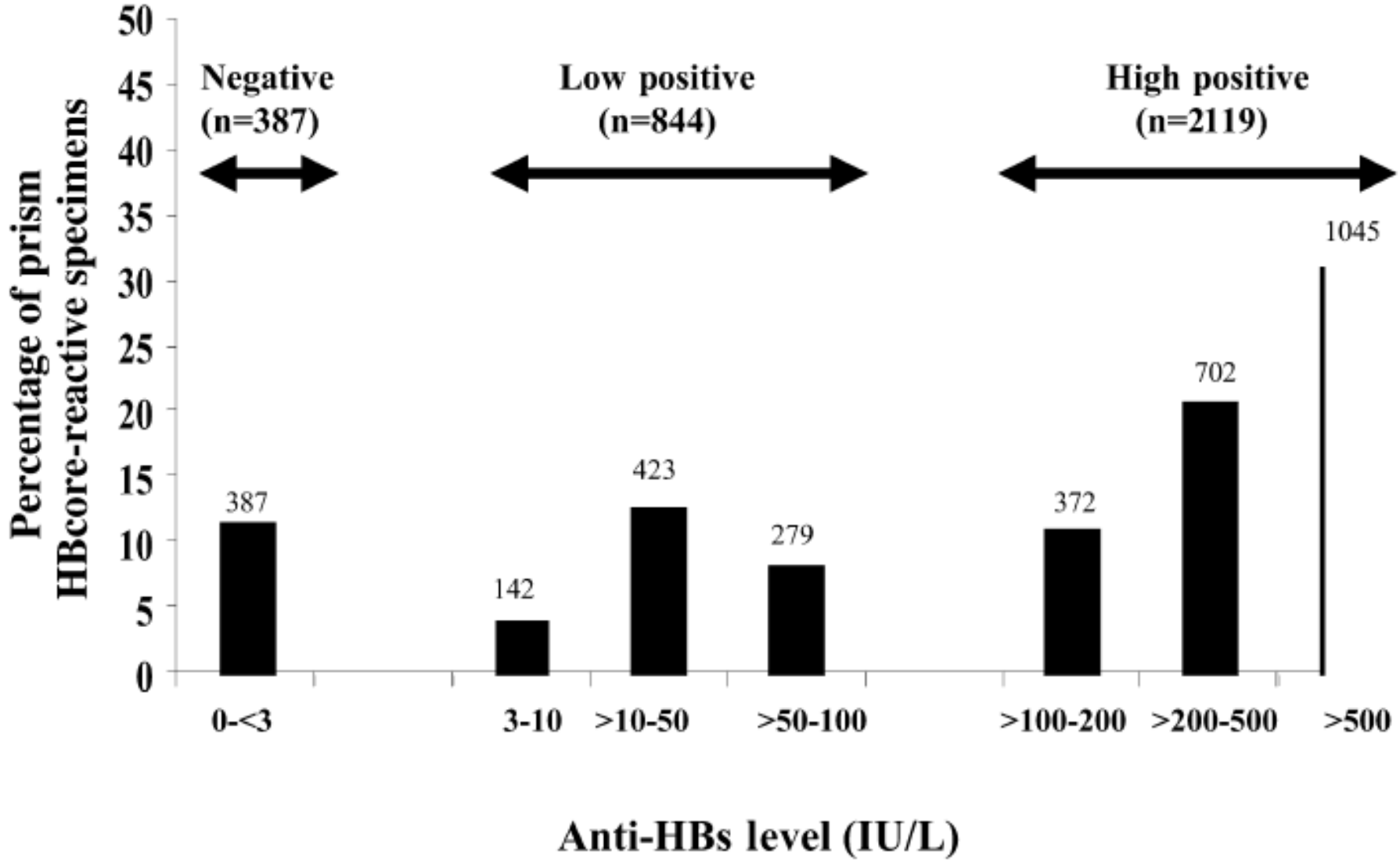


Fig. 2. Anti-HBs levels in specimens testing Prism HBcore-reactive. The 387 specimens that were negative for the presence of anti-HBs and the 844 specimens that had low levels of anti-HBs (3-100 IU/L) met laboratory criteria for HBV DNA PCR testing.

HBV DNA in “anti-HBc-only” units

Parameter	REDS	ARC	Roche
Sample dates	1991-95	2001	2002-03
No. tested	395	3,000	3,956
No. DNA-pos	4	19	14
Rate:	Calc’ted	Direct	Direct
per HBc-pos	0.24%	0.63%	0.35%
per tx unit	1:49,000	1:37,000	1:54,000
Viral Load (copies/mL)	all ≤ 100	68% ≤ 100	93% MP-NAT (-)

PRISM anti-HBc

NGI HBV UltraQual 1000

	Reactive	Non-Reactive	Total
Positive	19*	0	19
Negative **	2335 (79%)	638 (21%)	2973
Total	2354	638	2992

* Mean S/CO = 0.14 (range 0.02-0.49); S/CO $\leq$ 1.00 = Reactive

** 7 Samples PCR Negative; PRISM HBcore QNS

Interpretation HBV serologic test results for HBV infection and Further Actions

	Profile 1	Profile 2	Profile 3	Profile 4	Profile 5
1. HBsAg	Negative	Negative	Positive	Negative	Negative
2. Anti-HBc	Negative	Negative	Positive	Positive	Positive
3. Anti HBs	Negative	Positive	Negative	Positive	Negative
Significance	1. No chronic infection; not a hepatitis B carrier.	1. No chronic infection; not a hepatitis B carrier.	1. Has acute or flare (if HBc IgM+) or 99% chronic hepatitis B infection.	1. No hep B infection in the blood if HBV DNA negative	1. Subclinical infection at the moment if HBV DNA + OBI
	2. Never been infected with hepatitis B virus.	2. Not infected with hep B virus.	2. Is infected with hep B virus. Has cccDNA in the liver	2. Has been infected with hep B virus.Has cccDNA in the liver	2. Has been infected with hep B virus. Has cccDNA in the liver
	3. No immunity (no protection) against hep B.	3. Has immunity due to vaccination.	3. No immunity or protection against hep B.	3. Has cleared the blood of HBV infection (when combined with negative HBsAg) And has immune control	3. OBI: subclinical infection HBV DNA + and has risk of reactivation.
Action	--	--	See Primary care provider for further tests. HBV DNA quant.	Watch for reactivation if becomes immune suppressed	Watch for risks of reactivation if patient become immune suppressed No vaccination boosting
	Provide vaccination	No vaccination needed	No vaccination needed	No vaccination needed	No vaccination needed

Summary and Conclusions

Preliminary data indicate feasibility of anti-HBc reentry algorithm

- All 19 HBV DNA-positive samples detected as reactive by Abbott PRISM anti-HBcore ChLIA
- All 19 strongly anti-HBc reactive
  - Mean S/CO = 0.14 (range 0.02-0.49)

Yield of reentry dependent on prior assay

- 25% for Ortho => Ortho (1X=>2X)
- 21% for Ortho => PRISM (pilot study)
- 40% for Ortho => PRISM (Hema-Quebec)
- ?? for Corzyme (prior Abbott) => PRISM

Future Considerations

- Role of Nucleic Acid Testing and subsequent organ allocation
- Determine natural history of de novo HBV infection
- Harmonize post transplant prophylaxis strategy

  use or non-use of HBIg
  Nucleos(t)ide analog use-finite duration Vs indefinite use
  HBV vaccination strategies

It's critical in this setting that HBV nucleic acid testing use a highly sensitive assay capable of detecting $\leq$10 copies/ml.

THANK YOU

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Professor of Medicine – Loma Linda University
Hepatitis B Foundation - Medical Director
Adjunct Professor of Medicine:
University of Nevada Las Vegas
University of Nevada Reno
UCSD Skaggs School of Pharmacy and Pharmaceutical Sciences

Hepatitis B Case Presentation

Katie Huynh, PA-C, MS, AAHIVM-S

Call for cases:

Please email Catherine.Freeland@hepb.org if you would like to submit a case for presentation.

CME Credit:

Post-Test: https://www.surveymonkey.com/r/6V2XHVJ

Next Session: Feb. 25th @12PM ET