Chronic Hepatitis B Infection

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Learning Outcomes

- Identify patients at high risk for hepatitis B infection
  - Epidemiology in Australia
  - Screening for high risk groups, including family members
- Be able to diagnose hepatitis B and what investigations need to be requested
  - Understanding serology
  - Recommended work up for new diagnosis
- Describe the treatment options for patients and the GPs role in management
  - When to treat patients – including special groups e.g. immunosuppression, oncology, pregnancy
  - Nucleoside analogues vs interferon
  - HCC surveillance
  - Vaccination
- Be able to evaluate underlying liver disease and describe factors which may progress liver disease in a patient with HBV infection
  - Co-infection with HCV or coexistent liver disease (e.g. alcohol, NAFLD)
  - Fibrosis assessment

Global HBV Prevalence

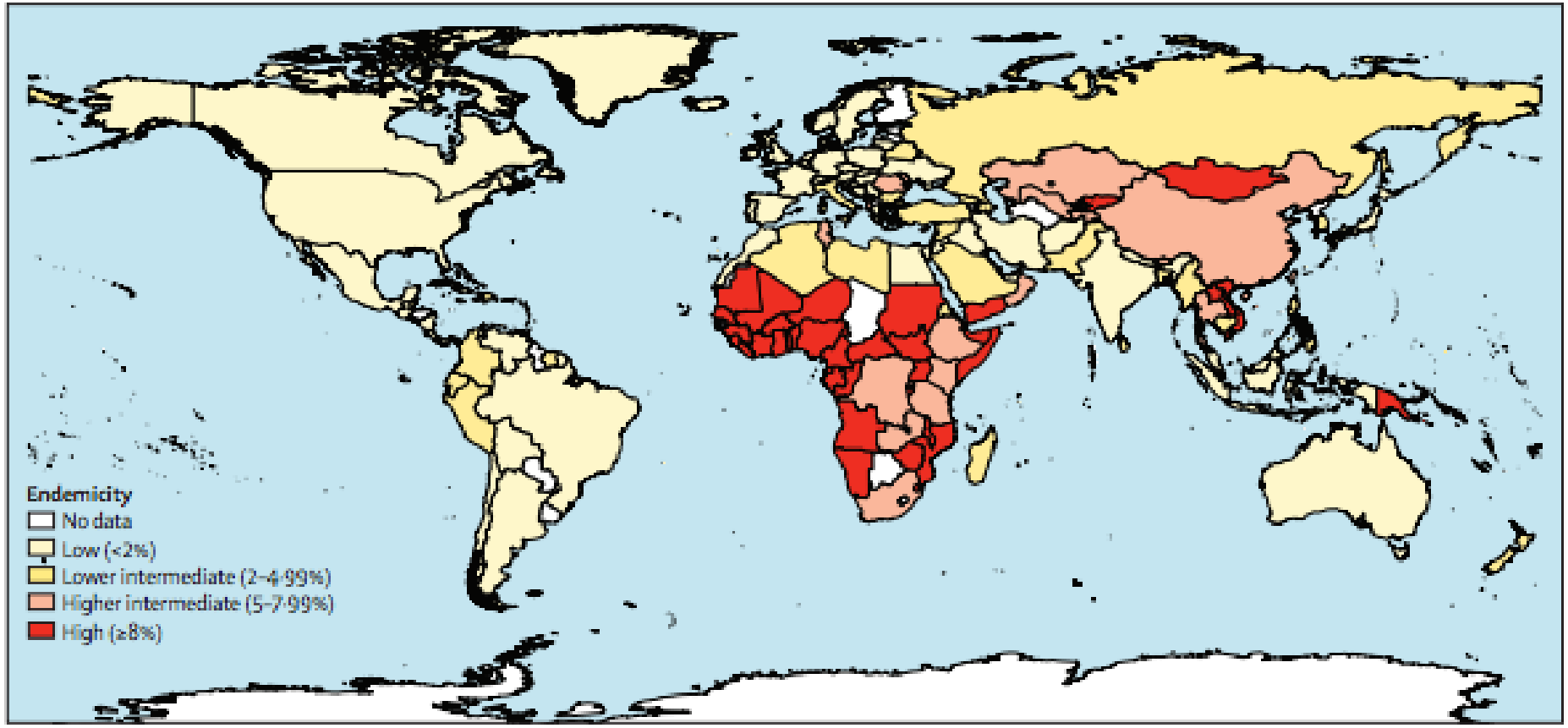

Figure 2: Global HBsAg endemicity (1957–2013)

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Horn et al. Lancet 2015.

HBV in Australia

- Australia considered low prevalence (<2%)
  - Estimated 239,167 individuals with CHB in Australia (1.01% of population)
  - Only 62% have been diagnosed
- Of those estimated to have CHB in Australia in 2015
  - 6% received treatment – majority by specialists (94.3%)
  - 15% were engaged in care
- Immunisation
  - 92.3% of 1-year-olds were vaccinated

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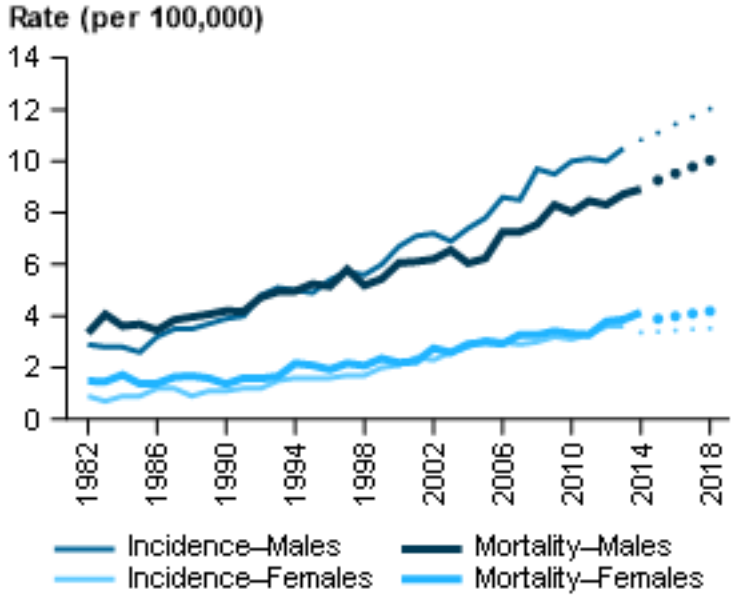
MacLachlan et al. Aust NZ J Public Health 2018.

HBV in Australia

- Rate of new diagnoses has steadily declined
  - 1.2 per 100 000 (2008) → 0.8 per 100 000 (2012)
  - 80% newly diagnosed patients > 25 years
  - 70% born overseas
- High burden of disease
  - Liver cirrhosis
  - Liver transplantation – overall 6% of liver transplants
  - Hepatocellular carcinoma



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2nd National HBV Strategy 2014.

Screening for HBV

- Clear need for targeted screening in high risk populations
- 30-65% chronically infected adults are unaware of infection until screened
- US data has established the cost-effectiveness of screening in high risk patients

Table 2. Patient Groups at Risk for Hepatitis B Virus (HBV) Infection[12]

Group Description	Prevalence Range for HBV Infection, %
A household contact of an individual with chronic HBV	3.0-20.0
A sexual contact of an individual with chronic HBV	3.5-9.0
Individuals born outside the United States[a]	1.0-2.6
Individuals infected with HIV	4.0-17.0
Individuals who inject illicit drugs	2.7-11.0
Men who have sex with men	1.0-3.0
Individuals who are incarcerated[13]	0.3-3.1

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Tang et al. JAMA 2018.

Screening for HBV

Born in Endemic Areas	Other Groups
Asia (except Sri Lanka)	Indigenous Australians
Africa	Intravenous Drug Users
South Pacific Islands	Household contacts
Middle East (except Cyprus)	HIV or HCV infection
Western Europe (Greece, Italy, Malta, Portugal, Spain)	Prisoners
Eastern Europe (except Hungary)	Men who have sex with men
South America (Argentina, Bolivia, Brazil, Ecuador, Guyana, Venezuela, Colombia, Peru)	Patients undergoing dialysis
Central America (Belize, Guatemala, Honduras, Panama)	Patients undergoing chemotherapy or immunosuppression
Caribbean	Pregnant women

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Tang et al. JAMA 2018.

Hepatitis B serology

Table 3. Diagnosis of Acute and Chronic Hepatitis B Virus (HBV) Infection

Interpretation	HBsAg	Anti-HBs	Anti-HBc	HBV DNA Detected	Interpretation Details
HBV infection	Positive	Negative	Positive	Positive	• Presence of HBsAg for >6 mo defines chronic infection • In acute infection, anti-HBc is in the form of IgM
Resolved infection	Negative	Positive	Positive	Negative	• Adults infected with HBV will resolve infection within 6 mo • HBsAg is no longer detected (termed *HBsAg loss*) • 80% of adults will develop anti-HBs (termed *anti-HBs seroconversion*)[20] • Anti-HBc is present in the form of IgG
Immunity	Negative	Positive	Negative	Negative	• Immunity gained through vaccination
Isolated core	Negative	Negative	Positive	Negative or positive	• Undetectable HBV DNA: previous infection without anti-HBs or level of anti-HBs is below the level of detection by serological test[a] • Detectable HBV DNA: occult HBV infection[a] • Period during acute infection either immediately after infection and before the appearance of HBsAg or during resolution of infection after HBsAg loss and before appearance of anti-HBs • False-positive test result

Abbreviations: anti-HBc, HBV core antibody; anti-HBs, HBV surface antibody; HBsAg, HBV surface antigen.

[a] Individuals at risk for disease reactivation and should be identified prior to immunosuppressive therapy.

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Tang et al. JAMA 2018.

Acute HBV infection

- Only one-third of adult patients develop symptoms
  - Fever, fatigue, malaise, abdominal pain, jaundice
  - Remainder have subclinical illness
- Markedly elevated transaminases are hallmark
  - ALT or AST > 1000
  - May have significant jaundice or elevated INR → specialist management indicated
  - Death from acute liver failure occurs in <1% of cases
- Key to determining acute infection is history of at risk behaviour
  - Develops 6-12 weeks following virus exposure
  - Patients not always forthcoming
- Serology demonstrates positive cAb IgM – indicating recent infection
- 90-95% of adult patients will clear virus and avoid chronic infection

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EASL. J Hep 2017.

Chronic HBV infection

- Defined as detection of HBsAg on 2 occasions, measured at least 6 months apart
- Natural history varies widely
- Infants more susceptible to developing CHB than adults
  - 90% infants vs 10% adults
- Progresses to cirrhosis is 40% of untreated patients
- Accounts for at least 50% of HCC
  - Observational study of > 650 patients showed 30% of HBV cirrhotic patients developed HCC during 10 years of follow up
  - Can develop in the absence of cirrhosis (10% of cases)

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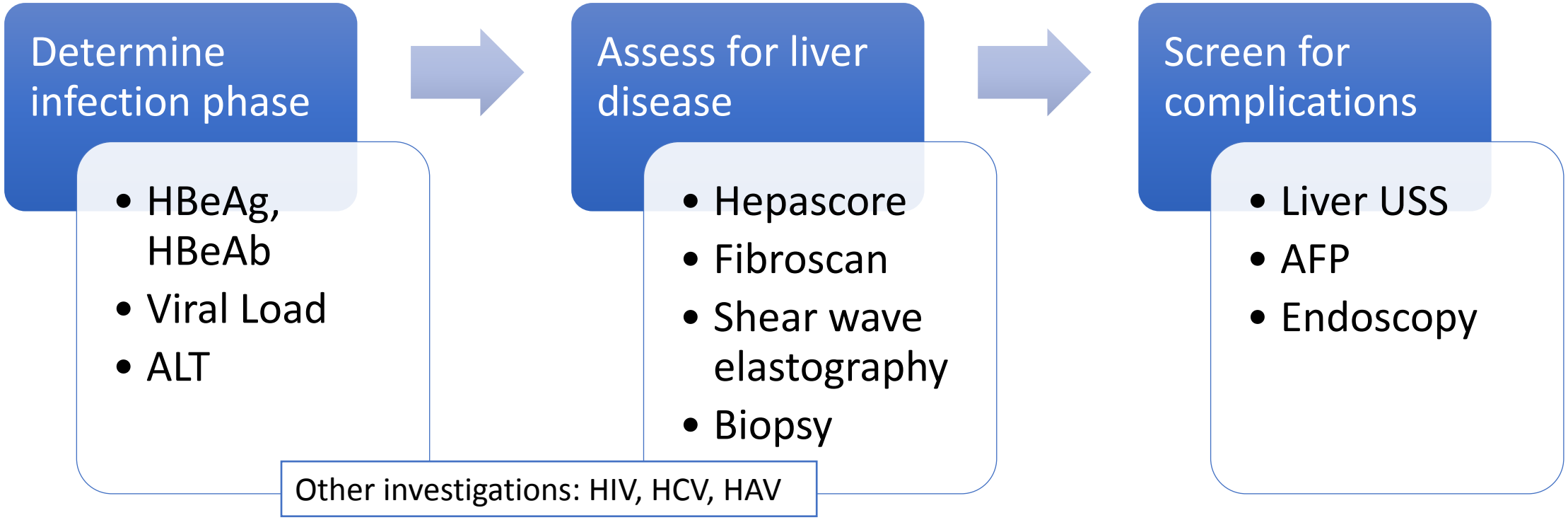
Tang et al. JAMA 2018.

Work up for newly diagnosed chronic HBV infection



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Tang et al. JAMA 2018.

Determining phase of infection

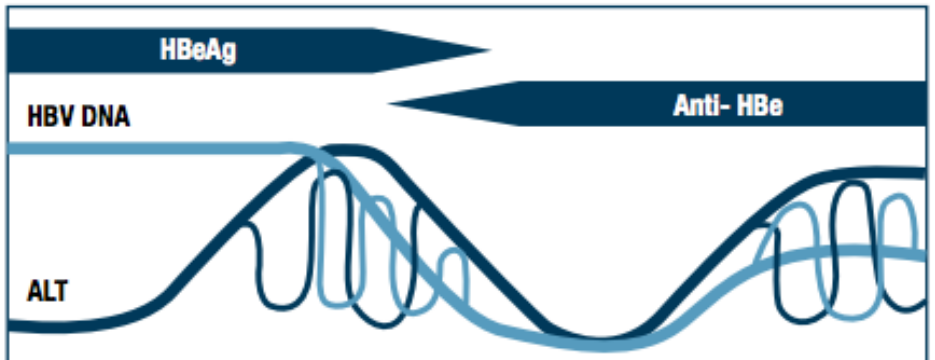
- The four recognised phases of chronic HBV are not distinguishable through symptoms or age
  - Serological markers needed to determine disease phase and management
- E antigen status
  - Development of eAb suggests some immune control over infection
  - eAb seroconversion associated with decrease in viral load and liver inflammation
- Viral load
  - Necessary to determine viral replication; infectivity directly proportional to viral load
- ALT
  - Determinant of liver inflammation (replaces liver biopsy)
  - Indirect measurement – can be affected by non-viral inflammation (e.g. ETOH, NAFLD)
  - AASLD guidelines recommend
    - Males: <35 IU/L
    - Females: <25 IU/L

Terrault et al. Hepatology 2018.

HBV infection phases

- Hepatitis B does not directly kill hepatocytes
  - Immunologic recognition of the virus as foreign leads to targeting and destruction of infected liver cells and inflammation
- Patients will have periods of immunologic activity and inactivity over a lifetime
  - Repeated periods of activity with liver injury leads to fibrosis and HCC
- Duration of each phase is not well described
  - By 4th decade most perinatally infected patients will have undergone HBeAg loss – only 6-10% adults > 40 years old remain positive for HBeAg
- Spontaneous clearance (SAg loss with undetectable viral load) may occur (0.5-2% pa)

Figure 1: Natural History and Phases of CHB



	Phase I Immune Tolerance	Phase II Immune Clearance	Phase III Immune Control	Phase IV Immune Escape
HBsAg	>6 months	>6 months	>6 months	>6 months
HBeAg	+	+	-	-
Anti-HBe	-	Spontaneous seroconversion to anti-HBe may occur	+	+
ALT	Persistently normal	Persistently or intermittently elevated	Persistently normal	Persistently or intermittently elevated
HBV DNA	≥20,000 IU/mL	Persistently or intermittently ≥20,000 IU/mL	<2,000 IU/mL	Persistently or intermittently ≥2,000 IU/mL

GESA 2010.

Assessment of liver disease

- Liver biopsy
  - Gold standard for presence of liver inflammation and fibrosis
  - Associated with significant risks: bleeding (0.6%), injury to other organs (0.08%), death (0.01%)
  - Subject to sampling error – discordance reported in 12% of patients having multiple biopsies
- Serum biomarkers
  - Hepascore – PathWest
  - APRI – website / calculator
  - Fib-4 – website / calculaor
- Transient Elastography (Fibroscan®)
- Shearwave Elastography

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Tang et al. JAMA 2018.

Assessment of liver disease

	Serum Tests	Fibroscan	Shear-wave Elastography
Advantages	Good reproducibility High applicability Cheap Well validated Performed in community	Most widely used and validated Performed as bedside High range of values Good reproducibility Highly accurate for cirrhosis	Implemented on regular US machine Measures liver stiffness in real-time High range of values High performance in cirrhosis
Weaknesses	Non-specific Unable to differentiate intermediate fibrosis stages Not as accurate for cirrhosis as fibroscan Affected by fasting, inflammation, Gilbert's	Requires specific device Unable to differentiate between intermediate fibrosis stages Affected by obesity and ascites Falsely elevated in acute hepatitis, cholestasis, hepatic congestion	Further validation needed Unable to differentiate between intermediate fibrosis stages Quality criteria, learning curve, influence on inflammation not defined

EASL J Hep 2015.

Non-invasive fibrosis markers

- Hepascore (age, gender, hyaluronic acid, bilirubin, GGT, alpha2-macroglobulin)
  - Cirrhosis cut-off: 0.85
  - Sensitivity 84%, Specificity 82%
- FIB-4 (age, AST, ALT, platelet count)
  - < 1.45 or > 3.25
  - NPV 90% for advanced fibrosis, PPV 65% advanced fibrosis
- APRI (AST, platelet count)
  - Threshold 1.0
  - Sensitivity 76%, Specificity 72%
- Fibroscan
  - Cirrhosis: >12.5 kPa
  - Sensitivity 83%, Specificity 87%
- Shear-wave Elastography
  - Comparable to fibroscan but well validated data lacking

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EASL J Hep 2015.

Factors associated with increased rates of cirrhosis or HCC

Modifiable

- Habitual alcohol consumption
  - >7 drinks per week for women, >14 drinks per week for men → associated with cirrhosis and HCC
  - Minimal intake or abstinence recommended
- Control of metabolic syndrome risk factors
- Co-infection with HCV, HDV or HIV
- Carcinogens such as aflatoxin (African patients) and tobacco

Non-modifiable

- Older age
- Male gender
- Family history of HCC
- HBV genotype C

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GESA 2010.

Screening for complications

- Liver ultrasound + AFP
  - Screening investigation for HCC
  - PPV for cirrhosis in the absence of portal hypertensive changes is poor (50%)
  - AFP may be falsely elevated due to inflammation → can result in unnecessary CT/MRI utilisation
- Gastroscopy
  - Necessary for variceal surveillance in patients with confirmed cirrhosis
  - Recent Baveno VI criteria suggest patients with Fibroscan < 20 kPa and platelet count > 150 are at low risk having varices requiring intervention
  - Surveillance interval determined by findings at index scope

EASL J Hep 2017; de Franchis et al J Hep 2015; Terrault et al Hepatology 2018.

Treatment

- Therapeutic goal is to reduce risk of liver failure and hepatocellular carcinoma
- Treatment is indicated during the immunoactive phases → when liver injury and fibrosis occur
- Patients with cirrhosis or HCC and detectable VL are treated regardless of ALT

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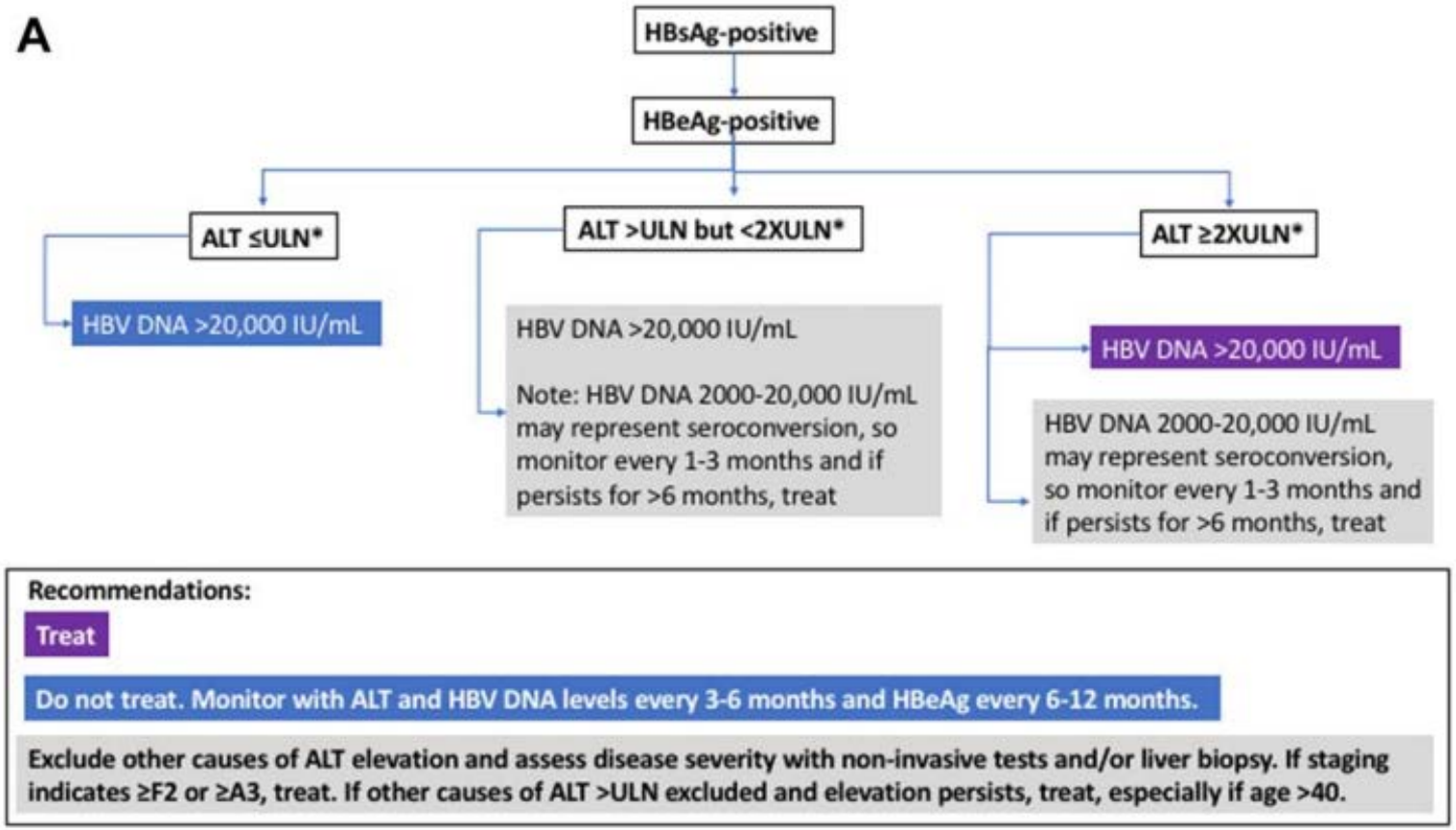
Tang et al. JAMA 2018.

Phase 2: Immune Clearance



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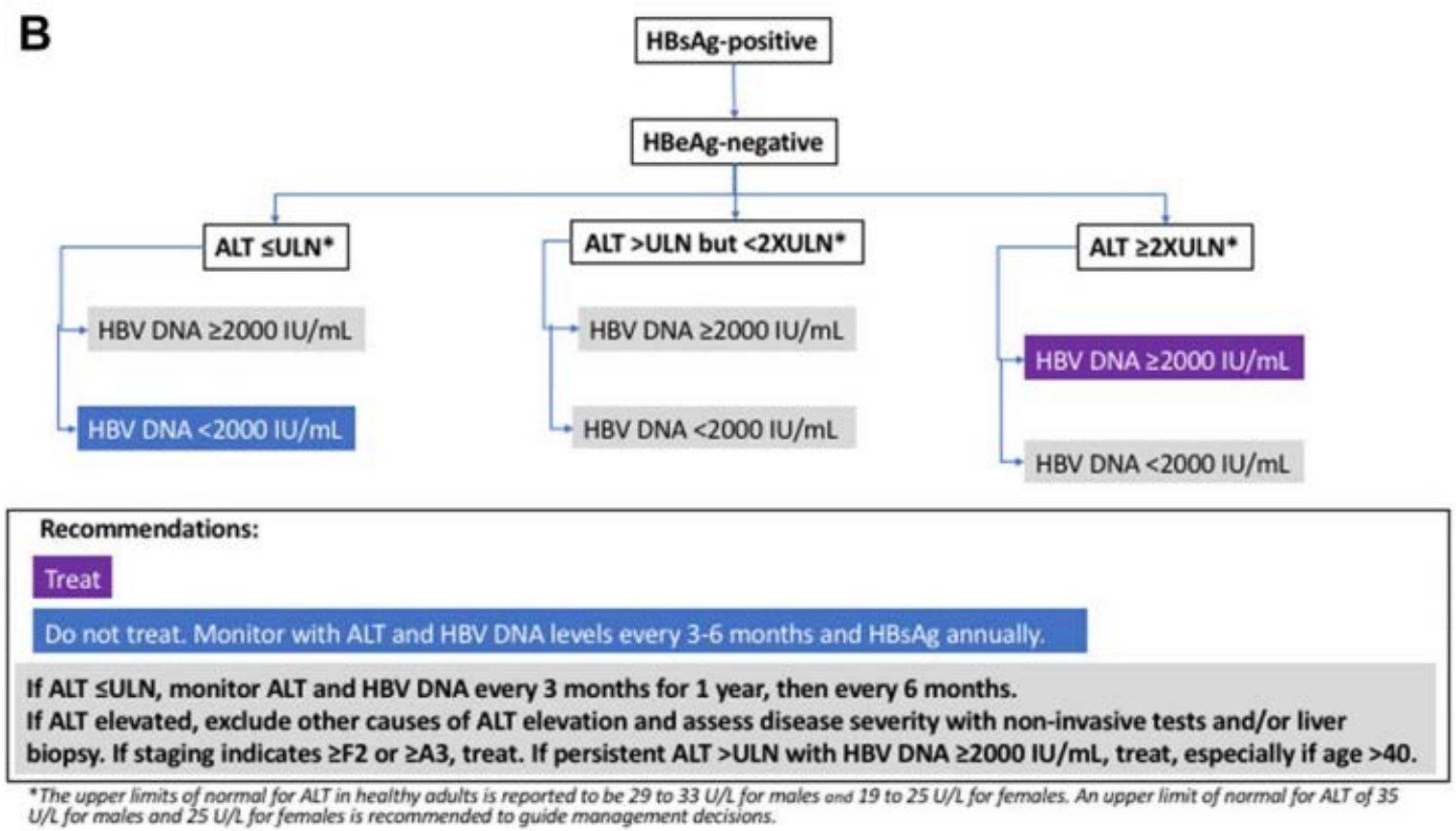
Terrault et al. Hepatology 2018.

Phase 4: Immune Escape



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Terrault et al. Hepatology 2018.

Interferon

- Endogenous cytokines with antiviral activity
  - Exact mechanism not well understood
- SC injection of pegylated interferon available for HBV infection
- Administered once weekly for 48 weeks
- Significant adverse effects
  - Cytopaenia, exacerbation of neuropsyciatric symptoms, induction of autoimmune disease (especially thyroiditis)
- Can achieved eAg loss in 30% and sustained viral load suppression
- Few achieve sAg loss

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Terrault et al. Hepatology 2018.

Nucleotide/Nucleoside analogues

- Lamivudine, entecavir (nucleoside), adefovir, tenofovir (nucleotide)
- Once daily, oral medications
- Well tolerated in clinical trials
  - Fatigue (3-10%), dizziness (5%), headache (5-15%), nausea (3-10%)
- All drugs show improvement in liver histology and reduce HBV VL in randomised trials
- Associated with decreased rate of HCC
- There is no available therapy associated with sAg loss
  - Average rate 1% pa on treatment

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Terrault et al. Hepatology 2018.

Nucleotide/Nucleoside analogues

- Entecavir and tenofovir are more potent but equivalent in treatment naïve patients
  - Viral suppression 76-93% at 12 months of treatment
  - Histological improvement ~70%; normalisation of ALT ~70-80%
- Tenofovir adverse effects
  - Reported concerns for renal toxicity (e.g. Fanconi syndrome) and phosphate loss
  - Not borne out in phase 3 clinical trials (>3 years duration)
  - Small decreases in bone mineral density (1-2.5%) but clinical relevance unclear
  - Increased monitoring of renal function usually undertaken but no recommendation for increased bone density screening
  - Usually avoided in patients with pre-existing renal or bone disease

Terrault et al. Hepatology 2018.

Antiviral resistance

- Lamivudine and adefovir use limited by resistance development
- In treatment naïve patients rates of resistance are low with entecavir
  - Entecavir has high resistance rates in patients previously treated with lamivudine or adefovir
- Resistance has not been reported with tenofovir use

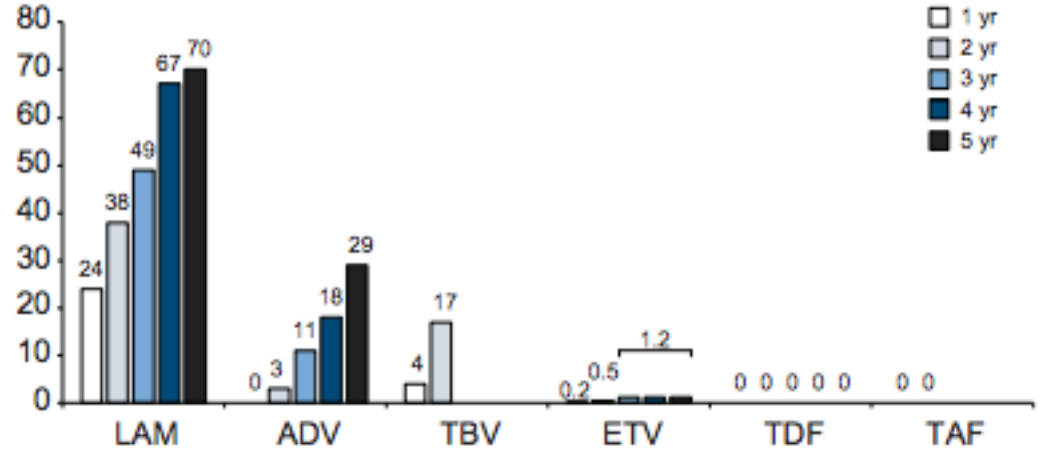

Fig. 3. Cumulative incidence of HBV resistance for lamivudine (LAM), adefovir (ADV), entecavir (ETV), telbivudine (TBV), tenofovir (TDF) and tenofovir alafenamide (TAF) in pivotal trials in nucleos(t)ide-naïve patients with chronic hepatitis B. (Collation of currently available data – not from head-to-head studies). No evidence of resistance has been shown after 8 years of TDF treatment.[69]

EASL J Hep 2017.

Treatment duration

- Treatment can be ceased if patients achieve sAg seroconversion – rare occurrence
- Interferon treatment is for a maximum of 48 weeks
- Nucleot(s)ide analogues – often indefinite
  - eAg positive patients – can consider cessation following 12 months consolidation therapy after eAb serconversion
  - eAg negative patients – indefinite
  - Cirrhosis or HCC – until sAg seroconversion but will continue to require cirrhosis/HCC follow up

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Terrault et al. Hepatology 2018.

Monitoring of patients not on treatment

- HBeAg positive
  - ALT every 3 months
  - HBV DNA every 6-12 months
  - Assessment of liver fibrosis every 12 months
- HBeAg negative, HBV DNA level > 2000 IU/mL
  - ALT every 3 months for first year, then every 6 months
  - HBV DNA / fibrosis assessment every 2-3 years
- HBeAg negative, HBV DNA level < 2000 IU/mL
  - ALT every 6-12 months
  - HBV DNA / fibrosis assessment every 2-3 years

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Terrault et al. Hepatology 2018.

Immunosuppression

- HBsAg positive patients should receive entecavir or tenofovir as prophylaxis for high risk immunosuppression
  - Anti-CD20 therapy
  - Chemotherapy
  - Moderate-high dose steroids (prednisolone >10 mg/d for ≥ 4 weeks)
- HBsAg negative, HBcAb positive patients should receive prophylaxis if at high risk (anti-CD20 therapy, stem cell transplant)
  - Close monitoring (LFT, VL every 3 months) for all other cases
- Prophylaxis should continue for 6-12 months following cessation of immunosuppression

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Terrault et al. Hepatology 2018.

Pregnancy

Already on antiviral treatment

- Can continue tenofovir
  - Risk of viral flare outweighs risk to child
- Interferon or entecavir should be discontinued and switched to tenofovir

High viral load

- If HBV VL > 200 000 IU/mL the patients should commence tenofovir at week 24-28 gestation
- Continue for 12 weeks post-delivery

- Breastfeeding is not contraindicated in untreated women with CHB or those on tenofovir
- The mode of delivery does not affect risk of vertical transmission
- All children should received HBIG and vaccination within 12 hr of birth – reduces perinatal transmission rate from >90% to <10%
  - Tenofovir in women with high viral load reduces risk to <1%

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Terrault et al. Hepatology 2018.

Hepatitis Delta

- Defective virus that can only exist in the presence of HBV infection
- Associated with rapid progression to cirrhosis
- High risk populations include:
  - IVDU
  - Men who have sex with men
  - High endemic areas: West Africa, Northern Asia, Pacific Islands, Eastern Europe
- Suspect infection in patients with elevated ALT but low HBV viral load
- Test for HDV IgG initially then viral load if positive
- Treatment is with interferon for at least 48 weeks
  - Improved outcomes with viral suppression and normalisation of ALT
  - Response is not durable – undetectable VL in 48% at completion but on 12% at three years post-treatment

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Terrault et al. Hepatology 2018.

Vaccination

- Routine
  - 0, 1 and 6 months of age for all newborn infants
- Targeted
  - Sexual and household contacts of HBV-infected persons who are negative for HBsAg and HBsAb
  - Healthcare workers, haemodialysis patients, immunocompromised patients
- Follow up testing
  - Newborns of HBV-infected mothers should have post-vaccination testing at 9-12 months
  - HCWs, sexual contacts, haemodialysis or immunocompromised patients should have response to vaccine assessed at 1-2 months
- Non-responders
  - Repeat 3-dose series recommended
  - Double dose for immunocompromised patients
- Booster doses not recommended unless HBsAb remains < 10 IU/L after initial vaccination in HCWs, infants from infected mothers, dialysis or immunocompromised

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Terrault et al. Hepatology 2018.

HCC surveillance

- HCC tumour volume doubles every 4-6 months → USS +/- AFP recommended every 6 months to screen for HCC
  - RCT 18,816 patients screening with USS+AFP every 6 months was associated with earlier detection and improved HCC 5-year survival (46.4% v 0%)
  - No RCTs to compare different screening intervals
  - Insufficient evidence to advise for or against AFP – generally utilised in practice
  - Cost effective if annual risk of HCC ≥0.2% per year
- Abnormal USS must be followed up with contrast enhanced (triphasic) CT or gadolinium MRI

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Tang et al. JAMA 2018

HCC surveillance

- All patients with cirrhosis
- Non-cirrhotic patients
  - Family history of HCC in 1st degree relative
  - HDV co-infection
  - Asian or Indigenous men > 40 years old
  - Asian or Indigenous women > 50 years old
  - African patients > 20 years old

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Terrault et al. Hepatology 2018.

HCC surveillance

- PAGE-B
  - HCC risk stratification tool developed for Caucasian patients
  - Not applicable in cirrhosis
  - Uses age, gender and platelet count
  - Maximum score 25
  - Score ≤ 9 equates to minimal 5-year risk of HCC development
- REACH-B
  - HCC risk stratification tool for Asian patients
  - Non-cirrhotic patients
  - Uses sex, age, ALT, HBeAg status, HBV DNA level
  - Maximum score 17

	3 years	5 years	10 years
0	0·0%	0·0%	0·0%
1	0·0%	0·0%	0·1%
2	0·0%	0·0%	0·1%
3	0·0%	0·1%	0·2%
4	0·0%	0·1%	0·3%
5	0·1%	0·2%	0·5%
6	0·1%	0·3%	0·7%
7	0·2%	0·5%	1·2%
8	0·3%	0·8%	2·0%
9	0·5%	1·2%	3·2%
10	0·9%	2·0%	5·2%
11	1·4%	3·3%	8·4%
12	2·3%	5·3%	13·4%
13	3·7%	8·5%	21·0%
14	6·0%	13·6%	32·0%
15	9·6%	21·3%	46·8%
16	15·2%	32·4%	64·4%
17	23·6%	47·4%	81·6%

Table 3: Cumulative risk score and associated 3-year, 5-year, and 10-year risk of developing hepatocellular carcinoma in patients with chronic hepatitis B

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Papatheodoridis et al, J Hep 2016; Yang et al, Lancet Oncol 2011.

Summary

- Screen for HBV in high risk groups – don't forget to vaccinate family members
- Diagnosis of active infection requires only HBsAg and HBV DNA level
- Treatment decisions are based on presence of cirrhosis, HCC or ALT elevation
  - ALT surrogate marker for hepatic inflammation
  - HBeAg/Ab status necessary for further stratification
- Fibrosis assessment can be difficult, however most available tests have reasonable negative predictive value for cirrhosis
- Treatment with oral antiviral therapy is effective but likely to be indefinite
- Tenofovir in pregnancy and breastfeeding is safe
- HBV reactivation from immunosuppression can be fatal
- HCC surveillance is important, even for patients without cirrhosis

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Thank you.