Hepatitis B virus and solid organ transplantation

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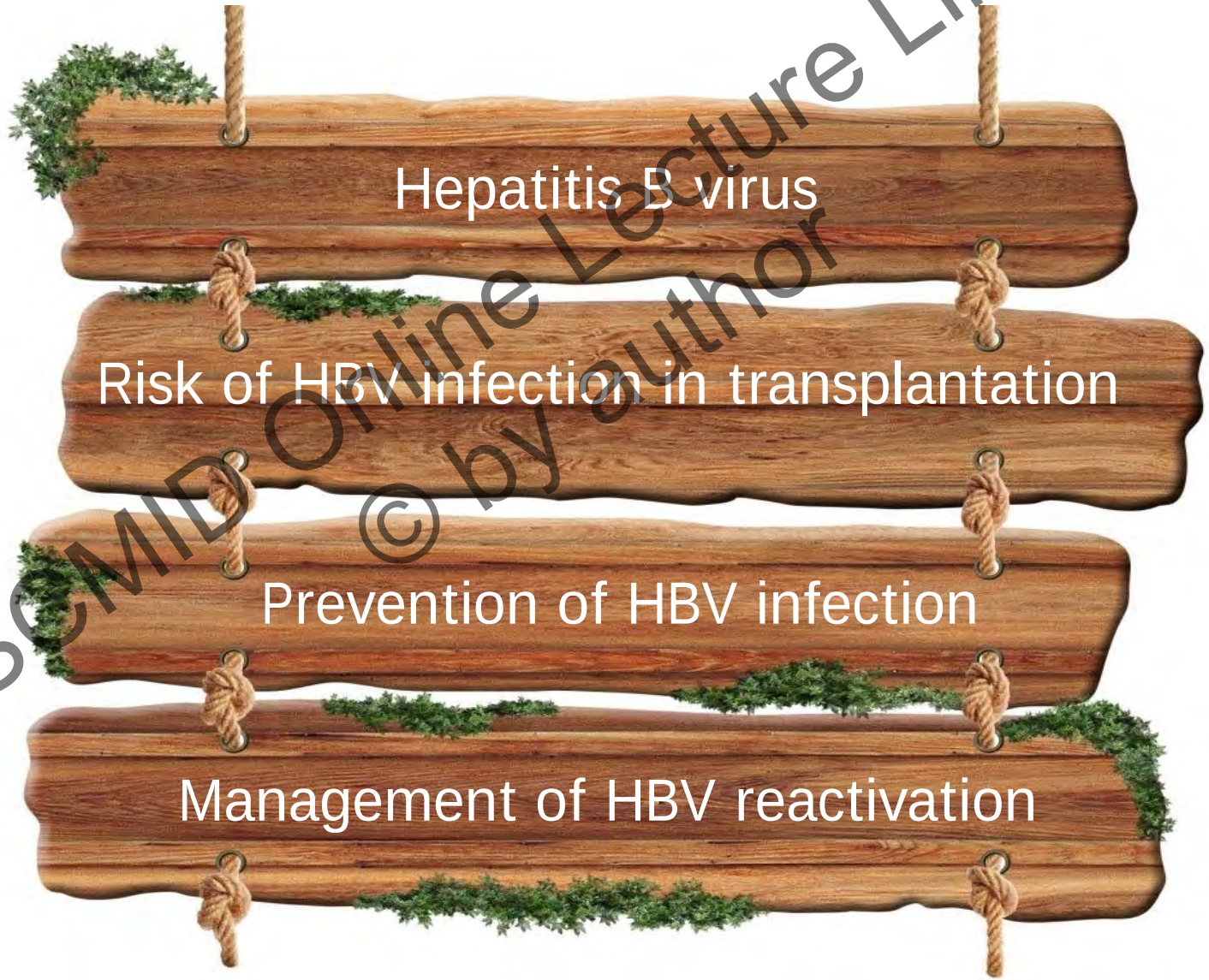
Conflict of interest

Outline

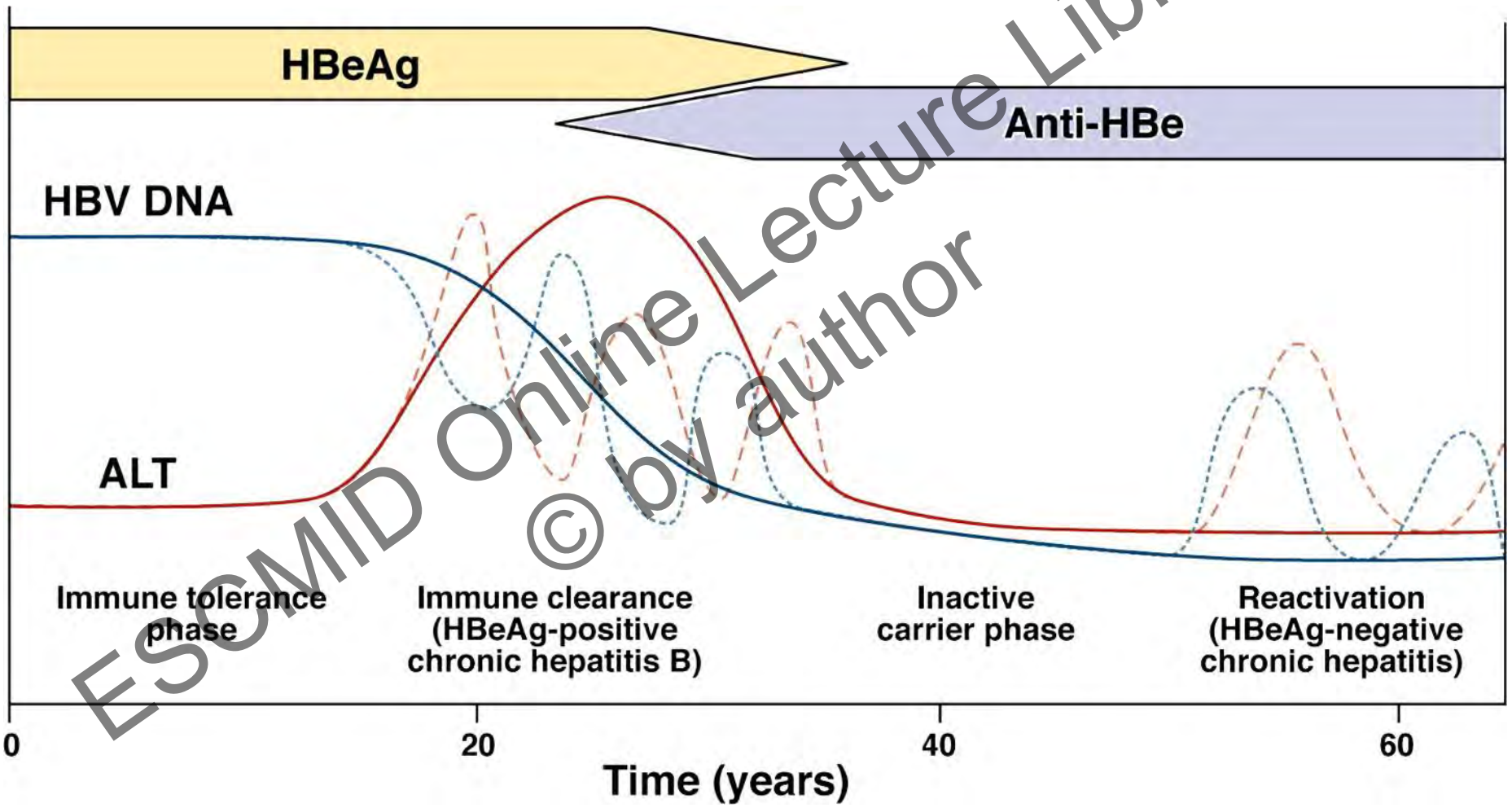


Hepatitis B virus

- HBV is an DNA virus
- Spread through mother to child transmission, unprotected sex, blood transfusion and exposed to infected blood and body fluids
- Chronic HBV infection affects 350-400 million people worldwide
  - Causes over one million deaths per year
- Cirrhosis and hepatocellular carcinoma are frequent complications
- Common indication for liver transplantation

Jonas M. Liver Int. 2009;29 (suppl 1):133–139
Levitsky J et al. Am J Transplant 2013;13:147-68

Natural course of HBV infection



Yapali S, et al. Clin Gastroenterol Hepatol 2014;12:16-26

Interpretation of serologic tests for HBV

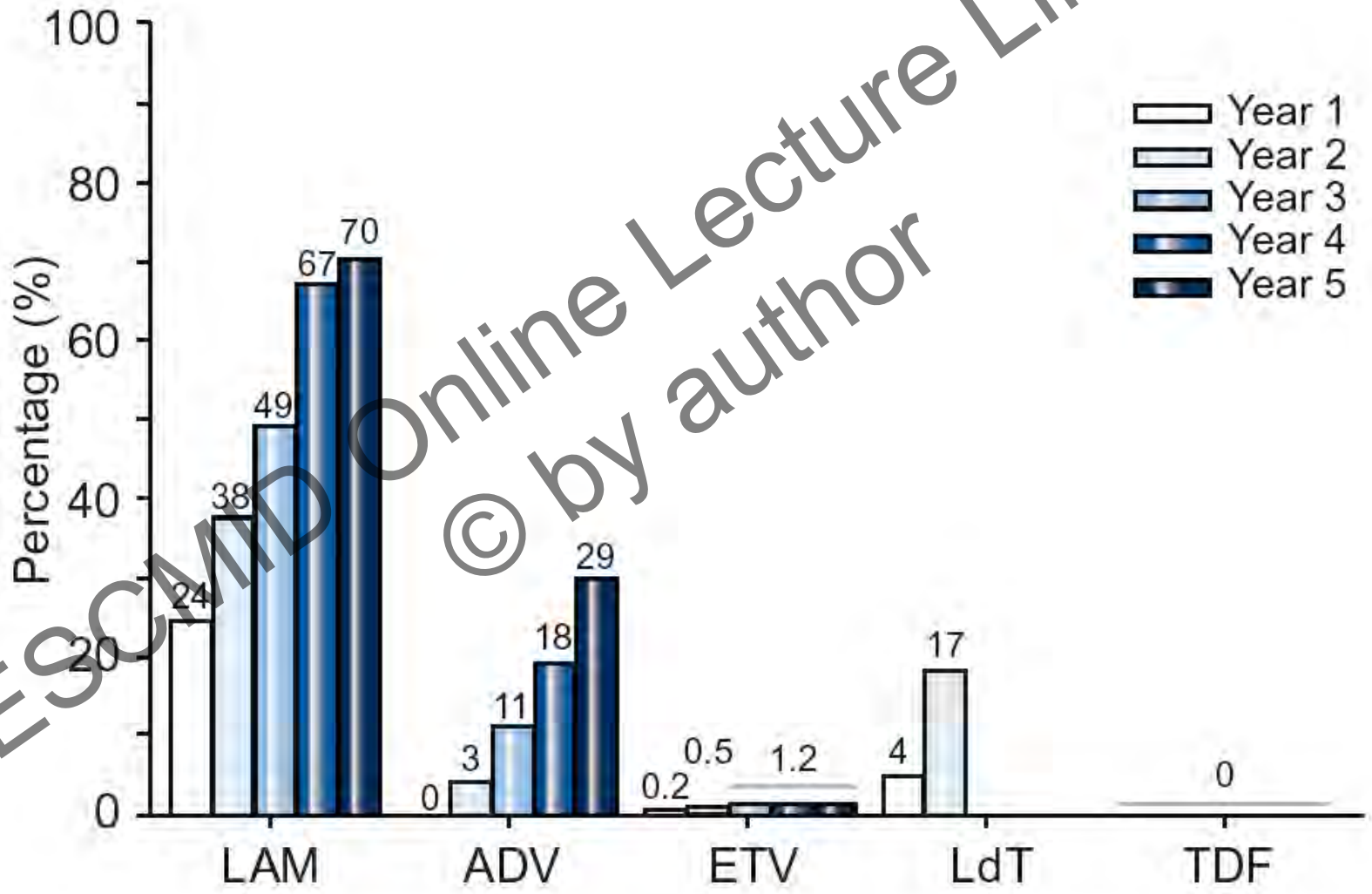
HBsAg	Anti-HBc IgM	Anti-HBc	Anti-HBs	Status
Negative	Negative	Negative	Negative	No infection and immunity
Negative	Negative	Positive	Positive	Natural immunity
Negative	Negative	Negative	Positive	Vaccine immunity
Positive	Positive	Positive	Negative	Acute hepatitis
Negative	Positive	Positive	Negative	Resolving acute infection
Negative	Negative	Positive	Negative	Resolved infection Occult infection
Positive	Negative	Positive	Negative	Chronic infection

Adapted from Huprikar S et al. American Journal of Transplantation 2015;15:1162-72

Oral Anti-Viral Agents: Potency and Resistance

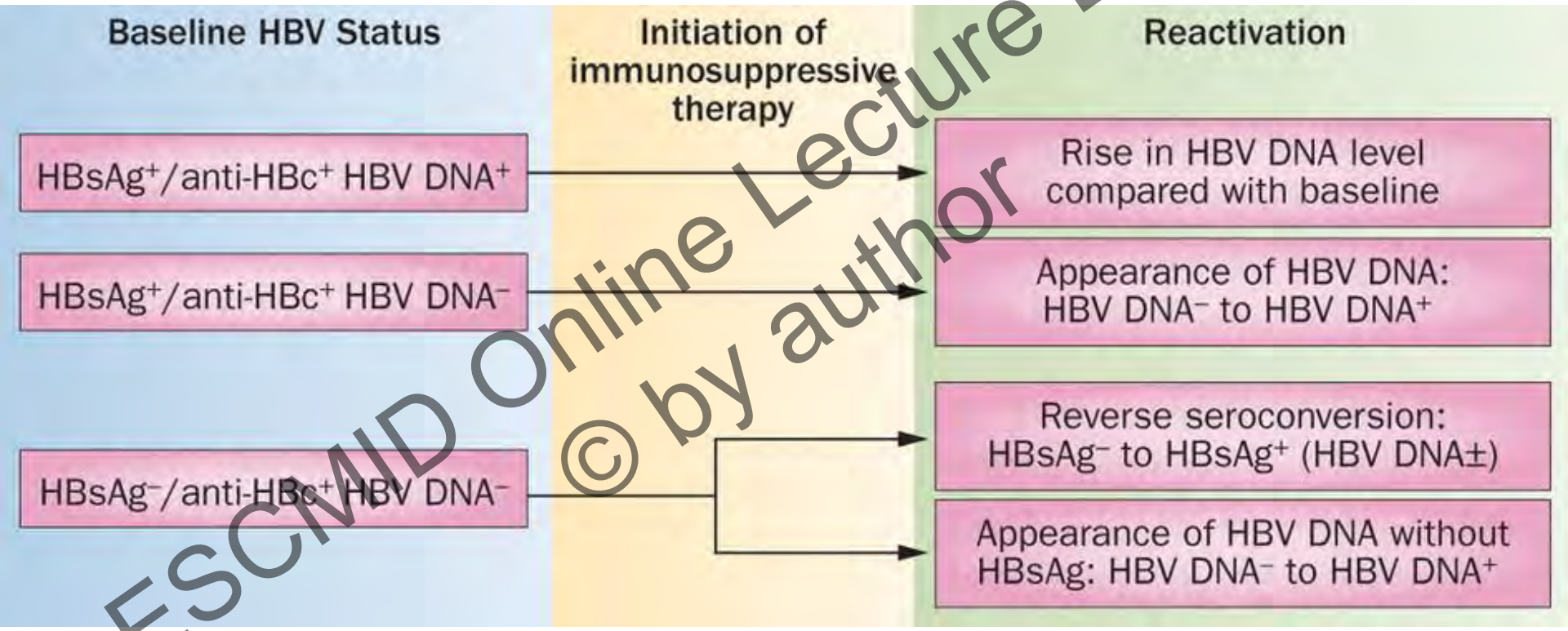
Drug	Anti-viral potency	Genetic barrier	Cost
Lamivudine	++	+	+
Telbivudine	+++	++	++
Adefovir	+	+++	++
Entecavir	++++	++++	+++
Tenofovir	++++	+++++	++

Risk of resistance in naïve patients



EASL. J Hepatol 2012;57:167-85

Reactivation



Hwang JP, Lok AS. Nat Rev Gastroenterol Hepatol 2014;11(4): 209-19

Agents reported to cause HBV reactivation

Class	Agents
Corticosteroids	Dexamethasone, methylprednisolone, prednisolone
Antitumor antibiotics	Actinomycin D, bleomycin, daunorubicin, doxorubicin, epirubicin, mitomycin-C
Plant alkaloids	Vinblastine, vincristine
Alkylating agents	Carboplatin, chlorambucil, cisplatin, cyclophosphamide, ifosfamide
Antimetabolites	Azauridine, cytarabine, fluouracil, gemcitabine, mercaptopurine, methotrexate, thioguanine
Monoclonal antibodies	Alemtuzumab, rituximab
Anti-TNF	Infliximab, etarnercept, adalimumab, certolizumab, golimubab
Others	Colaspase, docetaxel, etoposide, fludarabine, folinic acid, interferon, procarbazine

Yeo W, et al. Hepatology 2006;43:209-20

Risk factors for reactivation

- Patients with cirrhosis
- HBeAg positive patients
- HBeAg negative but high HBV DNA levels (20.000 IU/mL)
- Patients with antiviral drug resistance prior to transplantation

Impact of HBV infection on RT recipients Risk of mortality

Authors	Adjusted RR (95% CI)	Country	Reference year
Lee et al	1.8 (0.9–3.4)	Taiwan	2001
Chan et al	9.7 (4.7–19.9)	Hong Kong	2002
Breitenfeldt et al	1.90 (1.8–1.9)	Germany	2002
Morales et al	1.57 (0.7–3.1)	Spain	2004
Ridruejo et al	2.50 (0.7–8.8)	Argentina	2004
Aroldi et al	2.36 (1.5–3.7)	Italy	2005

RR 2.49 (95% CI, 1.64-3.78)

Kalia H et al. Transplantation Reviews 2011;25:102-9

Impact of HBV infection on RT recipients
Risk of graft loss

Authors	Adjusted RR (95% CI)	Country	Reference year
Hsieh et al	0.97 (0.17–5.4)	Taiwan	2000
Lee et al	1.17 (0.7–3.4)	Taiwan	2001
Chan et al	1.0 (NA)	Hong Kong	2002
Breitenfeldt et al	1.66 (1.3–1.8)	Germany	2002
Morales et al	1.13 (0.57–2.2)	Spain	2004
Ridruejo et al	7.19 (2.06–25.11)	Argentina	2004
Aroldi et al	1.55 (1.12–2.14)	Italy	2005

RR 1.44 (95% CI, 1.02-2.04)

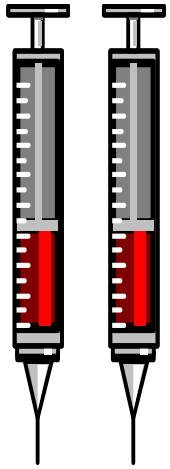
Kalia H et al. Transplantation Reviews 2011;25:102-9

Pretransplant evaluation

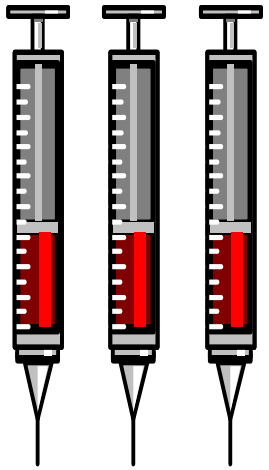
- All living potential donors and recipients should be tested for HBV
- Baseline tests
  - HBsAg, Anti HBc, Anti HBs
- Further tests
  - HBeAg, Anti-HBe
  - HBV DNA
  - Liver enzymes
  - Abdominal USG
  - Assesment of liver necroinflamation and fibrosis

Vaccine schedule

- Hepatitis A
  - 2 doses given 6 months apart



- Hepatitis B
  - 3 doses given over a 6-month period
  - 0,1,6 months



- Combined Hepatitis A & B vaccine

higher dose (40 **m**g antigen per dose) vaccine is recommended in the pretransplant setting in hemodialysis patients and other immunocompromised hosts

Donor and recipient matching

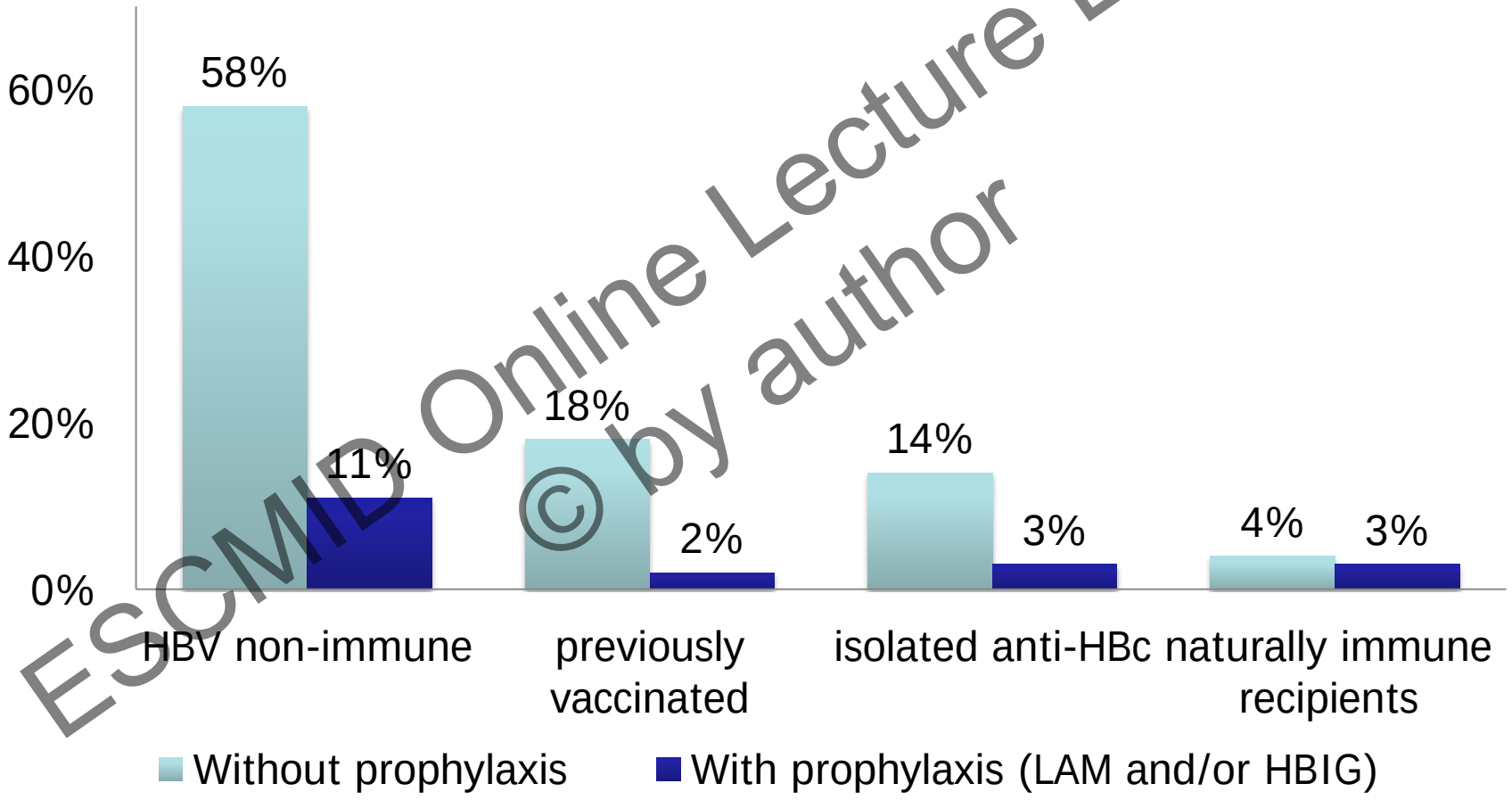
- HBsAg (+) donor, HBsAg (±) recipient
- Anti-HBc (+) donor, HBsAg (±) recipient
- HBsAg (-) donor, HBsAg (+) recipient

Recipient of any organ from HBsAg donors

- Organs from HBsAg (+) donors may be carefully considered in all adult transplant candidates after an individualized assessment of the risk and benefits and appropriate patient consent
- HBsAg (+) livers should only be considered when significant donor liver disease has been ruled out by histology
- Indefinite prophylaxis with entecavir or tenofovir is recommended for all recipients
- HBIG should be considered in all recipients when the anti-HBs titer is **<**100 IU/L
- HBV DNA with or without HBsAg should be monitored every 3 months for 1 year and then every 3–6 months indefinitely

Huprikar S et al. American Journal of Transplantation 2015;15:1162-72

Isolated Anti-HBc (+) and de nova HBV (DNH) in liver transplantation (LT)



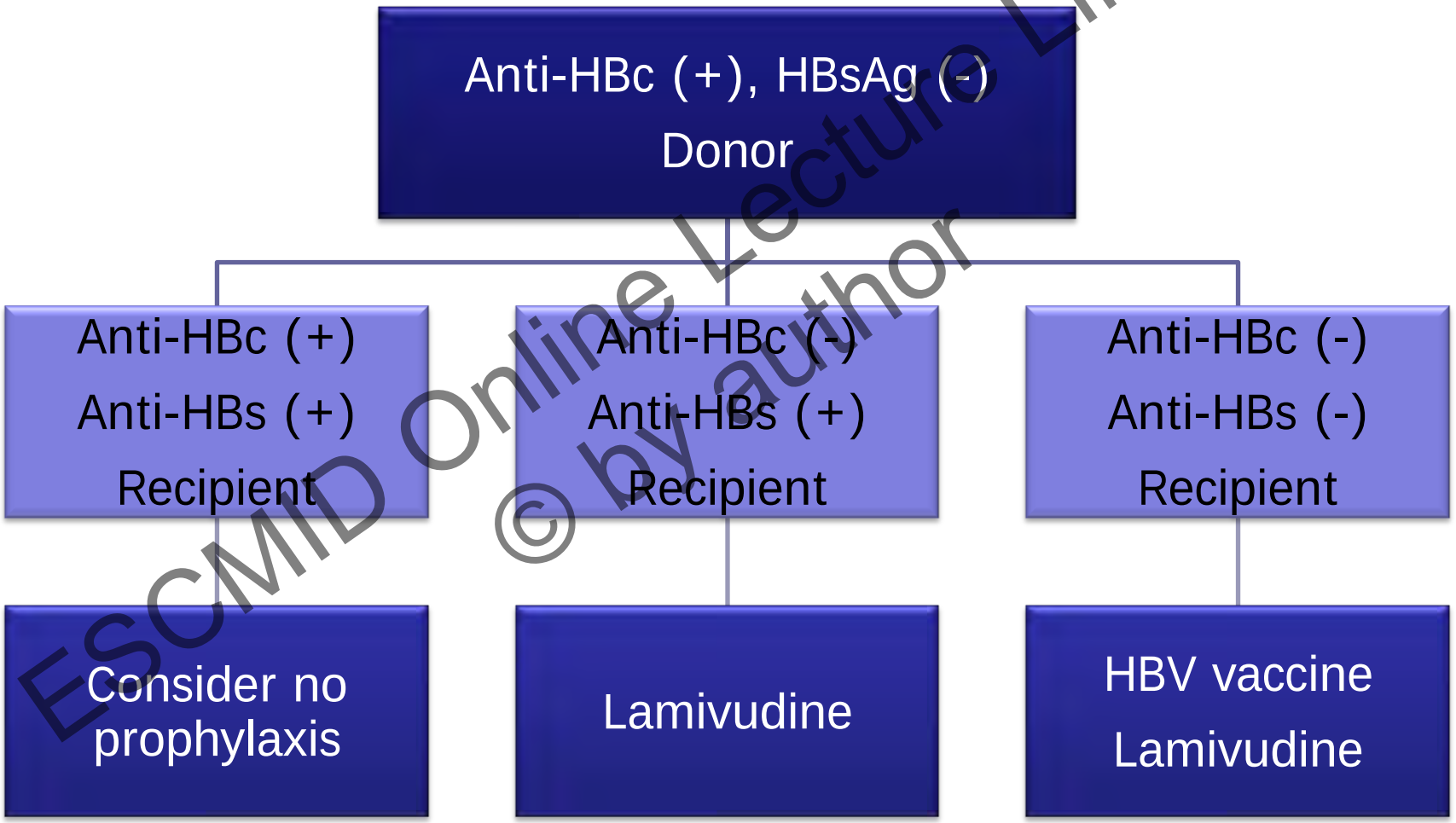
Skagen CL, et al. Clin Transplant 2011;25:E243-E249

Risk factors for de novo HBV infection following kidney transplantation

- The reported risk of DNH in HBV naive kidney recipients ranges from 0% to 27%
- There is a low risk of transmission of HBV infection from HBsAg-negative, Anti-HBc positive donors to HBsAg negative recipients (3.2%) 0.011 (95% CI 0.0070–0.0182)
- The risk is even lower if the recipient is anti-HBs positive
- HBV vaccination prior to transplant, with target anti-HBs titers >10 IU/L, has been demonstrated to be protective for renal recipients of anti-HBc positive donors

Huprikar S et al. American Journal of Transplantation 2015;15:1162-72
Ouseph R, et al. Transplant Rev 2010;24:167-71

Algorithm for use of liver grafts from Anti-HBc (+) donors in recipients without chronic HBV



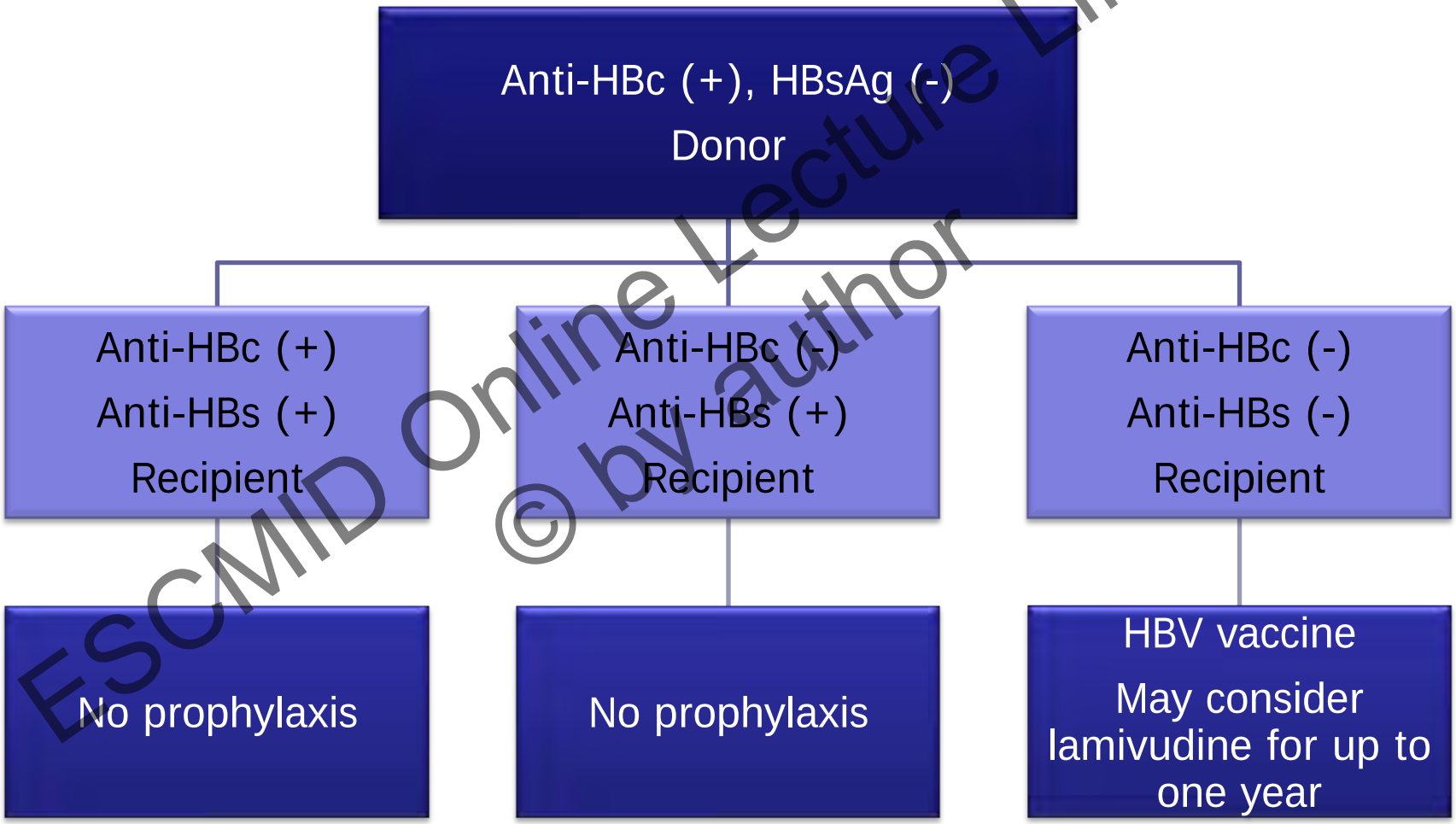
Adapted from: Huprikar S et al. American Journal of Transplantation 2015;15:1162-72

Antiviral use

- Lamivudine is recommended as the most cost effective choice for prophylaxis
- Entecavir or tenofovir may also be considered for prophylaxis due to their higher genetic barrier to resistance
- Indefinite duration of prophylaxis for non-immune recipients
- Discontinuation of prophylaxis may be considered after 1 year in recipients with confirmed persistence of immunity (anti-HBs 10 IU/mL)
- HBIG is not recommended
- HBV DNA with or without HBsAg should be monitored every 3 months for 1 year and then every 3–6 months indefinitely in all recipients regardless of current or prior prophylaxis strategy

Huprikar S et al. American Journal of Transplantation 2015;15:1162-72

Algorithm for use of non-liver grafts from Anti-HBc (+) donors in recipients without chronic HBV



Huprikar S et al. American Journal of Transplantation 2015;15:1162-72

Decompensated cirrhosis

- Risk of HBV reactivation
- LAM is not recommended
- First line agents; tenofovir, entecavir
  - Life long therapy
- With or without HBIG
- Risk of nephrotoxicity
  - Entecavir is recommended (Low risk of nephrotoxicity)
- NUCs on adjusted doses for renal function

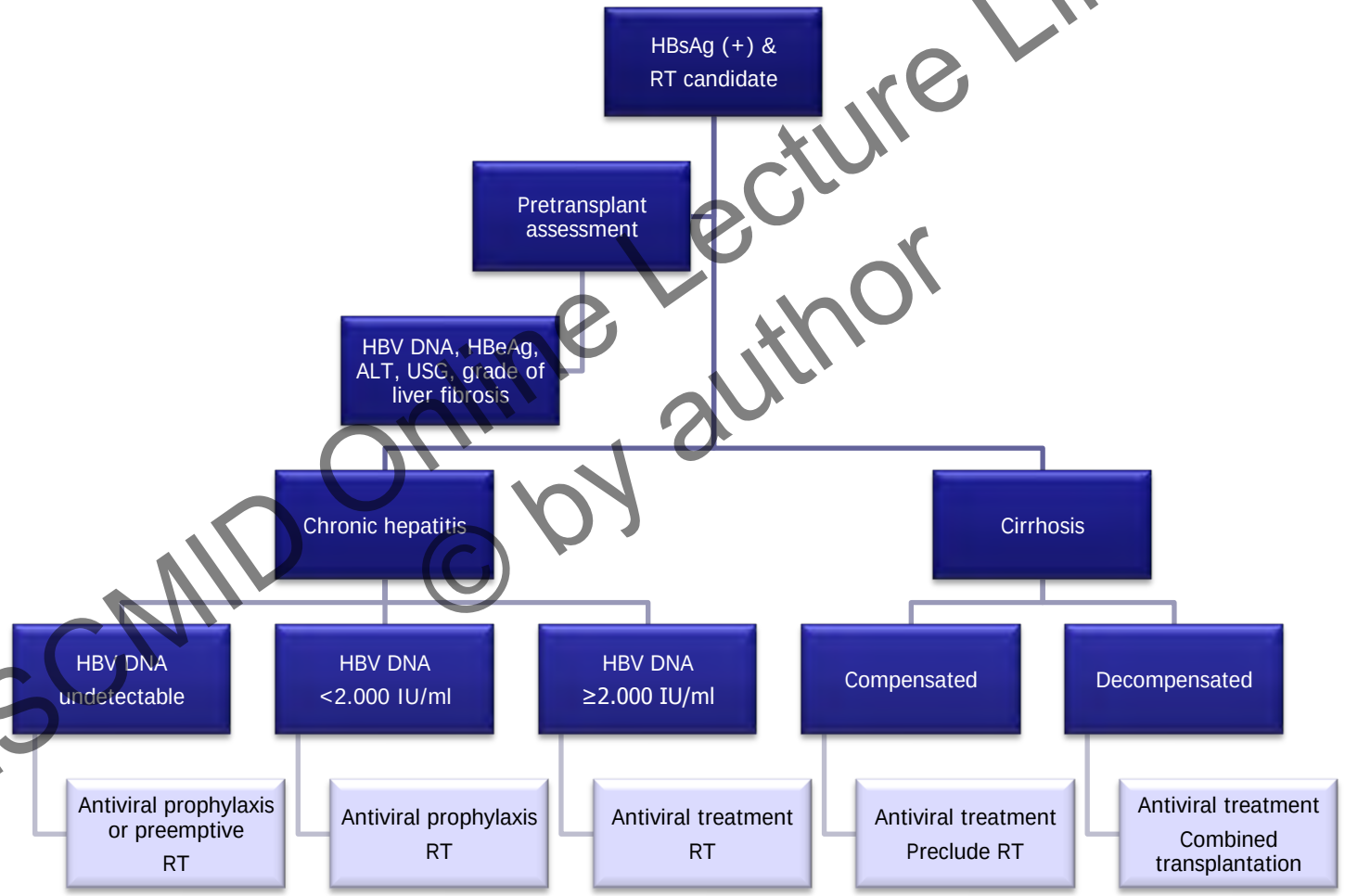
EASL. J Hepatol 2012;57(1):167-85

CHB and renal transplantation

- All HBsAg positive case should be considered for antiviral treatment before SOT
  - Entecavir or tenofovir
- Compensated cirrhotic patients are not candidates for RT
- Cirrhotic patients with decompensated disease should be evaluated for combined liver-kidney transplantation

Levitsky J et al. Am J Transplant 2013;13:147-68
Ridruejo E. World J Hepatol 2015;27:189-203

Treatment algorithm for management of renal transplant candidates with CHB



Adapted from: Tsai MC et al. World J Gastroenterol 2010;16(31):3878-87
Ridruejo E. World J Hepatol 2015;27:189-203

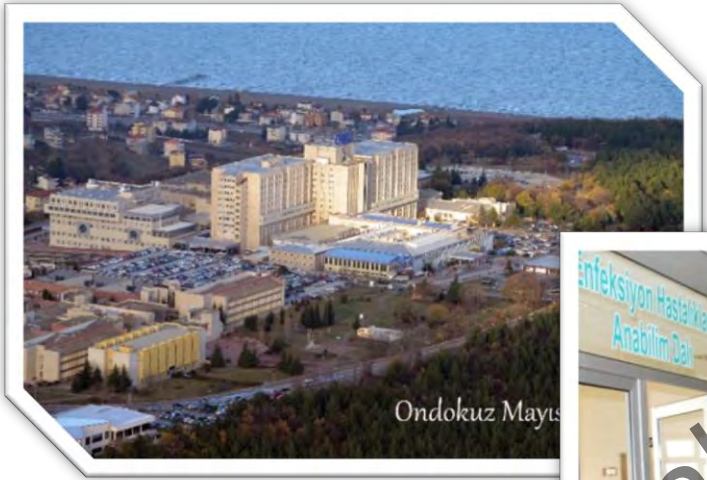
Treatment of HBV reactivation

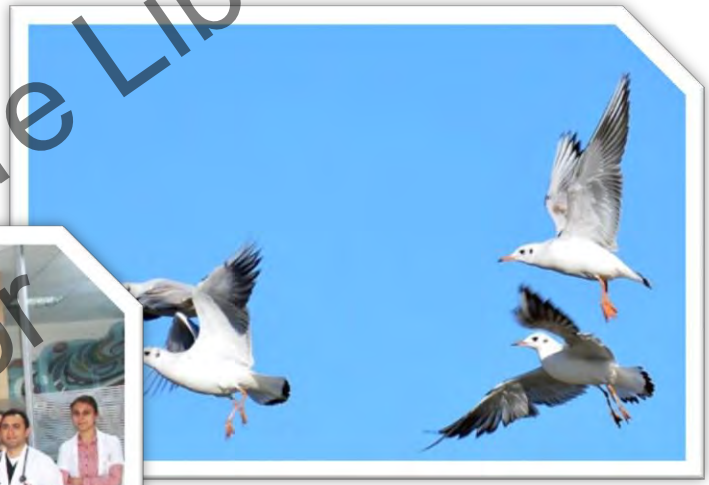
- Lead to liver failure
  - The risk is higher in patients with cirrhosis
- Lead to graft lost
- Check for causes of reactivation
  - Drug noncompliance, drug resistance
- Choice of drug
  - Prior prophylactic therapy
  - Presence of drug resistance mutants
- Entecavir and/or tenofovir

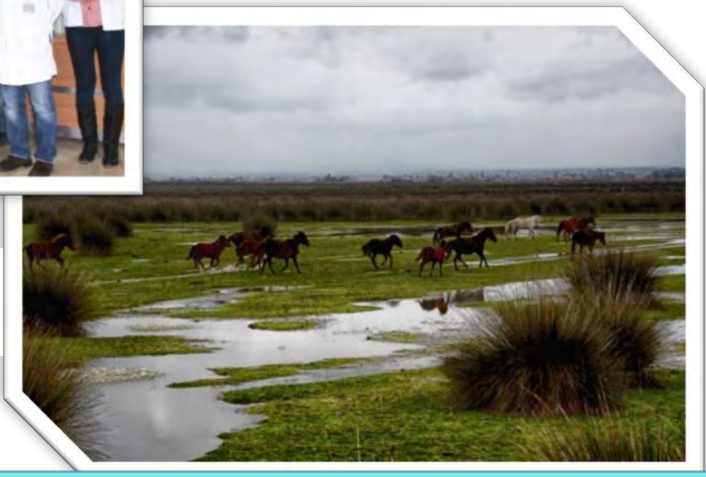
Take home messages

- Reactivation of HBV may result in graft loss, liver failure and death
- Screening of recipients and donors for HBV infection prior to transplantation is recommended
  - HBsAg, Anti-HBs, Anti-HBc
- All seronegative candidates should be vaccinated against HBV
- Early implementation of antiviral prophylaxis could prevent complications
- Antiviral therapy with NUCs before transplant decreases the risk of reinfection in CHB patients
  - First line agents; entecavir and tenofovir

ESCMID Observership Program
Collaborative Center







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