Immunosuppression and Hepatitis B Virus Reactivation

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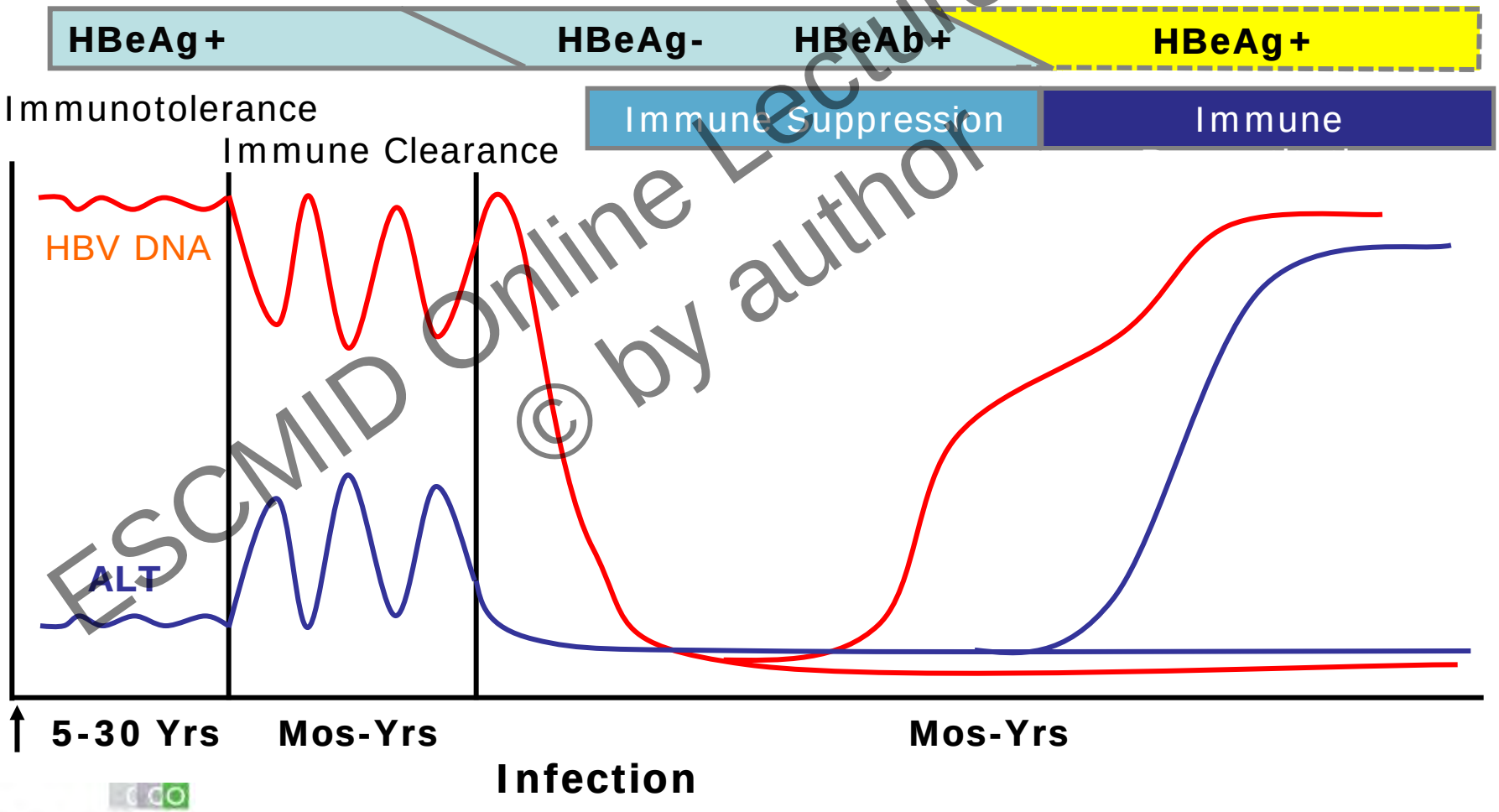
HBV reactivation



CLINICAL CARE OPTIONS HEPATITIS

Hoofnagle JH. Hepatology. 2009;49(5 suppl):S156-65

Definitions

HBV reactivation

- Increase in HBV replication (>2 $\log_{10}$ IU/mL) with ALT elevation

Reverse seroconversion

- Reappearance of HBsAg in a person who was HBsAg-negative, anti-HBc-positive

Recovered hepatitis B

- Seropositivity for anti-HBc without detectable HBsAg Anti-HBs

Di Bisceglie ET, et al. Hepatology. 2015;61:703-11

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

Immunomodulatory treatment

- Rheumatology
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Ankylosing spondylitis
  - Vasculitis
- Dermatology
  - Psoriasis
  - Pemphigus
- Gastroenterology
  - Irritable bowel syndrome
  - Autoimmune hepatitis

Rituximab and HBVr

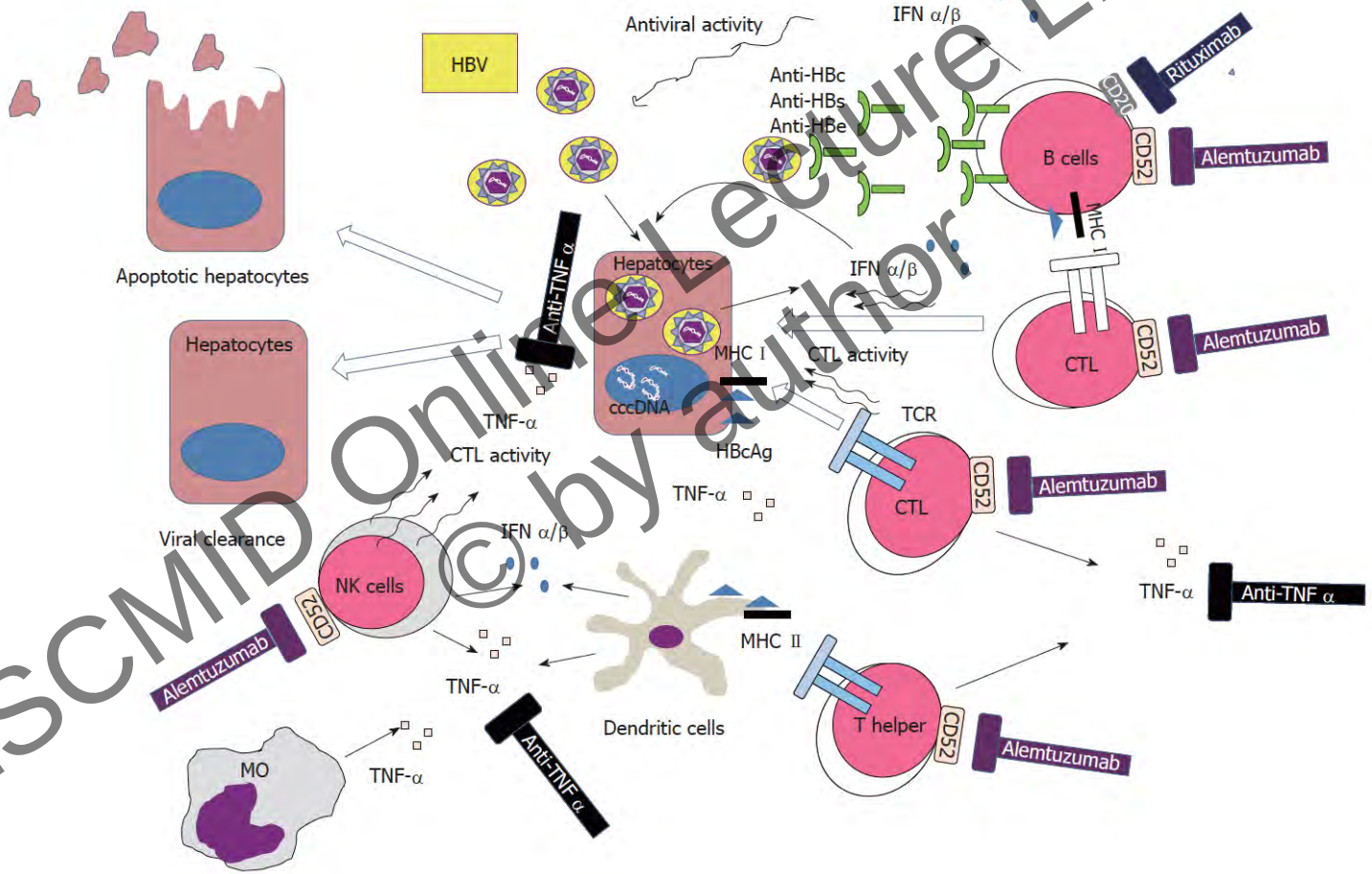
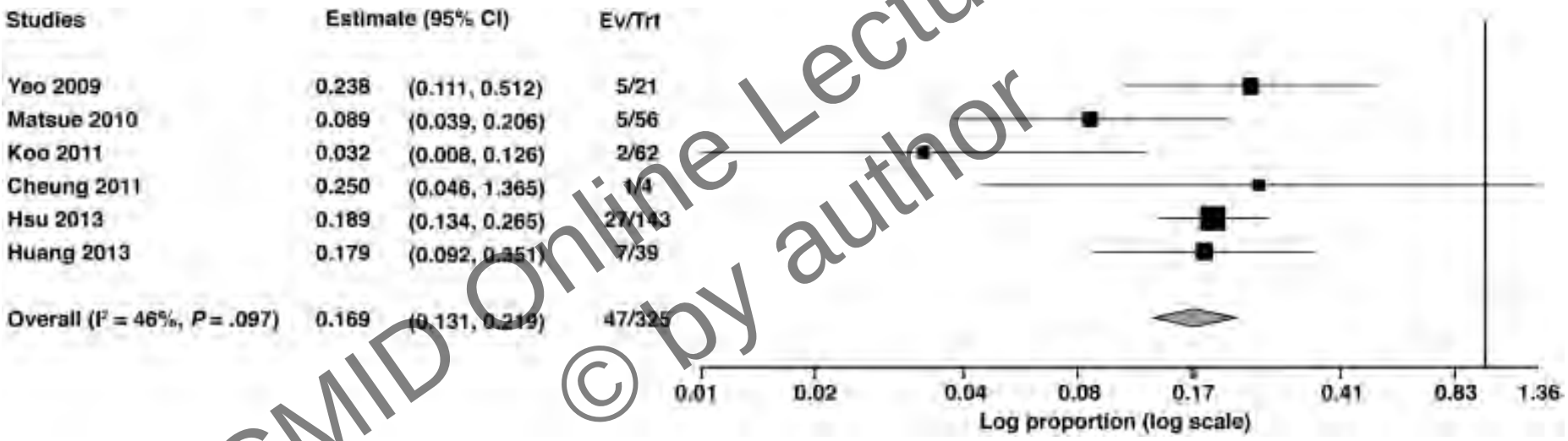


Figure 1 Pathogenetic hypothesis of hepatitis B virus reactivation following monoclonal antibody treatment. IFN: Interferon; TNF: Tumor necrosis factor; MHC: Major histocompatibility complex; NK: Natural killer; MO: Monocytes; TCR: T-cell receptor; CTL: Cytotoxic T lymphocyte; HBV: Hepatitis B virus; HBcAg: HBV core antigen.

Mastroianni CM, et al. World J Gastroenterol 2011;17(34):3881-7

Rituximab and HBVr



Perillo RP, et al. Gastroenterology 2015;148:221–244

Risk stratification for HBV reactivation

Therapy	HBsAg +ve	HBsAg -ve Anti-HBc +ve
Anti-CD20	Very high	Moderate
Hematopoietic stem cell transplantation	Very high	Moderate
High-dose corticosteroids	High	Low
Other cytokine inhibitors (anti-CD52)	High	Low
Combination cytotoxic chemotherapy	Moderate	Rare
Anti–tumor necrosis factor	Moderate	Rare
Anti–rejection therapy for solid organ transplant recipients	Moderate	Rare
Methotrexate, Azathioprine	Low	Rare

very high >20%, high 11%- 20%, moderate 1% - 10%, low <1%

Di Bisceglie ET, et al. Hepatology. 2015;61:703-11

HBVr: Differential diagnosis

- Acute hepatitis
- Superinfection
- Spontaneous reactivation of HBV
- Viral hepatitis due to other viruses
- Reactivation due to immunosupressive treatment
- Withdrawal of nucleos(t)ide analogs
- Resistance to NUCs
- Precore/core mutant
- Pregnancy

Puri P. J Clin Exp Hepatol 2013;3:301-12
Kim HY, Kim W. World J Gastroenterol 2014;20:14581-8

Case 1

- 48 years old female, doctor
- Born in Samsun, Turkey
- No past medical history including liver disease
- Laboratory values are normal
  - ALT 24 IU/L
- Planning
  - Surgery with radical mastectomy for early breast cancer
  - Chemotherapy with doxorubicin plus cyclophosphamide followed by paclitaxel

Do you recommend to screen for HBV?

① No

② All patients

③ High risk patients

Q1

Screening for HBV

CDC, EASL, APASL, IOM

- All patients

AASLD

- High risk for HBV

ASCO

- High risk for HBV or highly immunosuppressive therapy

AASLD:High risk individuals

- Immigrants
  - Asia, Africa, Pacific Islands, Middle East, Eastern Europe, South/Central America, Caribbean, Aboriginal
- Children of immigrants
- Men who have sex with men
- HIV/HCV positive
- History of IDU, incarceration
- Hemodialysis patients

AASLD

Lok AS, et al. Hepatology 2009;50:661-2

Risk factors for HBVr

- Host factors
  - Male gender
  - Young age
  - Elevated baseline ALT
- Tumor related factors
  - Lymphoma
  - Hematologic malignancies
  - Breast cancer
- Treatment related
  - Hematopoetic stem cell transplantaion
  - Glucocorticoid use
  - Anthracycline use
  - Rituximab-based regimen
- Viral factors
  - High viral load
  - HBsAg positive
  - Presence of precore mutant
  - Occult HBV infection

Kim HY, Kim W. World J Gastroenterol 2014;20:14581-8

Risk of HBVr

- Hematologic malignancy ≈ 48%
- Breast cancer 41%- 56%
  - 35% chemotherapy interruption due to HBVr
- Non-Hodgkin lymphoma 24% - 67%
- Bone marrow transplantation
  - HBVr 54% (need preemptive therapy)
  - Reverse seroconversion in cases with anti-HBc positive alone
    - Become HBsAg positive 50%

The mortality rate is up to 25%

Kim HY, Kim W. World J Gastroenterol 2014;20:14581-8
Lau GK, et al. Bone Marrow Transplant. 1997;19:795-9
Onozawa M, et al. Transplantation. 2005;79:616-9
Lok AS, et al. Gastroenterology. 1991;100:182-8

HBVr: French survey

- Screening for HBV
  - Corticosteroids 44%
  - Immunosuppressive 67%
  - Immunomodulatory (rituximab, anti-TNF) 76%
  - No detection 19%
- HBV vaccination for seronegative cases <50%
- 89% of participants think that they are not sufficiently educated regarding the risks of HBV reactivation and its prevention

Terrier B, et al. Rev Med Interne 2012;33:4-12

HBVr: International survey

- 30-point questionnaire to members of AASLD
  - Diagnostic criteria, HBV screening, antiviral prophylaxis and clinical outcomes
- 99 respondents reported 188 patients with HBVr
  - Hepatologists or gastroenterologists
- 128 patients had hematologic malignancies
  - of which 88 (70%) had lymphoma
- 75 patients (40%) had screening for both HBsAg) and anti-HBc, 24 patients (13%) had HBsAg screening alone
- 10% of patients was given prophylactic antiviral therapy
- Death due to liver failure was 23%

Hwang JP, et al. J Viral Hepatitis 2015;22:346-52

Delayed recognition of HBV reactivation

- Hepatitis
  - Severe or fulminant
- Misdiagnosis
  - HBV –ve & ALT elevation
    - HBV DNA may fall when ALT rises
- Interruption of chemotherapy
  - Poor prognosis of malignancy
  - Cancer related death

Seetharam A et al. Curr Hepatology Rep 2014;13:235-44

What is the optimal screening strategy?

- Screening high-risk individuals requires recognition of high-risk population
  - Surveys indicated that there is need for education of physicians
- Screening all patients is most cost-effective and easiest to implement

Which test(s) dou you recommend?

① Test for HBsAg

② Test for HBsAg, Anti HBc

③ Test for HBsAg, Anti HBc, Anti HBs

Q2

Screening for HBV

AASLD, APASL, EASL

- HBsAg, Anti-HBc

CDC

- HBsAg, Anti-HBc, Anti-HBs

ASCO

- HBsAg

Case (con't)

- HBsAg +ve, Anti HBs –ve, Anti HBc +ve
- HBeAg –ve, Anti HBeAg +ve
- Anti HDV -ve
- HBV DNA 1.000 IU/ml
- ALT is normal
- Liver USG is normal

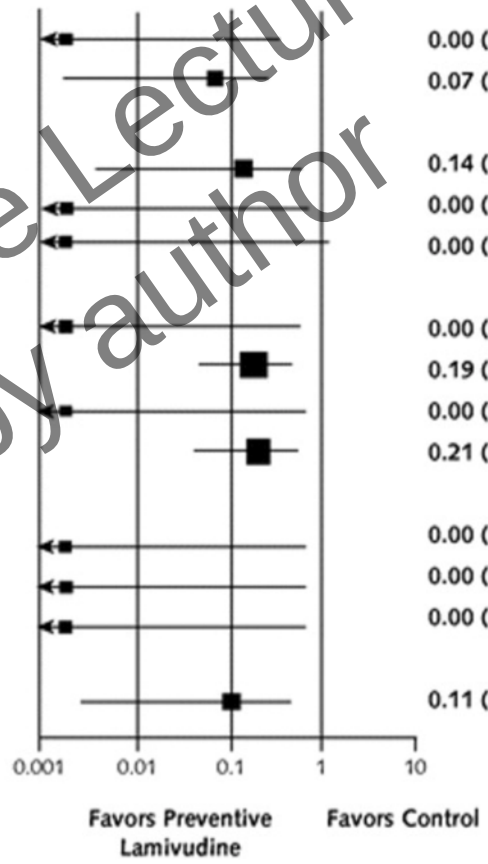
Which prophylaxis do you prefer?

① Lamivudin
② Telbivudin
③ Entecavir
④ Tenofovir

Q3

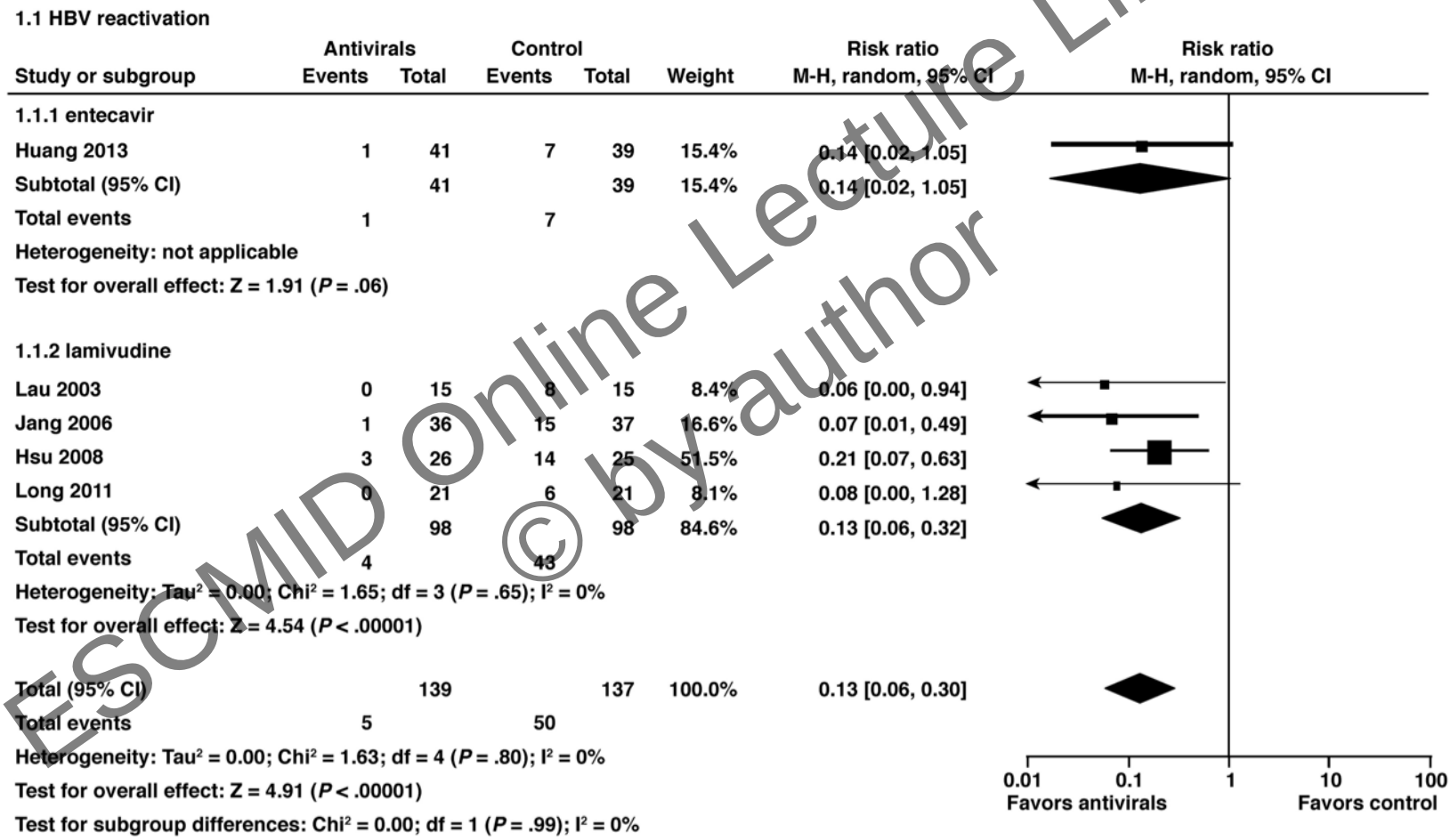
Pre-emptive treatment with LAM

Study, Year (Reference)	Lamivudine Group, *n/n*	Control Group, *n/n*	Relative Risk (95% CI)
Randomized, controlled trial*			
Lau et al., 2003 (8)	0/15	8/15	0.00 (0.00–0.39)
Jang et al., 2006 (21)	1/36	15/37	0.07 (0.01–0.35)
Prospective cohort study with controls*			
Jia and Lin, 2004 (20)	1/8	7/8	0.14 (0.01–0.67)
Idilman et al., 2004 (24)	0/8	5/10	0.00 (0.00–0.79)
Shibolet et al., 2005 (25)	0/9	2/5	0.00 (0.00–1.31)
Prospective cohort study with historical controls*			
Dai et al., 2004 (22)	0/11	5/9	0.00 (0.00–0.61)
Yeo et al., 2004 (15)	3/65	47/193	0.19 (0.04–0.52)
Yeo et al., 2005 (13)	0/16	6/21	0.00 (0.00–0.75)
Hsu et al., 2006 (23)	3/26	14/25	0.21 (0.04–0.59)
Retrospective cohort study†			
Lim et al., 2002 (17)	0/16	7/19	0.00 (0.00–0.56)
Leaw et al., 2004 (19)	0/11	17/53	0.00 (0.00–0.86)
Nagamatsu et al., 2004 (16)	0/8	6/9	0.00 (0.00–0.66)
Retrospective cohort study*			
Lee et al., 2003 (18)	1/11	17/20	0.11 (0.01–0.46)



Loomba R et al. Ann Intern Med. 2008;148:519-28

Efficacy of pre-emptive treatment



1.1 HBV reactivation

Study or subgroup	Antivirals Events	Antivirals Total	Control Events	Control Total	Weight	Risk ratio M-H, random, 95% CI
1.1.1 entecavir						
Huang 2013	1	41	7	39	15.4%	0.14 [0.02, 1.05]
Subtotal (95% CI)		41		39	15.4%	0.14 [0.02, 1.05]
Total events	1		7			
Heterogeneity: not applicable						
Test for overall effect: Z = 1.91 (*P* = .06)						
1.1.2 lamivudine						
Lau 2003	0	15	8	15	8.4%	0.06 [0.00, 0.94]
Jang 2006	1	36	15	37	16.6%	0.07 [0.01, 0.49]
Hsu 2008	3	26	14	25	51.5%	0.21 [0.07, 0.63]
Long 2011	0	21	6	21	8.1%	0.08 [0.00, 1.28]
Subtotal (95% CI)		98		98	84.6%	0.13 [0.06, 0.32]
Total events	4		43			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.65$; df = 3 (*P* = .65); $I^2 = 0\%$						
Test for overall effect: Z = 4.54 (*P* < .00001)						
Total (95% CI)		139		137	100.0%	0.13 [0.06, 0.30]
Total events	5		50			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.63$; df = 4 (*P* = .80); $I^2 = 0\%$						
Test for overall effect: Z = 4.91 (*P* < .00001)						
Test for subgroup differences: $Chi^2 = 0.00$; df = 1 (*P* = .99); $I^2 = 0\%$						

Risk ratio M-H, random, 95% CI

0.01 0.1 1 10 100

Favors antivirals Favors control

87% relative risk reduction (RRR) of reactivation with prophylaxis

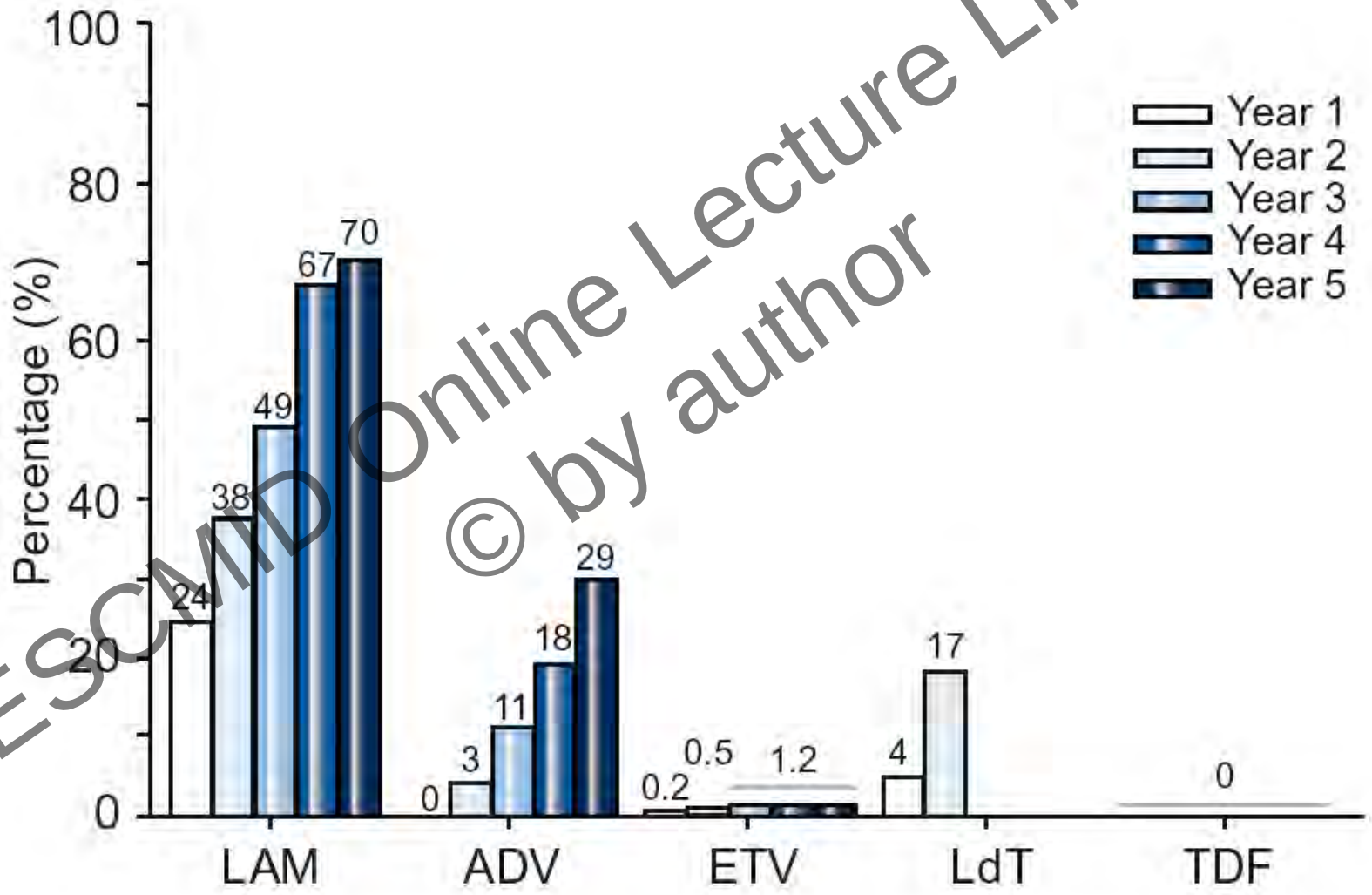
Perillo RP, et al. Gastroenterology 2015;148:221–244

Tenofovir: Real life experience

- 38 patients
- 25 cases received prophylaxis
  - No HBV flare
- 13 cases were treated for HBV reactivation
  - All patients became HBV-DNA negative at 9 months

Koskinas JS et al. Journal of Hepatology 2012;57:167-85

Risk of resistance in naïve patients



EASL CPG 2012. Journal of Hepatology 2012;57:167-85

Choice of antiviral therapy and monitoring

- Choice of therapy affected by HBV DNA level
  - HBV DNA < 2000 IU/mL: any therapy can be used (including lamivudine)
  - HBV DNA > 2000 IU/mL: entecavir or tenofovir
- Choice of therapy affected by duration of therapy
  - > 12 mos: entecavir or tenofovir
- HBV DNA and ALT should be monitored every 3 mos

EASL CPG 2012. Journal of Hepatology 2012;57:167-85
Lok AS, et al. Hepatology. 2009;50:661-2

What is the duration of treatment?

① During the immunosuppressive treatment

② During the immunosuppressive treatment and 6 months after cessation of IS treatment

③ During the immunosuppressive treatment and 12 months after cessation of IS treatment

④ Until seroconversion to Anti-HBs

⑤ Life long

Q4

When to stop

EASL

- Regardless of baseline HBV DNA, 12 months after cessation of therapy

AASLD

- If baseline HBV DNA < 2000 IU/mL: continue antiviral therapy 6 months after cessation of therapy

AASLD

- If baseline HBV DNA > 2000 IU/mL: continue antiviral therapy until reach the therapeutic endpoints

Do you recommend prophylaxis for cases with Anti-HBc +ve alone?

① No

② No, I monitor HBV DNA for 1-3 months interval

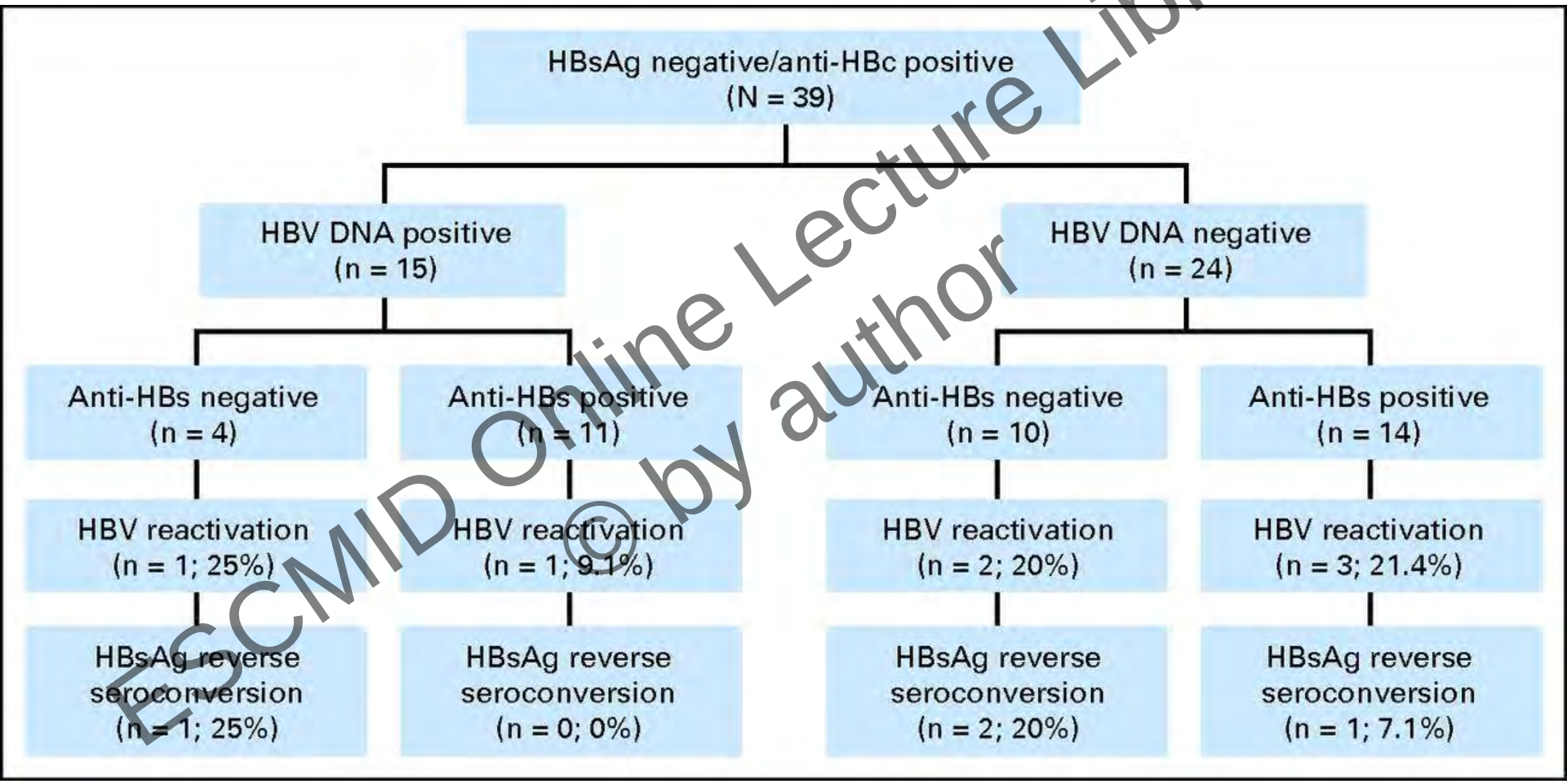
③ Yes, if HBV DNA positive

④ Yes if in those receiving anti- CD20 therapies and in those undergoing HSCT or solid organ transplantation even HBV DNA –ve

You can choose more than one option

Q5

Rituximab and HBVr



Huang YH, et al. J Clin Oncol 2013;32:2765-72

Anti HBc alone

AASLD

- Monitor HBV DNA, treat if becomes detectable

APASL

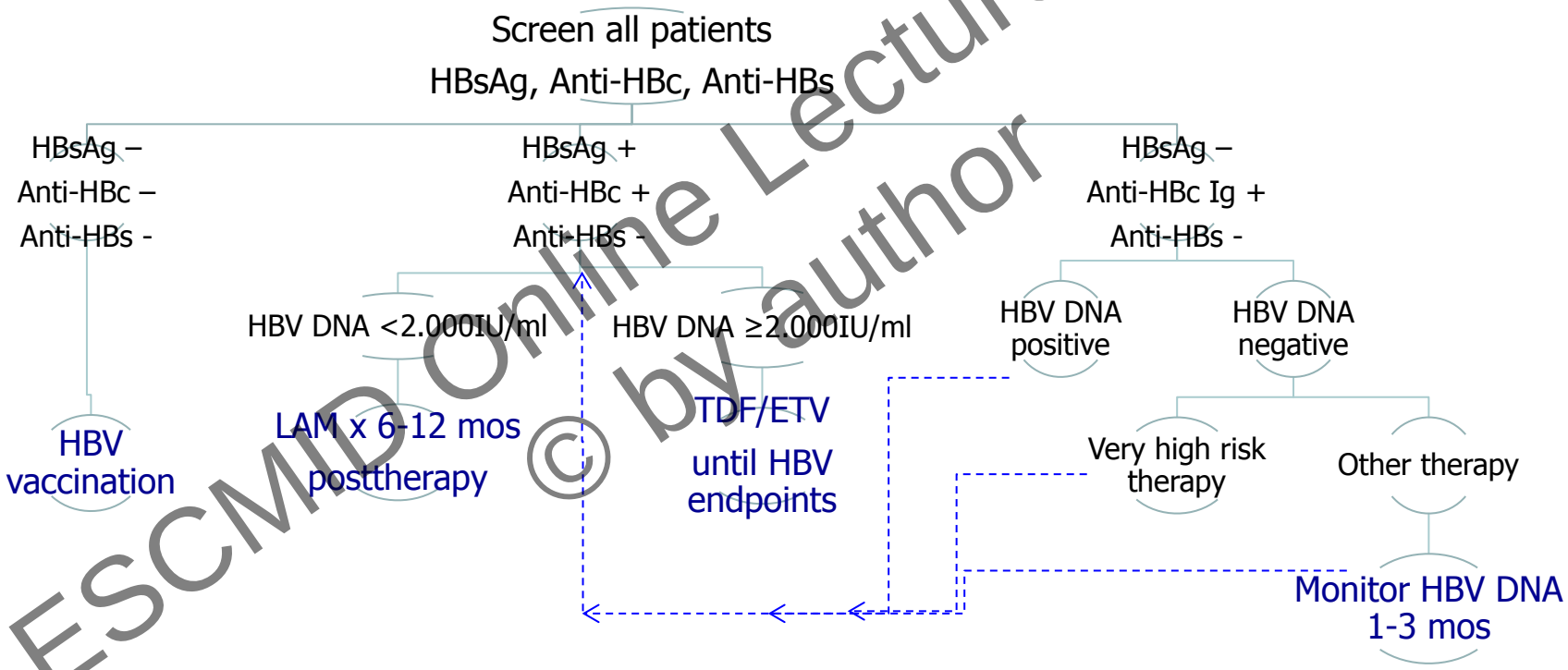
- Monitor HBV DNA, treat if needed

Anti HBc alone

- If HBV DNA is detectable patients should be treated similarly to HBsAg positive patients
- If HBV DNA is undetectable should be followed carefully by means of ALT and HBV DNA testing (1–3 months interval)
- Some experts recommend prophylaxis with lamivudine in all HBsAg-negative, anti-HBc positive patients who receive rituximab and/or combined regimens for hematological malignancies

EASL CPG 2012. Journal of Hepatology 2012;57:167-85

Management



Di Bisceglie ET, et al. Hepatology. 2015;61:703-11

Conclusion

- HBV reactivation is common during immunosuppressive and immunomodulatory treatment including resolved HBV infection
- All patients should screened for HBV infection
  - HBsAg, Anti-HBc
- Early effective treatment prevent HBV reactivation and save lives