HBV reactivation and immunosuppression

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Agenda

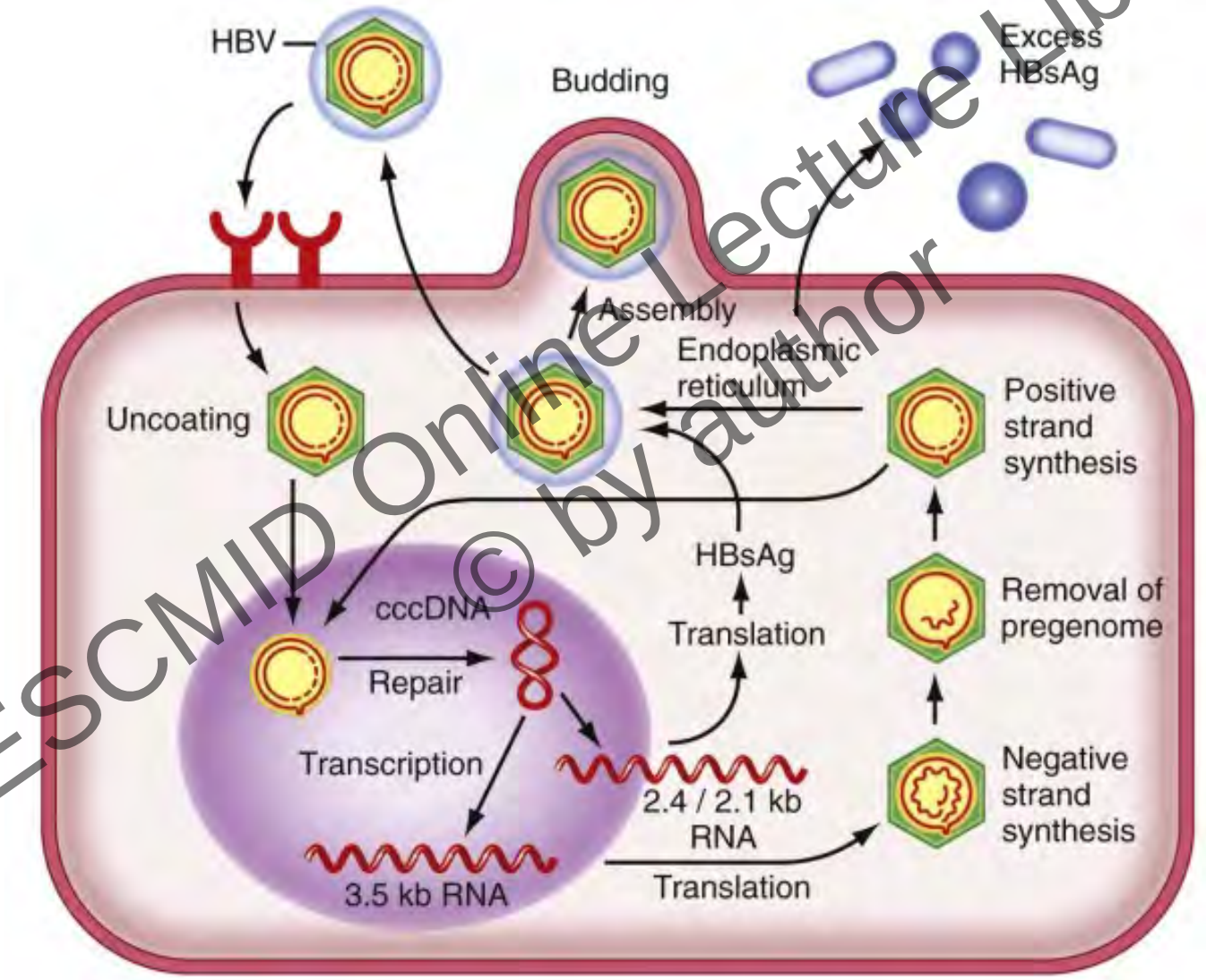
- What is HBV reactivation?
- Can we identify risk groups?
- What are the clinical consequences?
- How to prevent ?
- When to stop therapy?

DEFINITION OF HBV REACTIVATION

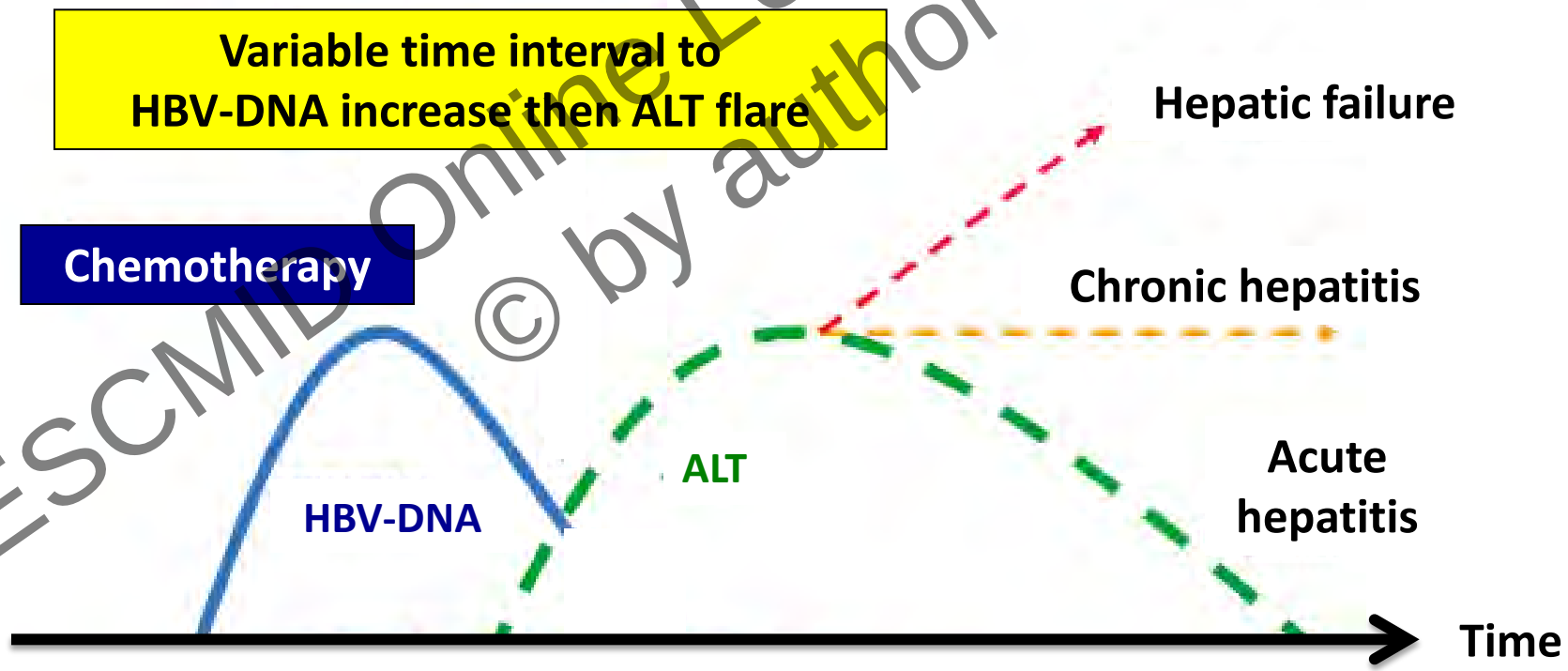
HBV infection is not cured but controlled by the immune system

- Inflammation: normal serum ALT
- Histology: normal liver biopsy
- Virology: serum HBV DNA below detection pcr assay
- Immunology:
  - HBeAg to anti-HBe seroconversion
  - HBsAg to anti-HBs seroconversion

Persistence of cccDNA in the nucleus of hepatocytes



HBV reactivation



Definition HBV reactivation

- At least 1 log increase in HBV-DNA or

reverse HBe-seroconversion HBe(-) → HBe(+)

- ALT elevation: three times upper limit of normal or absolute increase of 100 IU/l

- In a patient known with overt or occult HBV infection

- Other causes of hepatitis should be excluded

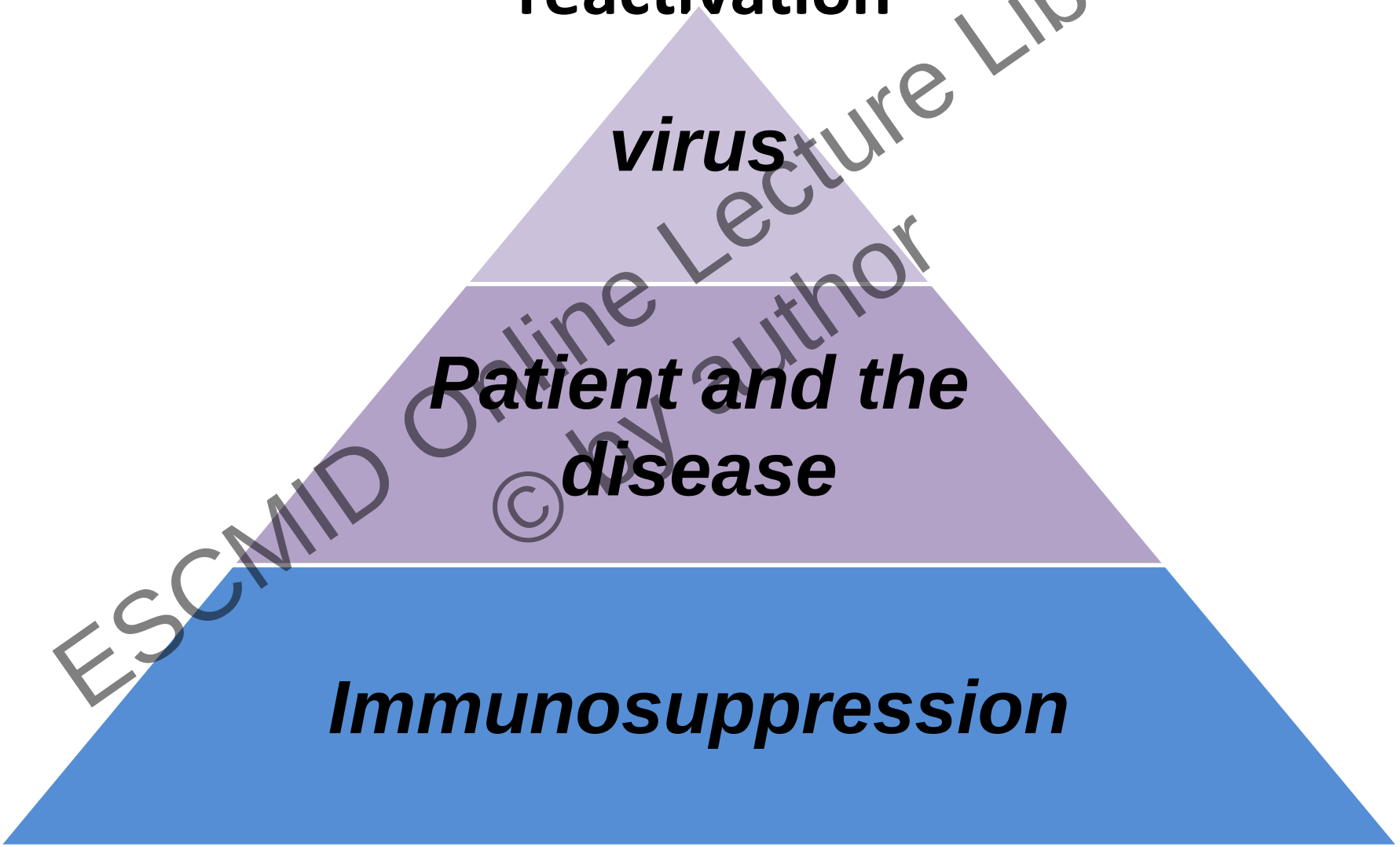
Situations at risk of reactivation

- **Overt HBV infection:** HBsAg (+)

- **Occult HBV infection:** HBsAg(-)
  - Anti-core (+) only
  - Anti-core (+) and anti-HBs (+)

WHO IS AT RISK OF REACTIVATION ?

Determinants of outcome of HBV reactivation



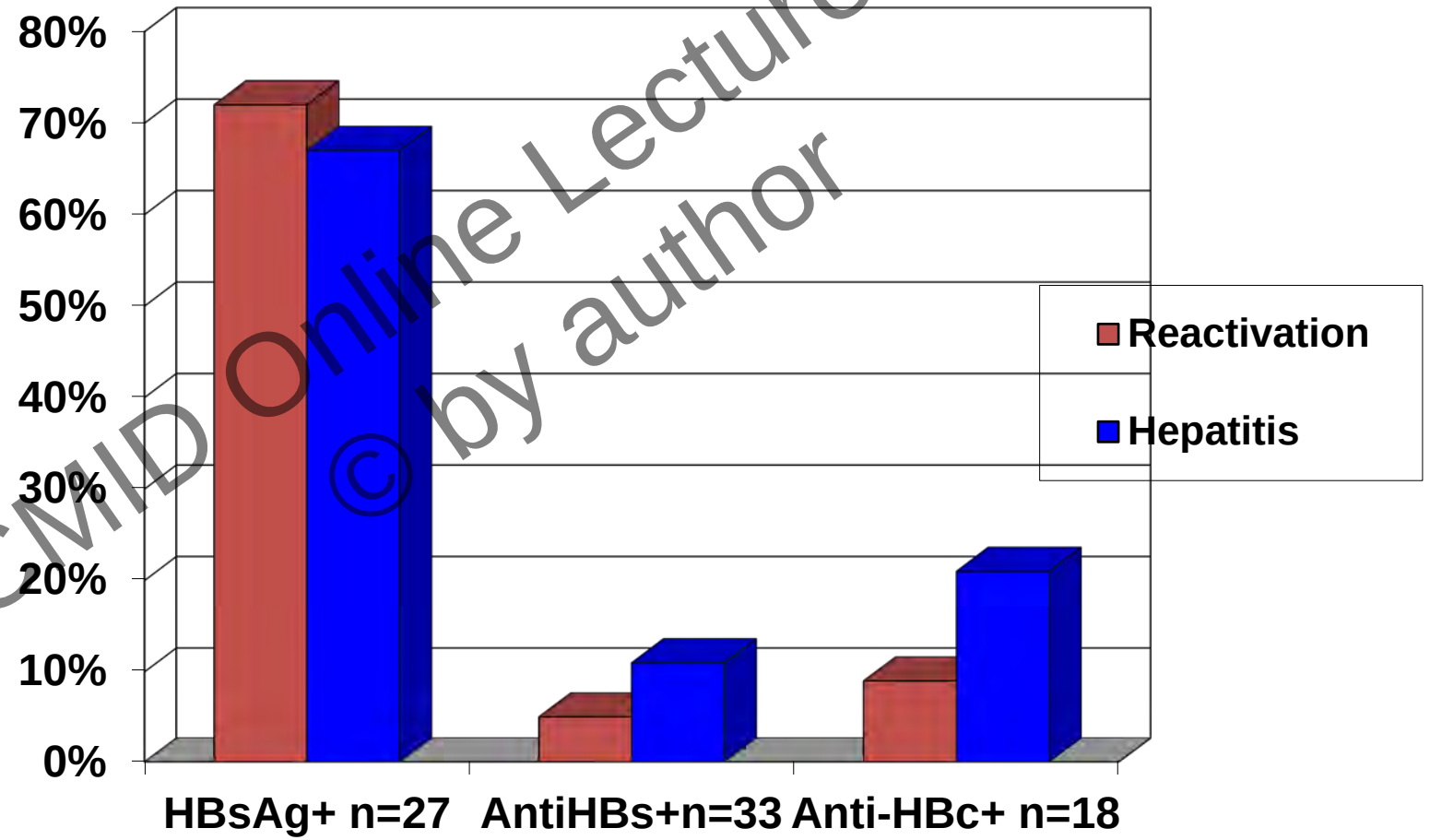
Br.J. Cancer 2004;90:1306

Determinants of outcome: viral factors

- HBsAg positivity
- HBeAg positivity
- High HBV-DNA
- Genotype B
- Absence of anti-HBs before therapy

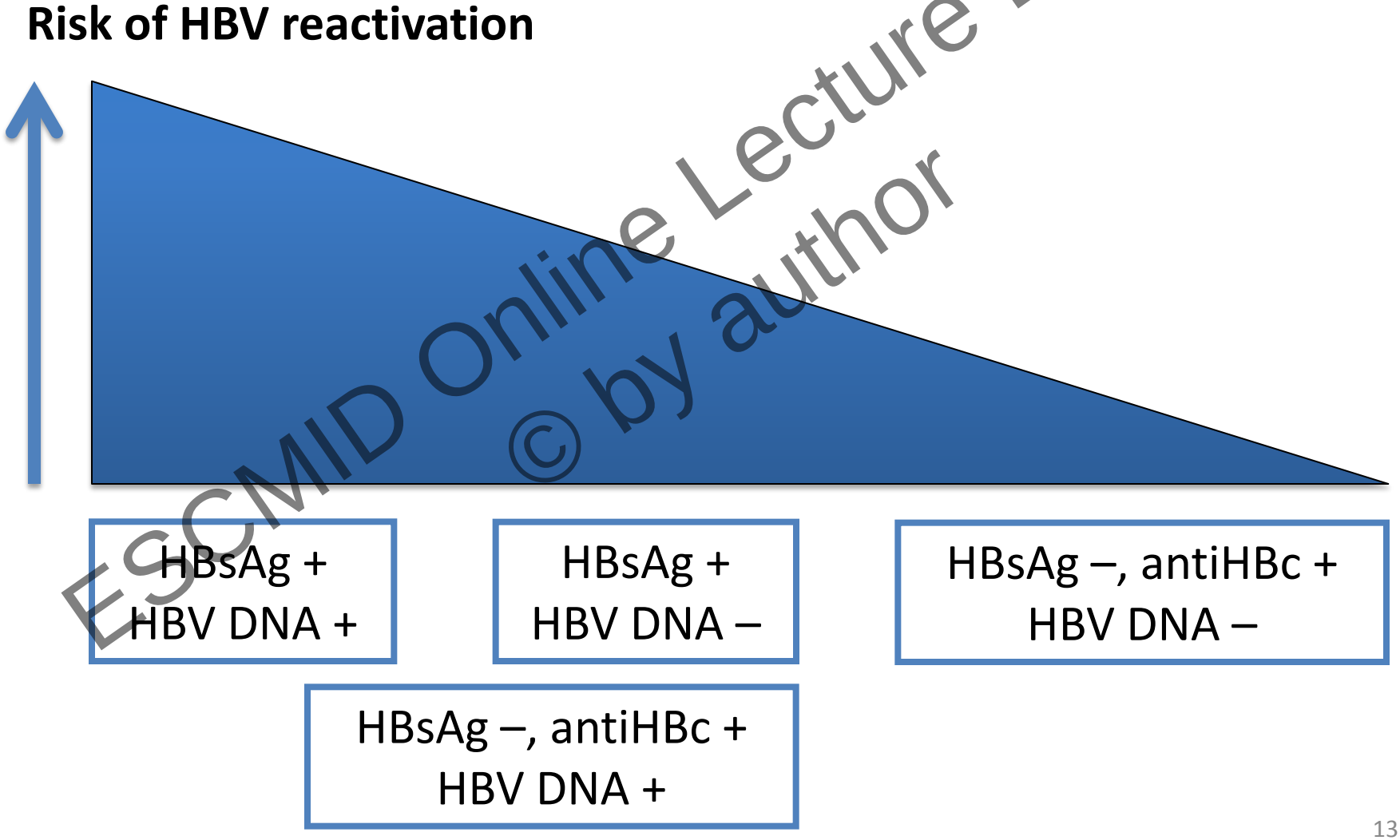
Determinants of outcome: viral factors

100 Chinese patients treated for a non hodgkin lymphoma



Lok;Gastroenterology 1991;100:182-188.

HBV reactivation: HBV-related risk factor



Determinants of outcome: intensity of immunosuppression

- Immunosuppressive drugs
  - Pulse corticosteroid therapy
  - Rituximab (anti-CD20)
  - CHOP or r-CHOP courses
- Other situations
  - HIV
  - Bone marrow transplants

HBV reactivation: Chemotherapy-related risk factor

- 244 consecutive patients treated for lymphoma
- and HBsAg – (Jan 2000 – May 2005)

➢ HBV-related hepatitis: 3.3%

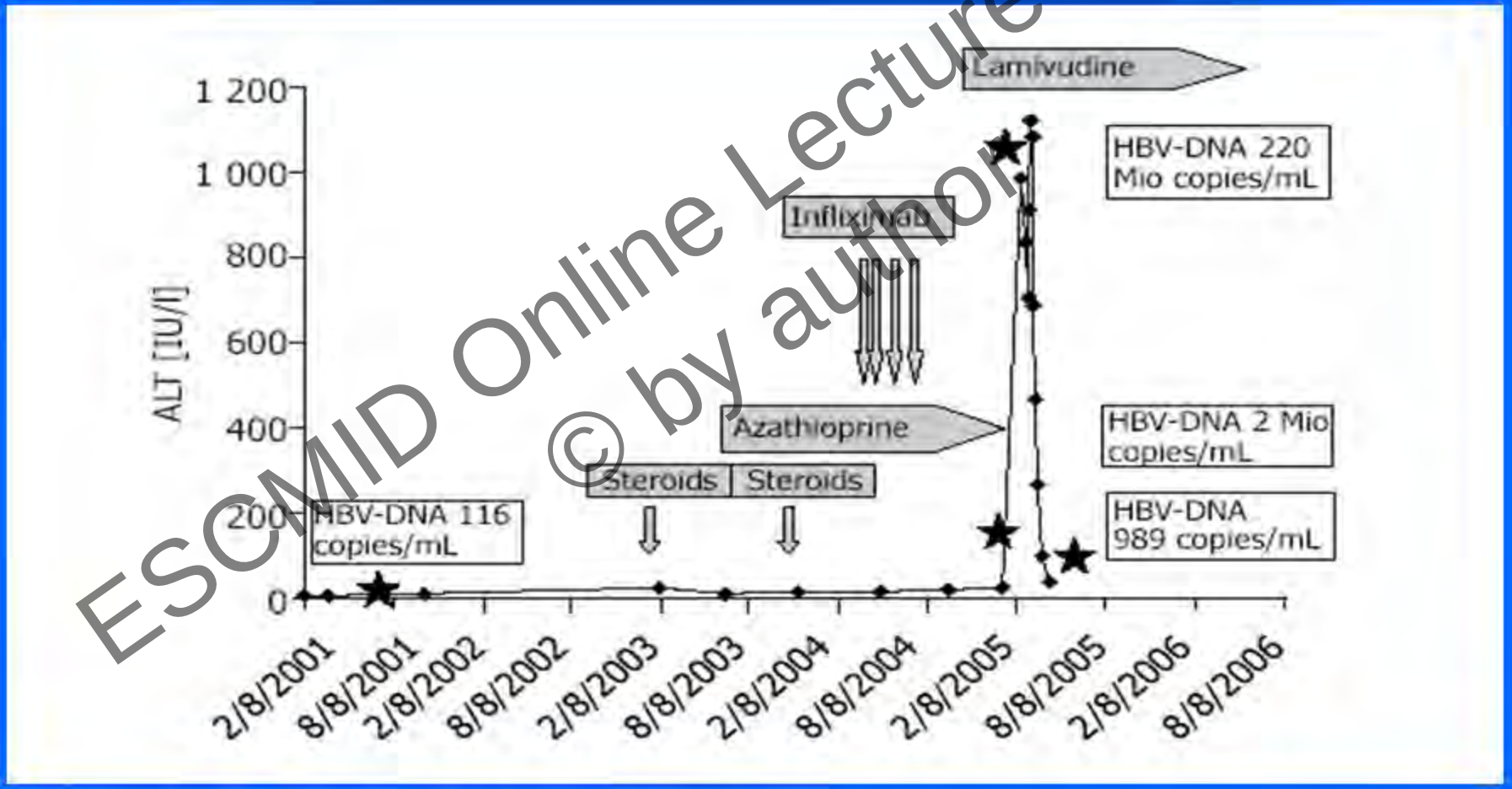
Multivariate analysis of risks for HBV reactivation in patients with HBsAg –

Regimen	aRR	CI 95%	p
Rituximab + Steroids-containing	13.8	2.8 – 68.3	.001
Rituximab-containing	1.3	0.1 – 20.4	.263
Steroids-containing	5.0	0.6 – 40.9	.105

Hui et al. Gastroenterology 2006

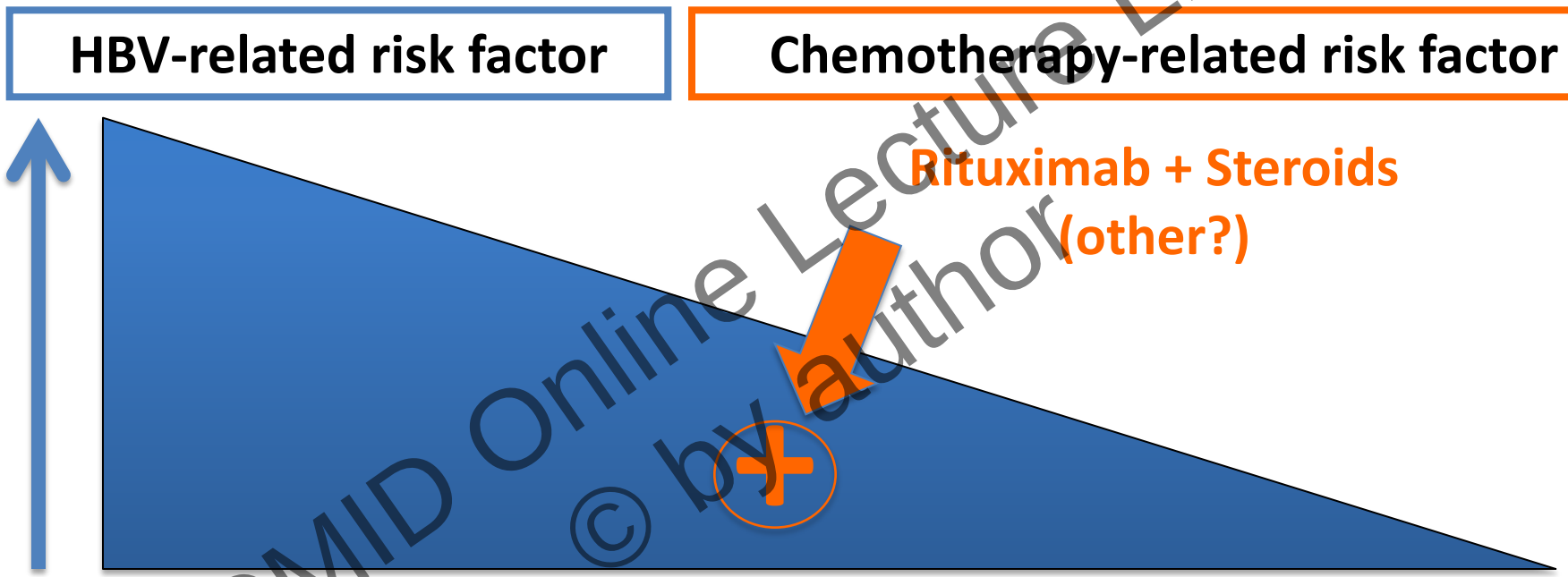
Subfulminant hepatitis B after infliximab in Crohn's disease: Need for HBV-screening?

Gunda Millonig, Michaela Kern, Othmar Ludwiczek, Karin Nachbaur, Wolfgang Vogel



Millonig et al. World J of Gastroenterol. 2006

HBV reactivation: risk factor



Determinants of outcome: host related factors

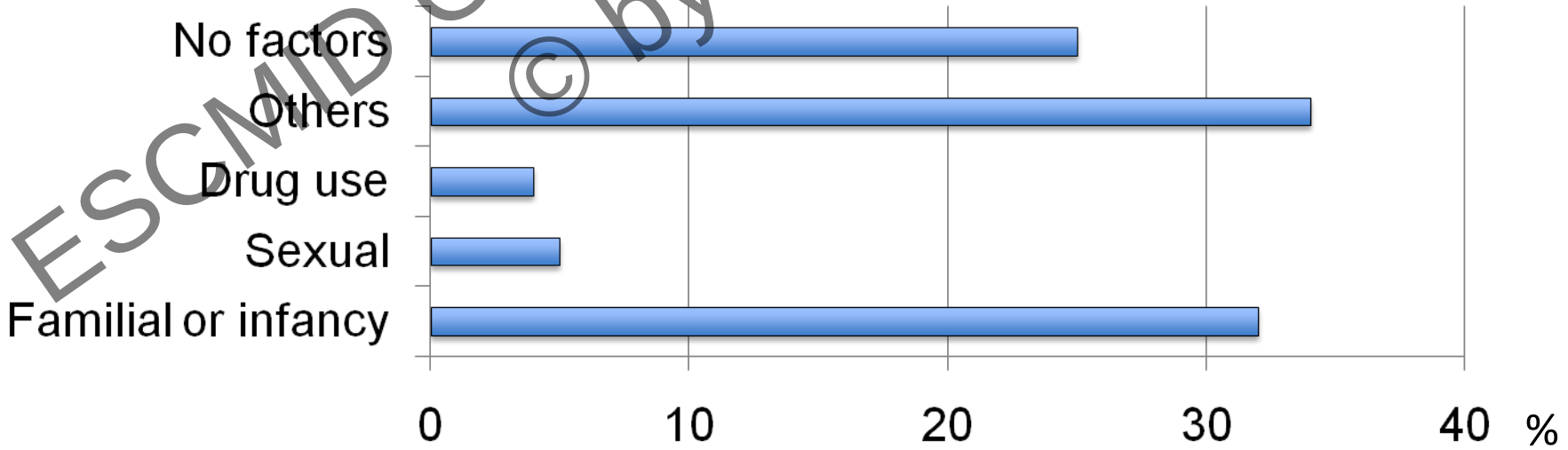
- Male sex
- Younger age
- Type of malignancy: lymphoma, bone marrow transplantation
- Failure to screen before therapy

WHO AND HOW TO SCREEN?

Screening high risk patients for HBV?

- French survey evaluating risk factors for HBsAg acquisition in patients followed in reference centers
- Naïve of treatment at first referral (n=1,016)
  - Born in moderate-high endemic countries 78%
  - Born in low endemic countries 22%

Identified risk factors in HBsAg + patients born in low endemic countries



Larsen et al. BEHweb 2010

Who to screen ?
Recommendations

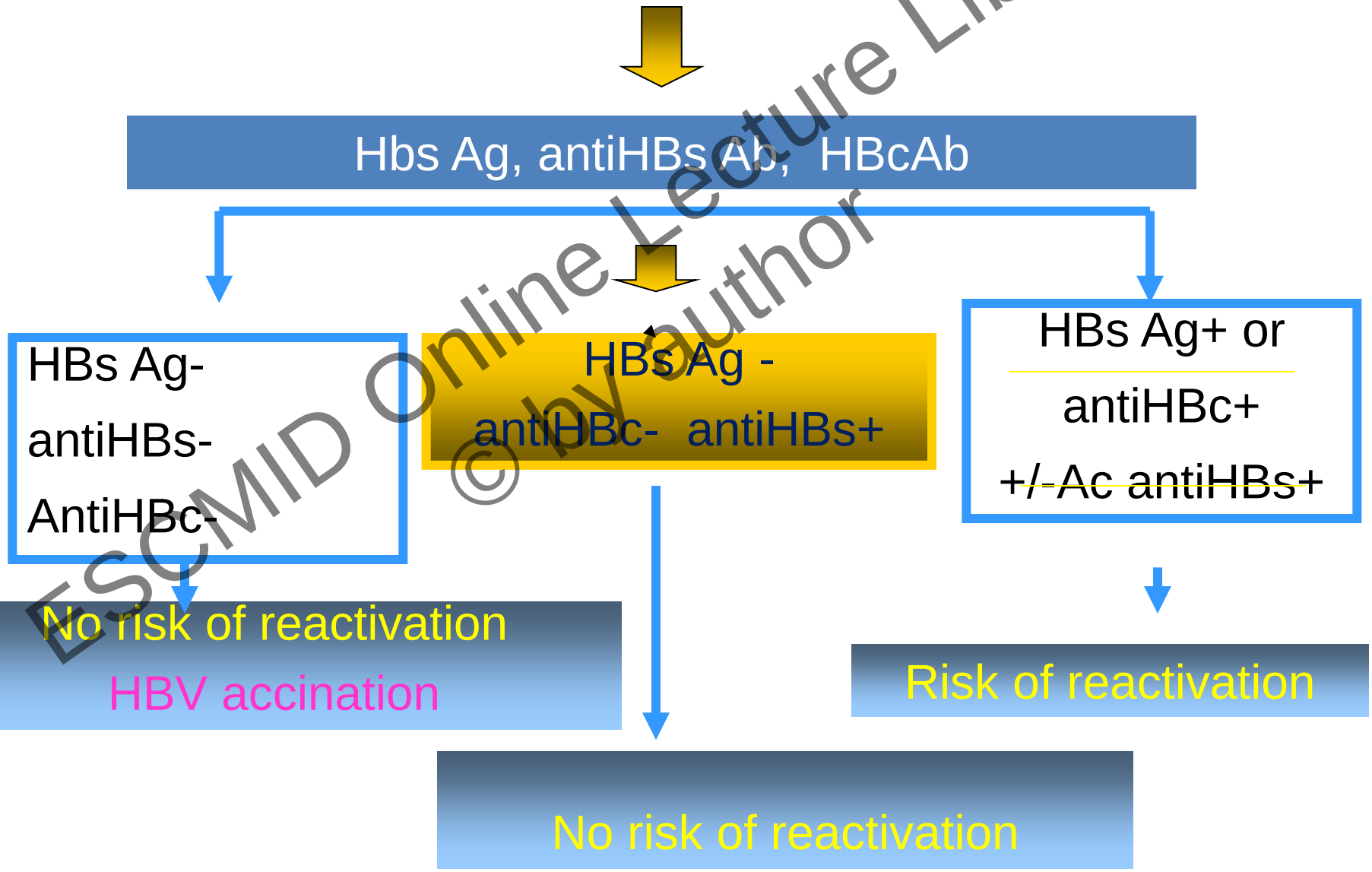
Center for Diseases Control[1]
Institute of Medicine[2]
European Association for the Study of Liver Diseases[3]

→ All patients with immunosuppression

"… all candidates for chemotherapy or immunosuppressive therapy should be screened for HBsAg and antiHBc prior to initiation of treatment (A1)"

[1]Weinbaum et al. MMWR Recomm Rep 2008
[2]Colvin & Mitchell (eds). Institute of Medicine 2010
[3]EASL – Clinical Practice Guidelines. J Hepatol 2012

Screening before immunosuppressive therapy



Evaluation to help treatment decision ?

- HBeAg, anti-HBe, HBV DNA ,
- Delta Ab
- Hepatic evaluation, PT, albumin, hemogram
- Liver echography

HBV screening in clinical practice
Prior immunosuppressive therapy

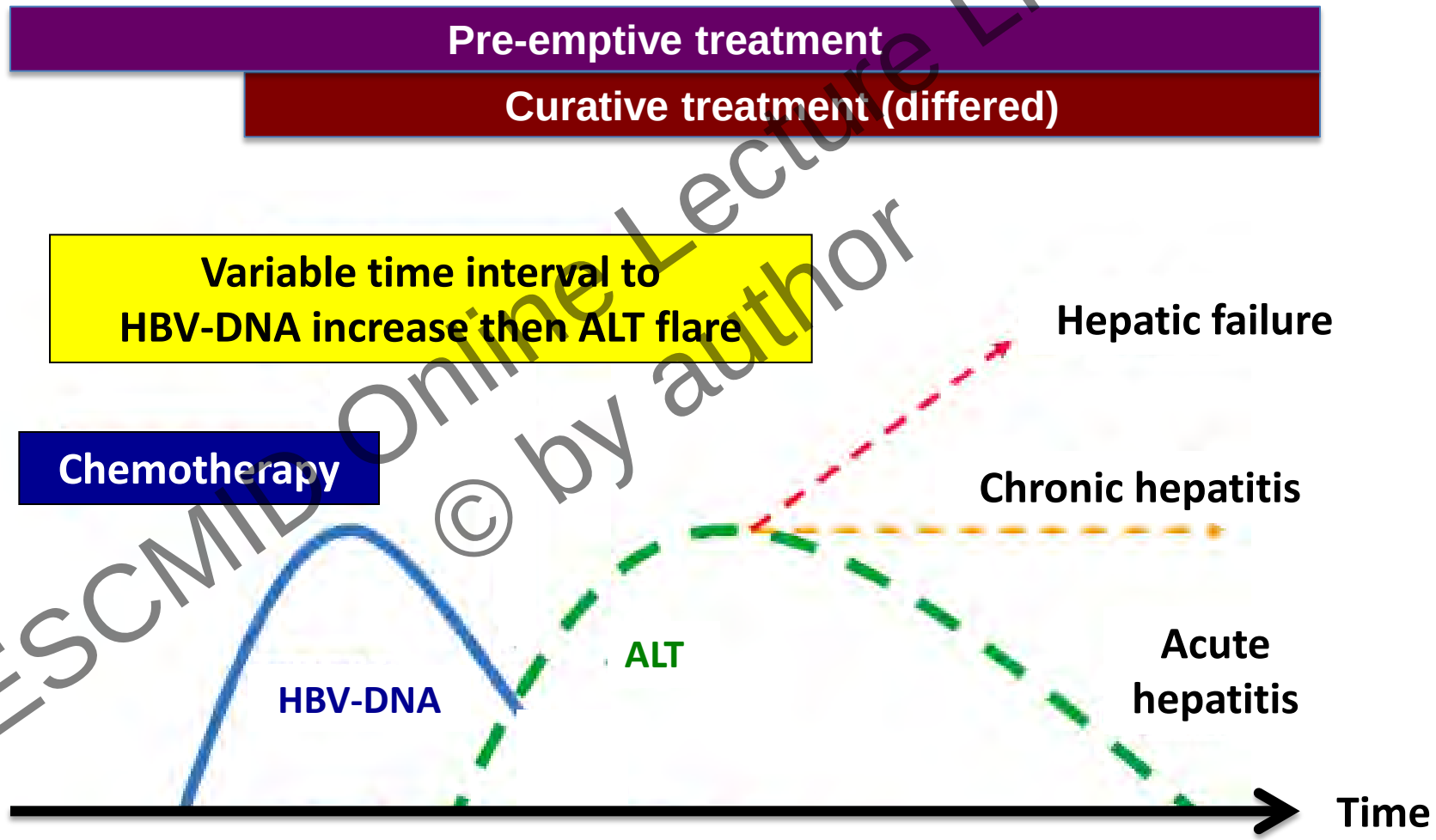
- Cross-sectional survey of members of the French National Society of Internal Medicine (Jan 2011)

- Do you performed a screening for HBV in patients receiving or prior receiving (n=290)?
  - Corticosteroids 44%
  - Immunosuppressive (except biotherapy) 67%
  - Biotherapy (Rituximab, antiTNFalpha…) 76%
  - No detection 19%

Terrier et al. Rev Med Interne 2012

WHAT ARE THE CLINICAL CONSEQUENCES OF HBV REACTIVATION ?

HBV reactivation



HBV reactivation

AgHBs + patients receiving chemotherapy

Liver consequences (meta-analysis)

	Frequency	Range
Reactivation	46 %	24 – 88 %
Hepatitis	33 %	24 – 88 %
Liver decompensation	13 %	5 – 33 %
Liver-related death	5 %	0 – 33 %

Loomba et al. Ann Intern Med 2008

HBV reactivation

AgHBs + patients receiving chemotherapy

Tumor consequences (meta-analysis)

	Number of studies	Frequency
Premature stop of chemotherapy	6	39 %
Cancer-related death	4	35 %

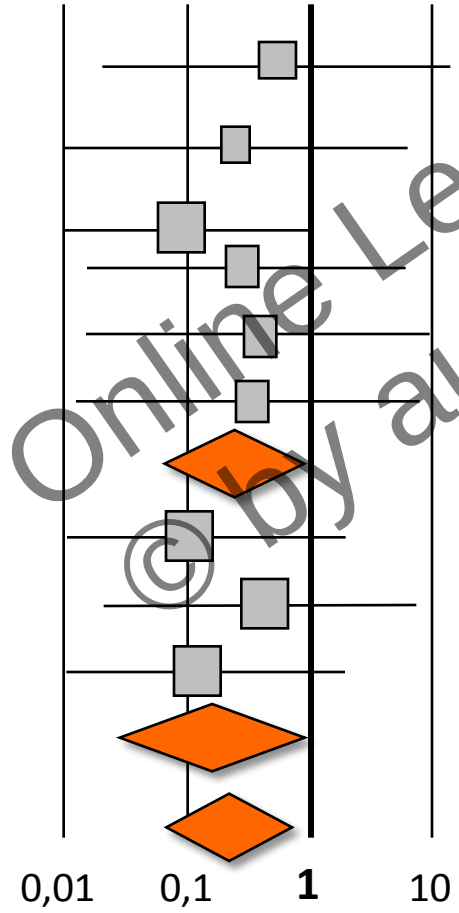
↗ liver-related complication and ↗ liver-related death
↘ chemotherapy efficiency and ↗ cancer-related death

Loomba et al. Ann Intern Med 2008

HOW TO PREVENT ?

HBV reactivation - Liver-related death

Beneficial effect of Lamivudine



	Odds ratio (CI 95%)	p
LAM pre-emptive		
Lee 2003	0.56 (0.21-15.0)	0.733
Dai 2004	0.25 (0.01-6.8)	0.408
Jia 2004	0.086 (0.01-1.1)	0.058
Yeo 2004	0.26 (0.01-4.8)	0.366
Yeo 2005	0.41 (0.02-11)	0.597
Jang 2006	0.33 (0.013-8.4)	0.505
vs. LAM differed	**0.25 (0.071-0.85)**	**0.027**
Lim 2002	0.08 (0.004-1.6)	0.096
Leaw 2004	0.38 (0.02-7.4)	0.526
Nagamatsu 2004	0.11 (0.005-2.5)	0.166
vs. no LAM	**0.15 (0.026-0.87)**	**0.034**
GLOBAL	**0.21 (0.076-0.57)**	**0.002**

Favor LAM pre-emptive **Favor control**

Loomba et al. Ann Intern Med 2008

HBV reactivation

Beneficial effect of pre-emptive Lamivudine

Tumor consequences (meta-analysis)

	Lamivudine	Controls
Premature stop of chemotherapy	17 %*	39 %
Cancer-related death	26 %*	35 %
All cause of death	18 %*	36 %

*: $p < 0.05$ vs. controls

Loomba et al. Ann Intern Med 2008

1st vs. 2nd generation antiHBV analogues

- No randomized study
- Comparative study (Jan 2007 – Feb 2008) in patients HBsAg treated for lymphoma (2/3 with Rituximab)

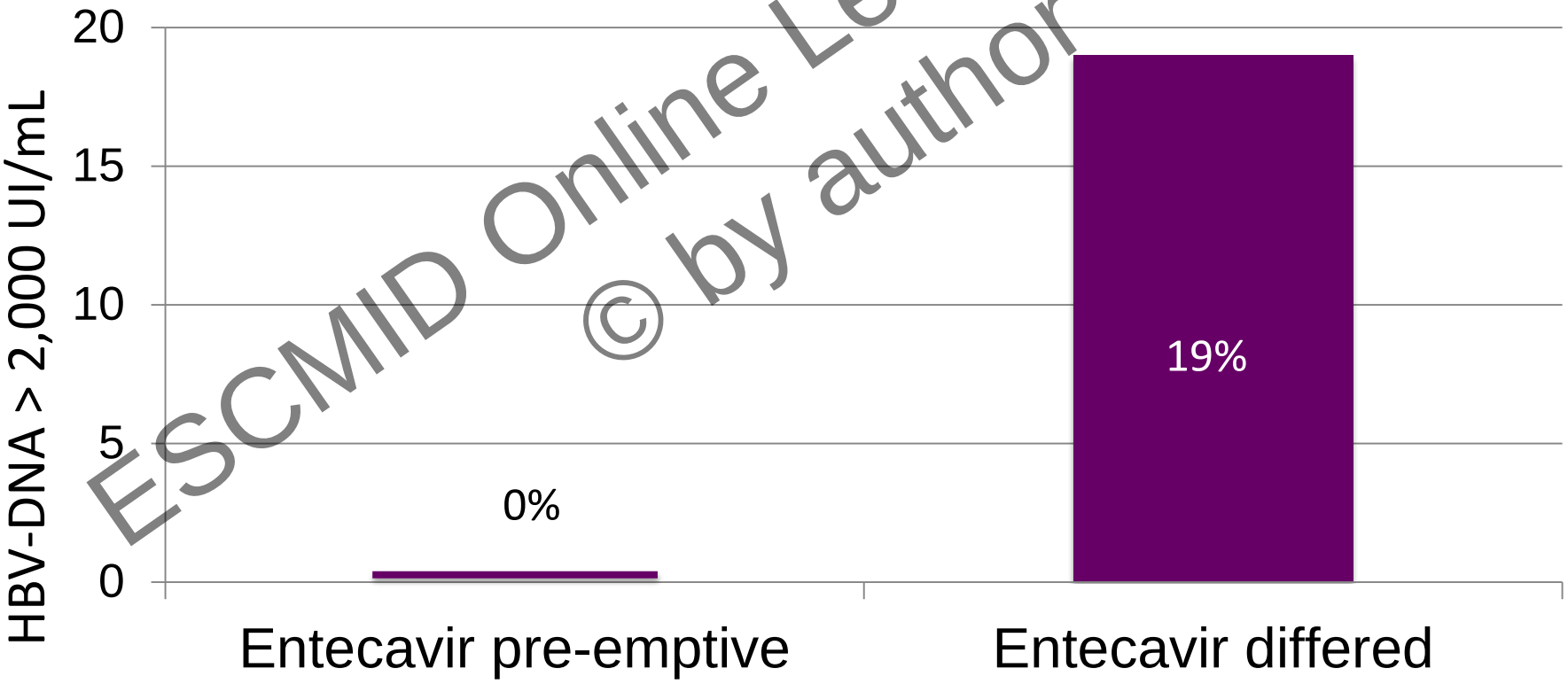
* p<0.05 vs. Entecavir	Lamivudine (n=89)	Entecavir (n=34)
HBV reactivation	20%	12%
HBV-related hepatitis	12%*	0
Chemotherapy disruption	20%*	6%
Mortality	1%	0

- No risk factor found in multivariate analysis

Li et al. J Viral Hepat 2011

Patients antiHBc +

Patients treated for lymphoma with CHOP-Rituximab
Patients HBsAg – and antiHBc + (+/- antiHBs +)
Randomization Entecavir pre-emptive vs. Entecavir differed



Huang et al. EASL 2012

Recommendation
European Association for the Study of Liver Diseases (EASL)

- "…prophylactic lamivudine reduces the risk of HBV reactivation and the associated morbidity and mortality (B1).
- It is, however, recommended that patients, who have a high HBV DNA level and/or may receive a lengthy and repeated cycles of immunosuppression, should be protected with a NA with high antiviral potency and a high barrier to resistance, i.e. entecavir or tenofovir (C1)."

- How to be sure of the duration of immunosuppression?
- How to be sure of the same regimen during the treatment?
- In case of reactivation, the risk of hepatic failure is probably higher in case of significant liver disease

EASL – Clinical Practice Guidelines. J Hepatol 2012

In practice, when and how to begin anti HBV therapy?

HbsAg + => regardless of HBV DNA levels

HbcAb+ => If HBV DNA+

Lamivudine: 100 mg QD

Entecavir: 0.5mg QD

Ténofovir: 300mg QD

Mostly used
Rapid action

DNA > 2000 UI/ml

Prolonged immune suprression

Contact with HBV

Anti HBc+

Surveillance

ALAT +

HBV DNA

3 months

ADN VHB detectable

Pre-emptive therapy with NA:

Before ALT increase

Risque of reactivation

WHEN CAN YOU STOP ANTI HBV THERAPY?

Duration

Pre emtive therapy

7 days before

immunosuppression

Stop : 12 months after chemotherapy stop

monitoring: ALAT/mths & AgHBs/3mths……+12 months

if chronic hepatitis and HBV > > 2 000 UI/ml

Prolonged duration

Conclusion (1)

- Persistance of liver cccDNA
- Loss of immune control often due to a medical intervention: drugs, transplant, chemotherapy
- HBV reactivation is followed by hepatitis reactivation
  - Mortality: in 3-5%
  - Morbidity: chemotherapy has to be stopped
  - High risk groups include: HBs Ag+ and antii HBC+ pats, pulse steroids, rituximab, bone marrow transplantation
  - HBV screening has to be performed systematically before chemotherapy or immunosuppressive therapy

Conclusion (2)

- IHBsAg + patients,
  - a pre-emptive treatment has to be initiated before immunosuppression regardless of HBV DNA levels
- AntiHBc + patients
  - have to be tested for HBV-DNA.
  - In case of HBV-DNA +, pre-emptive treatment has to be initiated.
  - In case of HBV-DNA –, follow-up with HBV-DNA and ALT every 3 months
- The choice of the analogue depends on HBV DNA level, the duration of immunosuppression and the presence or not of a significant liver disease
- The pre-emptive treatment has to be continue until (6 to) 12 months after cessation of therapy

Acknowledgements

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