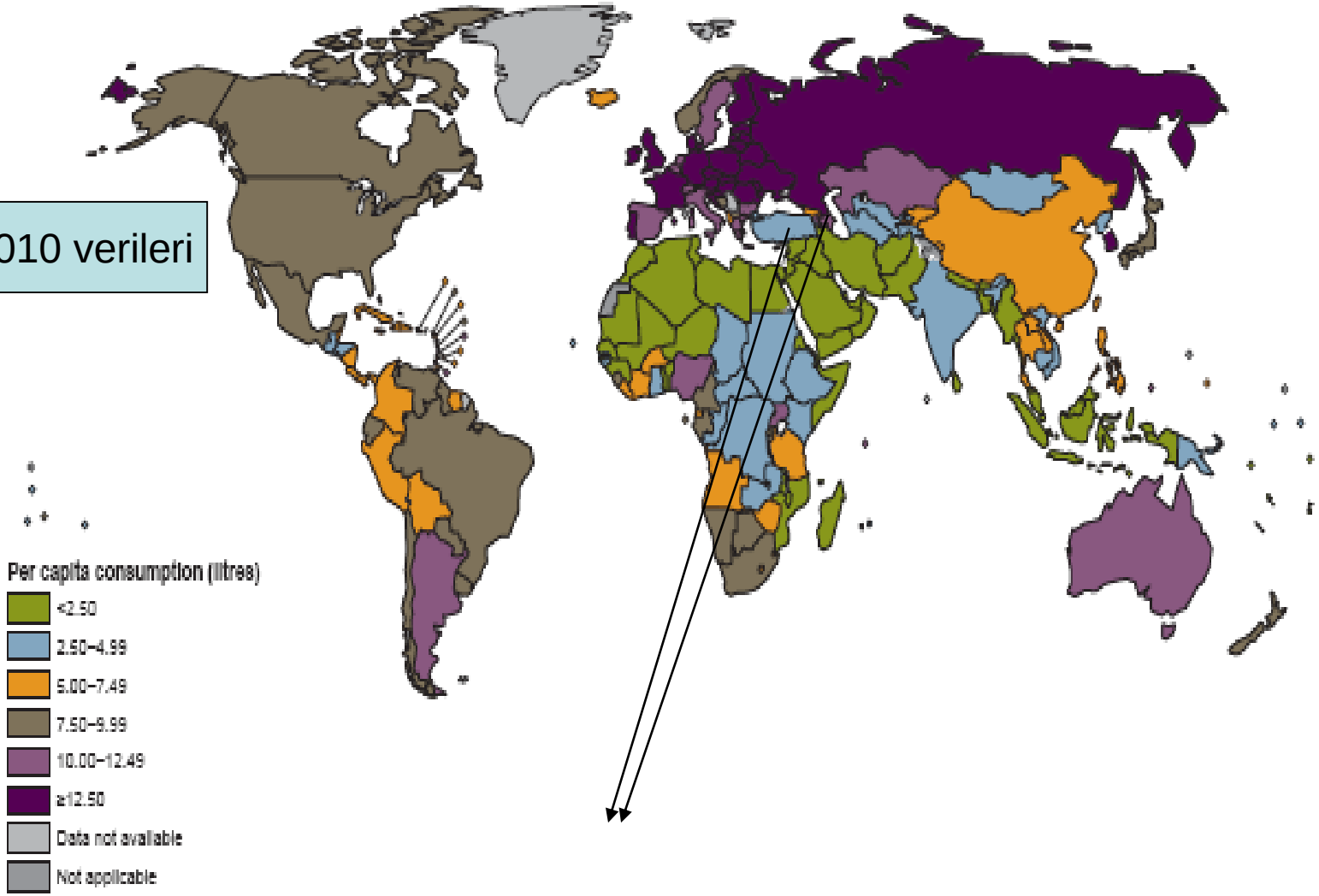
Alkolik Hepatit

Dr. Fatih Tekin

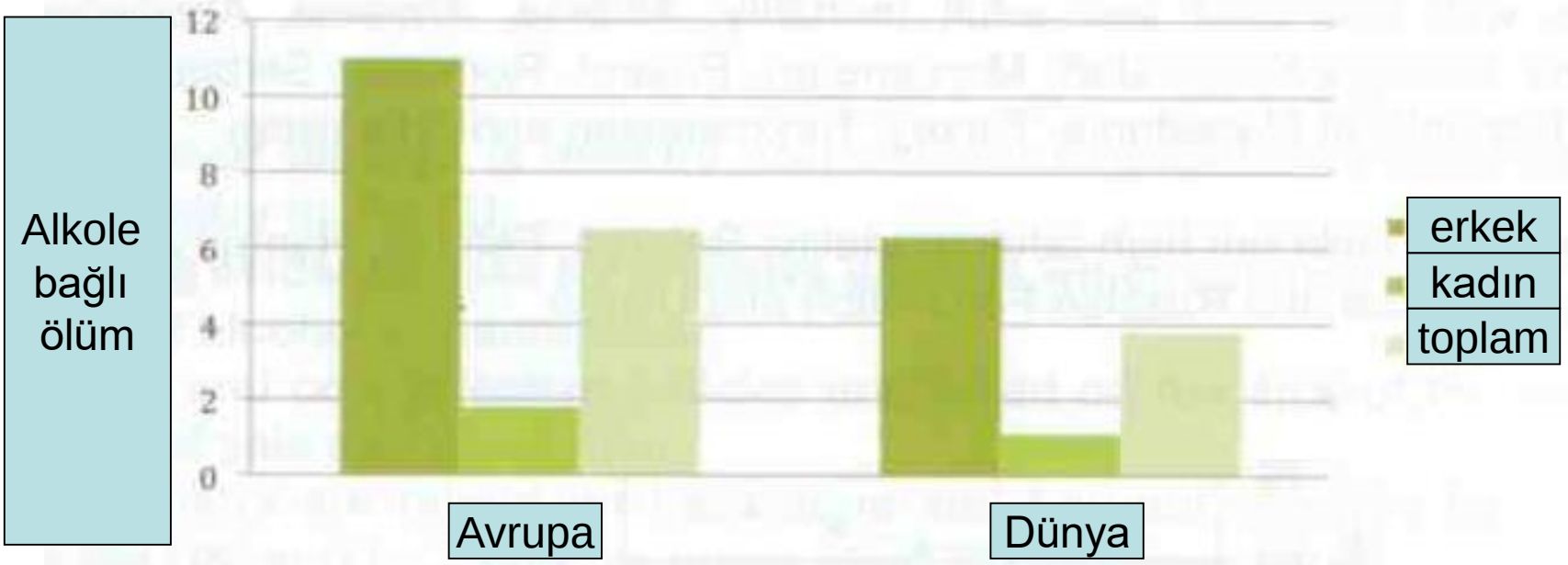
29 Eylül 2017
İstanbul

ALKOL: Asıl Avrupa'nın sorunu

WHO 2010 verileri



Avrupa’da tüm ölümlerin %6.5’inden alkol sorumlu



Türkiye'de Kronik Hepatit, Siroz ve Hepatosellüler Karsinoma Etiyolojisi

Prof. Dr. Atilla ÖKTEN

İstanbul Üniversitesi Tıp Fakültesi Gastroenteroloji Bilim Dalı, İstanbul

Tablo 6. Karaciğer sirozu: Yıllara göre etiyolojik değişim

Etiyoloji	1983-1993	1994-1997	1998-2001
	%	%	%
Viral	48.6	42.6	55.1
Kriptojenik	33.6	42.6	55.1
Alkol	33.4	16.8	16.4
Alkol+Viral	10.6	10.9	12.4
Diğerleri	7.4	8.9	12.1

ÜLKEMİZDE DE KULLANIMI GİDEREK ARTMAKTADIR!!!!!!!

JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Seroprevalence of hepatitis A,B, and C viruses in Turkish alcoholic cirrhotics and the impact of hepatitis B on clinical profile

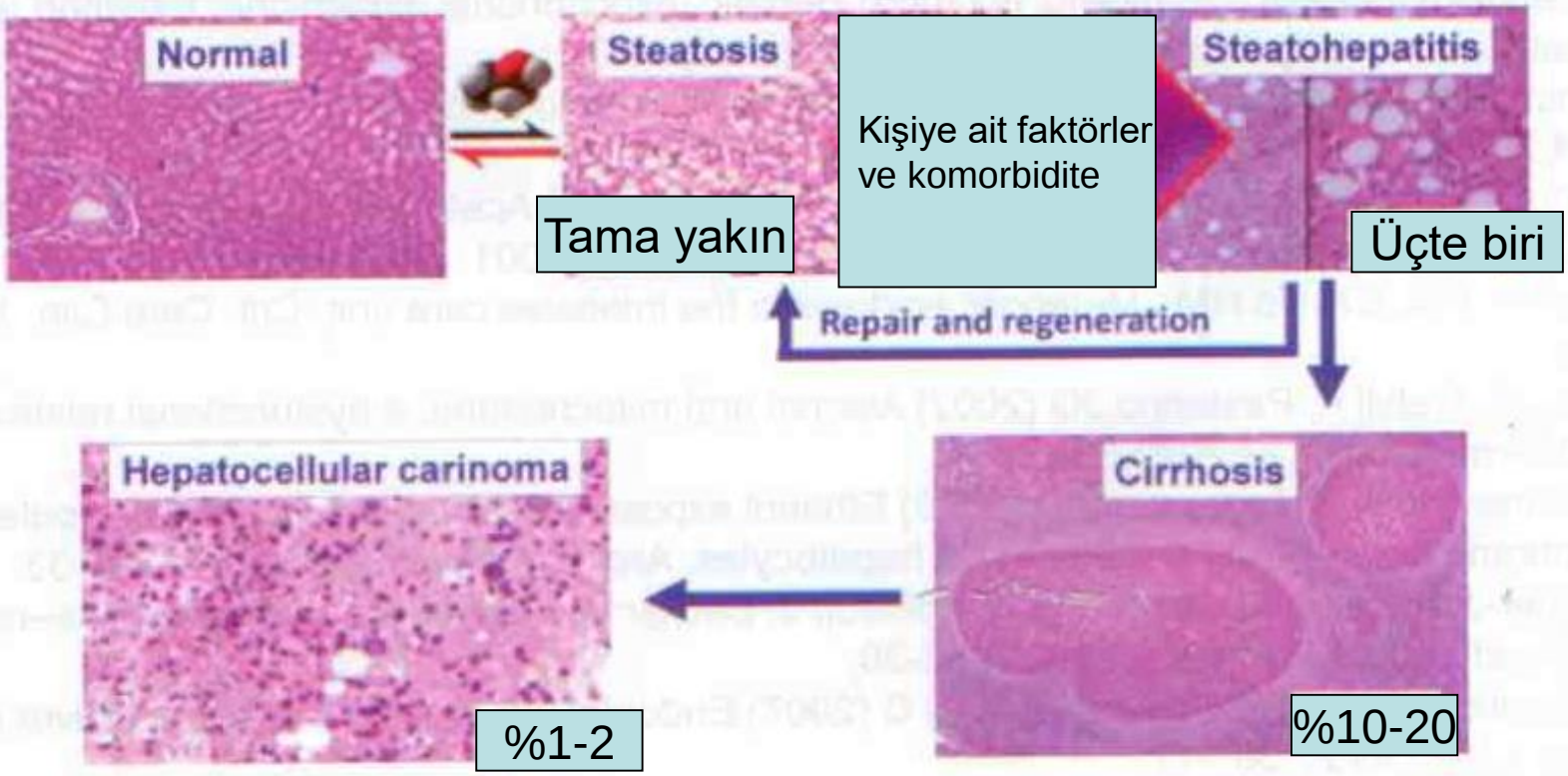
Fatih Tekin[1], Fulya Gunsar[1], Elvan Isik Erdogan[1], Ruchan Yazan Sertoz[2], Zeki Karasu[1], Galip Ersoz[1], Omer Ozutemiz[1], Ulus Akarca[1]

[1] *Department of Gastroenterology, Ege University Medical School, Izmir, Turkey*
[2] *Clinical Microbiology, Ege University Medical School, Izmir, Turkey*

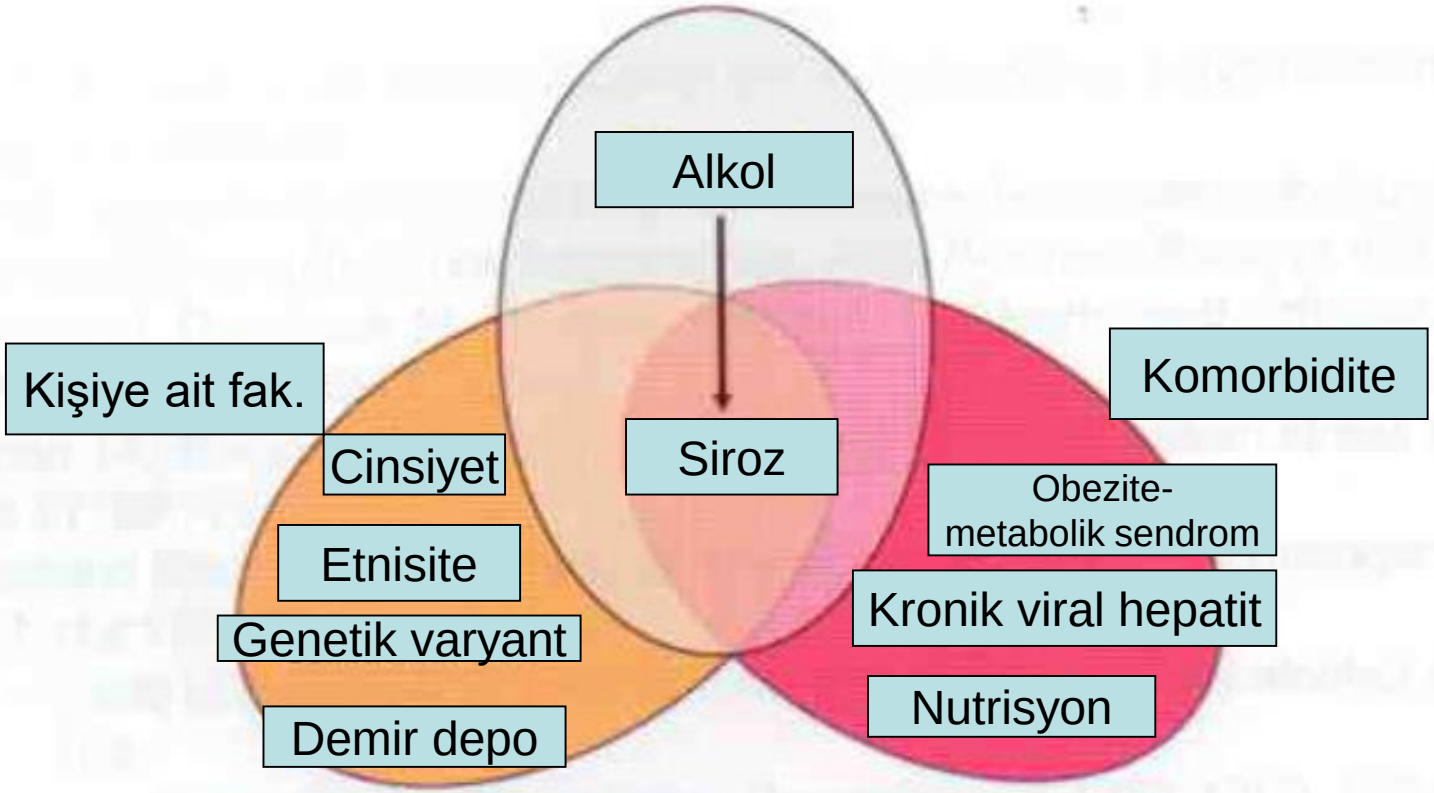
Table 1. Viral serological markers of alcoholic cirrhotic patients (n = 300)

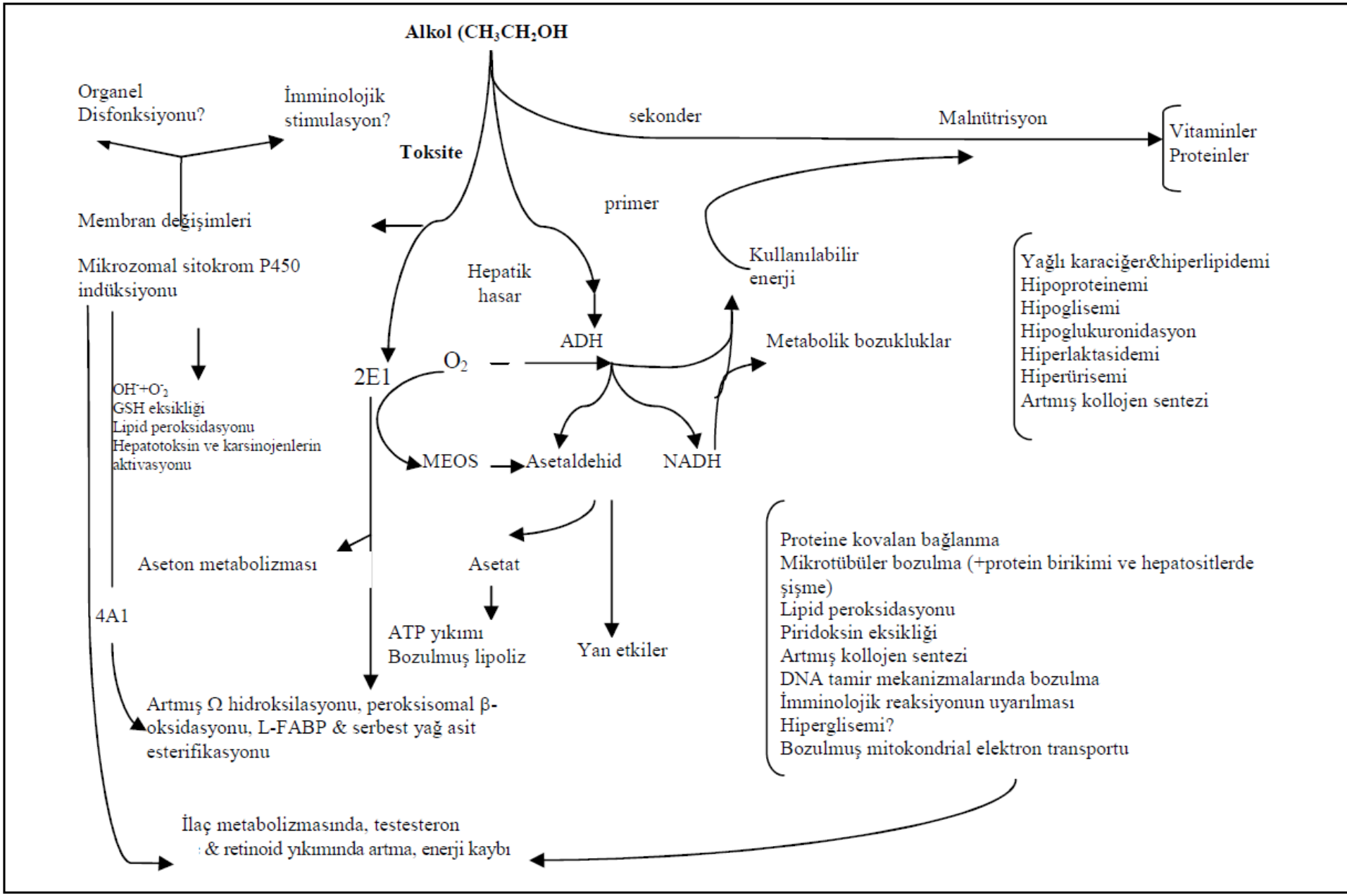
Serological marker	Data available n (%)	Positive n (%)
Anti-HAV total	188 (62.7)	172 (91.5)
Anti-HCV	280 (93.3)	23 (8.2)
HCV-RNA in anti-HCV positives	17 (74)	14 (82.4)
HBsAg in anti-HCV positives	23 (100)	1 (4.3)
HBsAg	300 (100)	49 (16.3)
HBV-DNA in HBsAg positives	29 (59)	12 (41.4)
HBeAg in HBsAg positives	43 (87.8)	7 (16.3)
Anti-delta in HBsAg positives	21 (42.9)	2 (9.5)
Anti-HCV in HBsAg positives	43 (87.8)	1 (2.3)

Hangi alkol kullanıcıları AKH için riskli?



AKH’nda progresyon için risk faktörleri



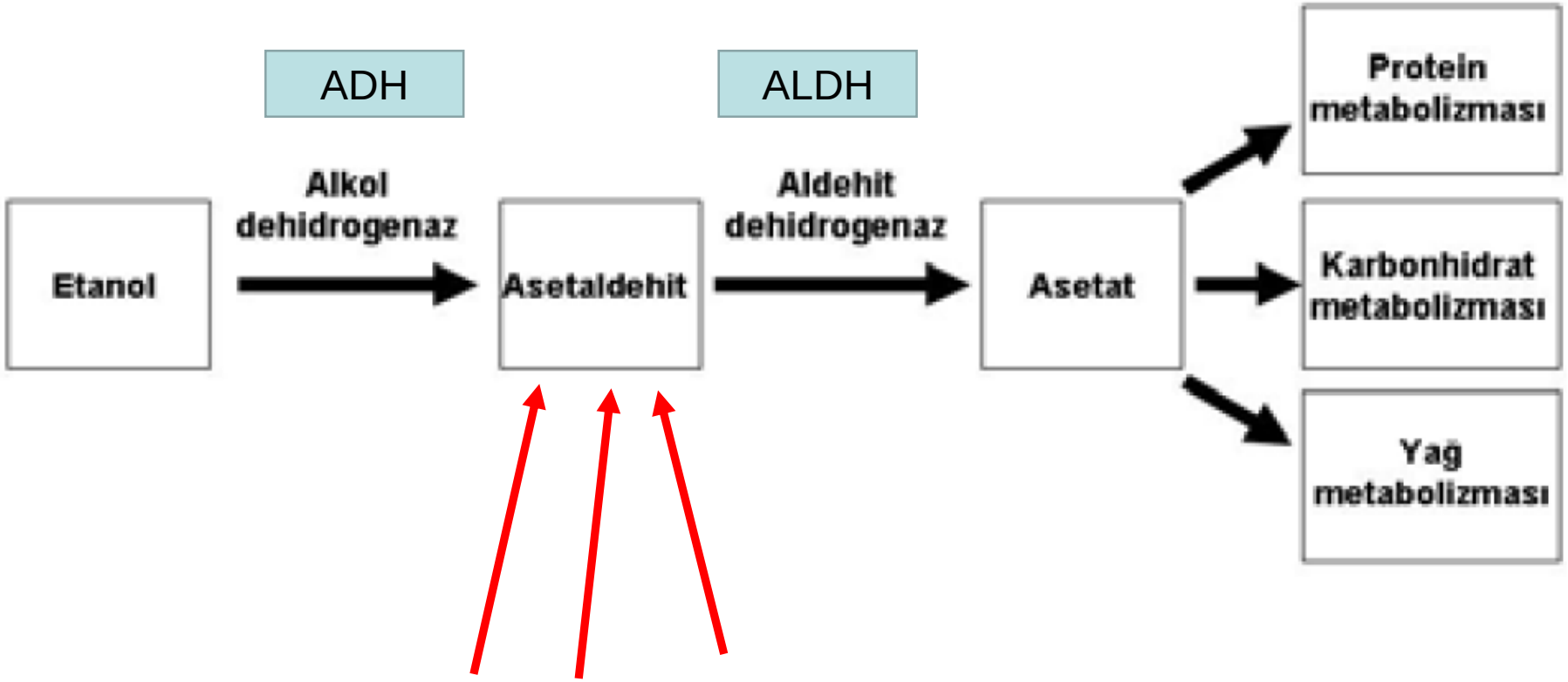

Alkol (CH_3CH_2OH)
Organel Disfonksiyonu?
İmminolojik stimulasyon?
Membran değişimleri
Toksite
sekonder
Malnütrisyon
Vitaminler
Proteinler
primer
Kullanılabilir enerji
Mikrozomal sitokrom P450 indüksiyonu
Hepatik hasar
ADH
Metabolik bozukluklar
Yağlı karaciğer&hiperlipidemi
Hipoproteinemi
Hipoglisemi
Hipoglukuronidasyon
Hiperlaktasidemi
Hiperürisemi
Artmış kollojen sentezi
2E1
O_2
$OH^- + O^-_2$
GSH eksikliği
Lipid peroksidasyonu
Hepatotoksin ve karsinojenlerin aktivasyonu
MEOS
Asetaldehid
NADH
Aseton metabolizması
Asetat
4A1
ATP yıkımı
Bozulmuş lipoliz
Yan etkiler
Proteine kovalan bağlanma
Mikrotübüler bozulma (+protein birikimi ve hepatositlerde şişme)
Lipid peroksidasyonu
Piridoksin eksikliği
Artmış kollojen sentezi
DNA tamir mekanizmalarında bozulma
İmminolojik reaksiyonun uyarılması
Hiperglisemi?
Bozulmuş mitokondrial elektron transportu
Artmış Ω hidroksilasyonu, peroksisomal β-oksidasyonu, L-FABP & serbest yağ asit esterifikasyonu
İlaç metabolizmasında, testesteron & retinoid yıkımında artma, enerji kaybı

Karaciğerde alkol (etanol) metabolizmasından sorumlu olan başlıca 3 yolak vardır. Bunlar sırasıyla:

1. Hepatosit sitozolünde bulunan alkol dehidrogenaz yolağı

2. Hepatosit endoplazmik retikulumunda bulunan mikrozomal enzimler

3. Hepatosit peroksizomlarında bulunan katalaz yolaklarıdır.



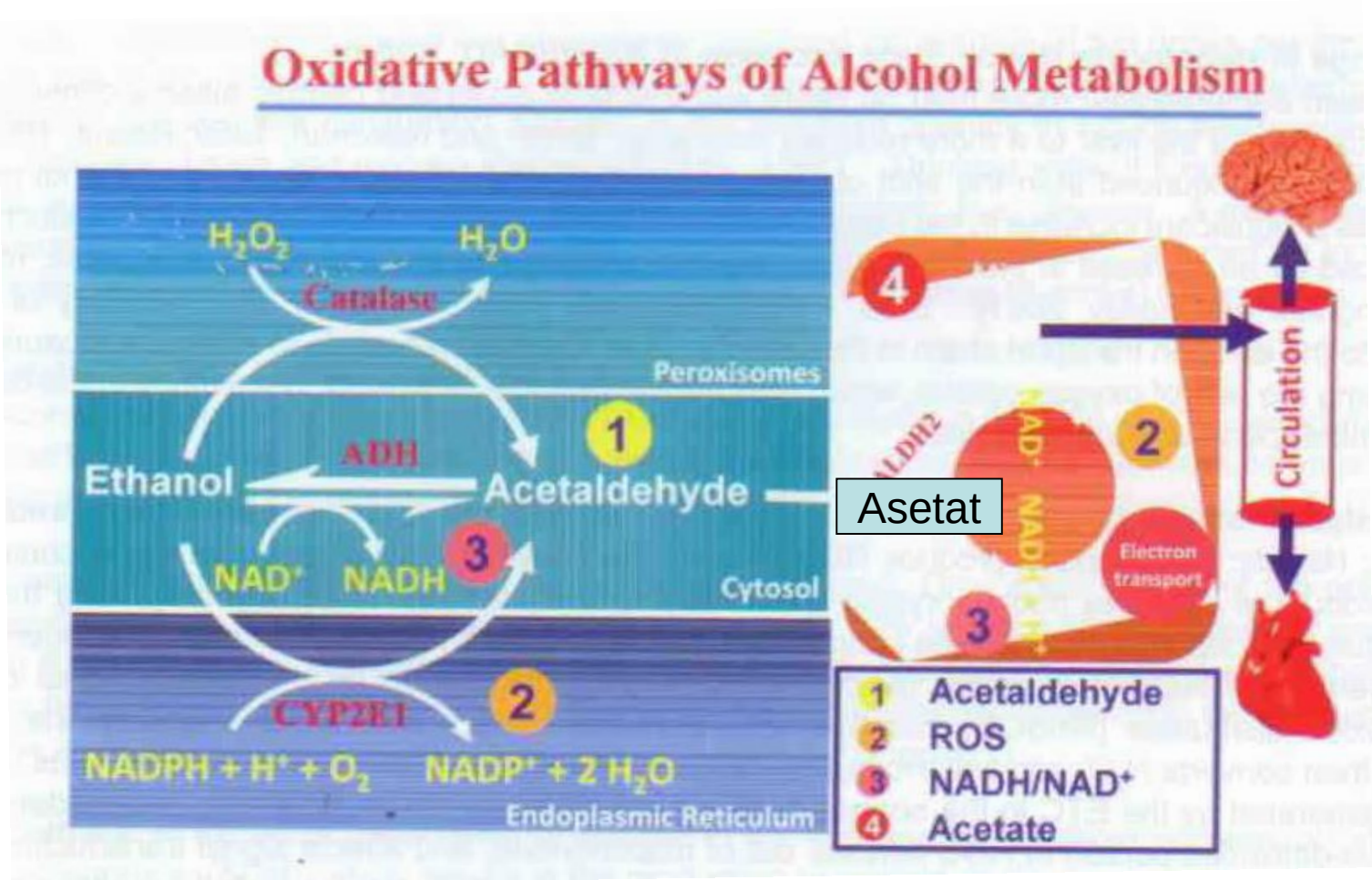
ADH ve ALDH genetik yapımız batı dünyası ile aynı

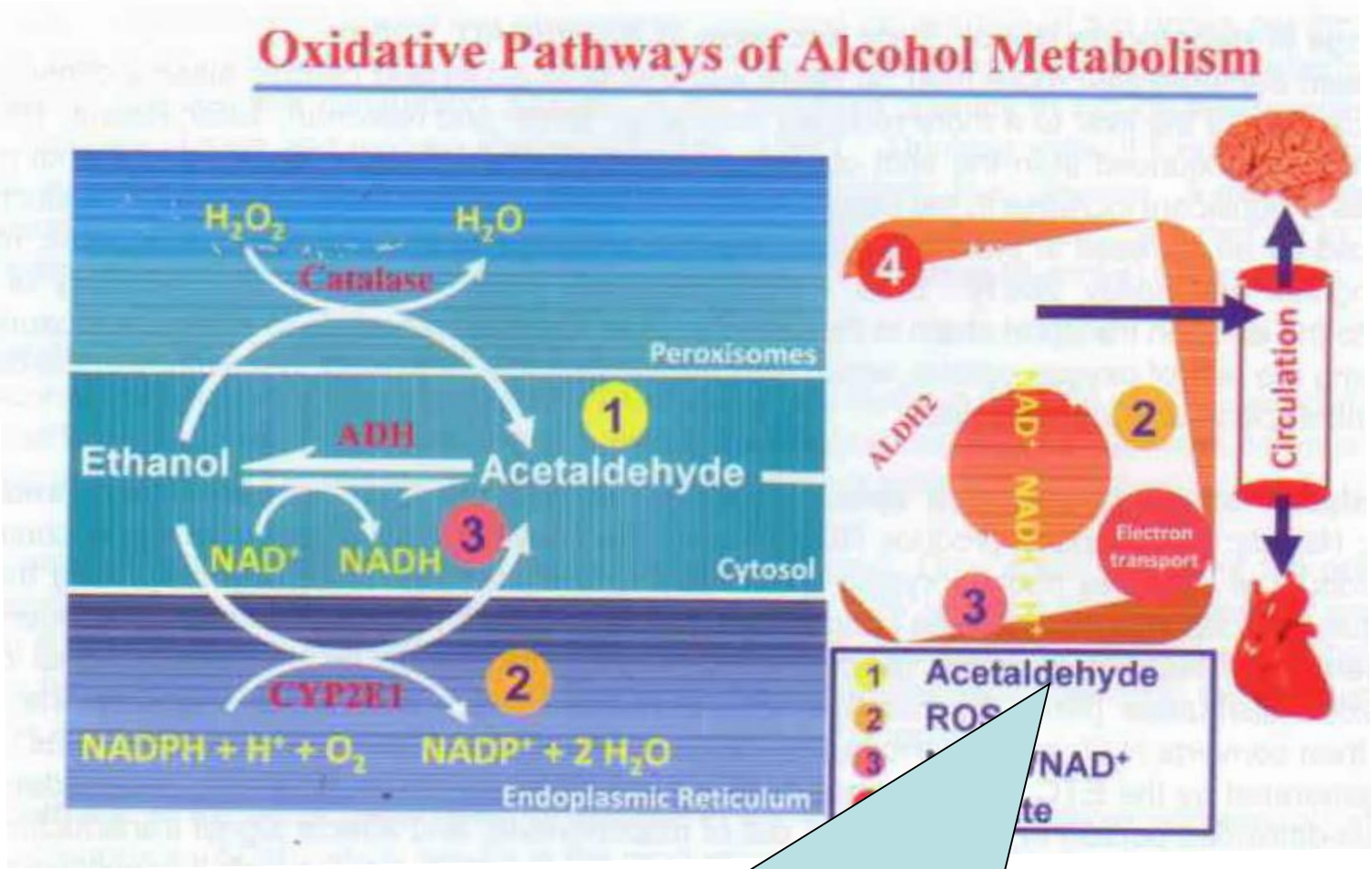
BOSNIAN JOURNAL OF BASIC MEDICAL SCIENCES
RESEARCH ARTICLE
WWW.BJBMS.ORG

Genetic polymorphisms of *ADH1B*, *ADH1C* and *ALDH2* in Turkish alcoholics: lack of association with alcoholism and alcoholic cirrhosis

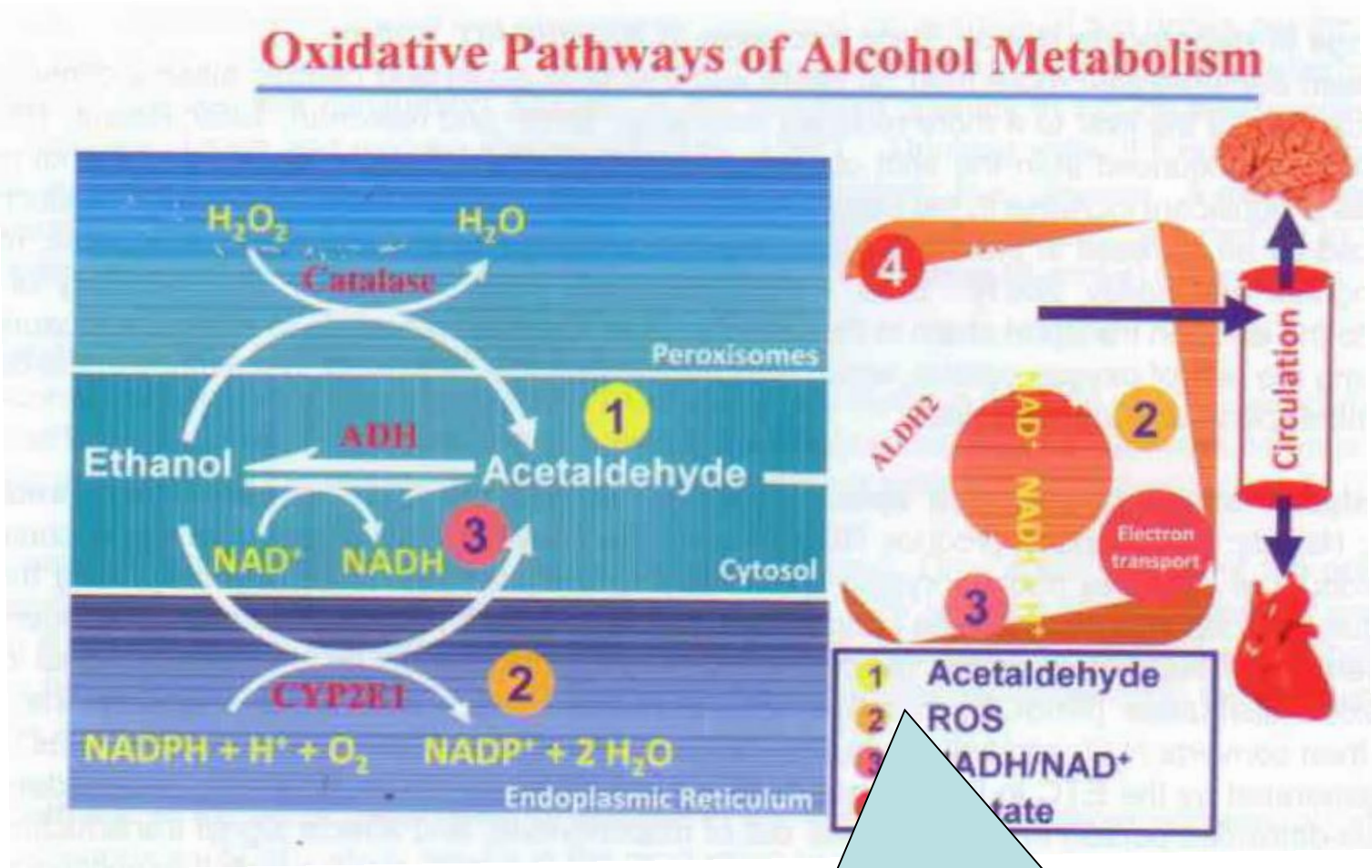
Sezgin Vatansever[1], Fatih Tekin[1*], Esin Salman[1], Ender Altintoprak[2], Hakan Coskunol[2], Ulus Salih Akarca[1]

[1]Department of Gastroenterology and [2]Department of Psychiatry, Ege University Medical School, Izmir, Turkey

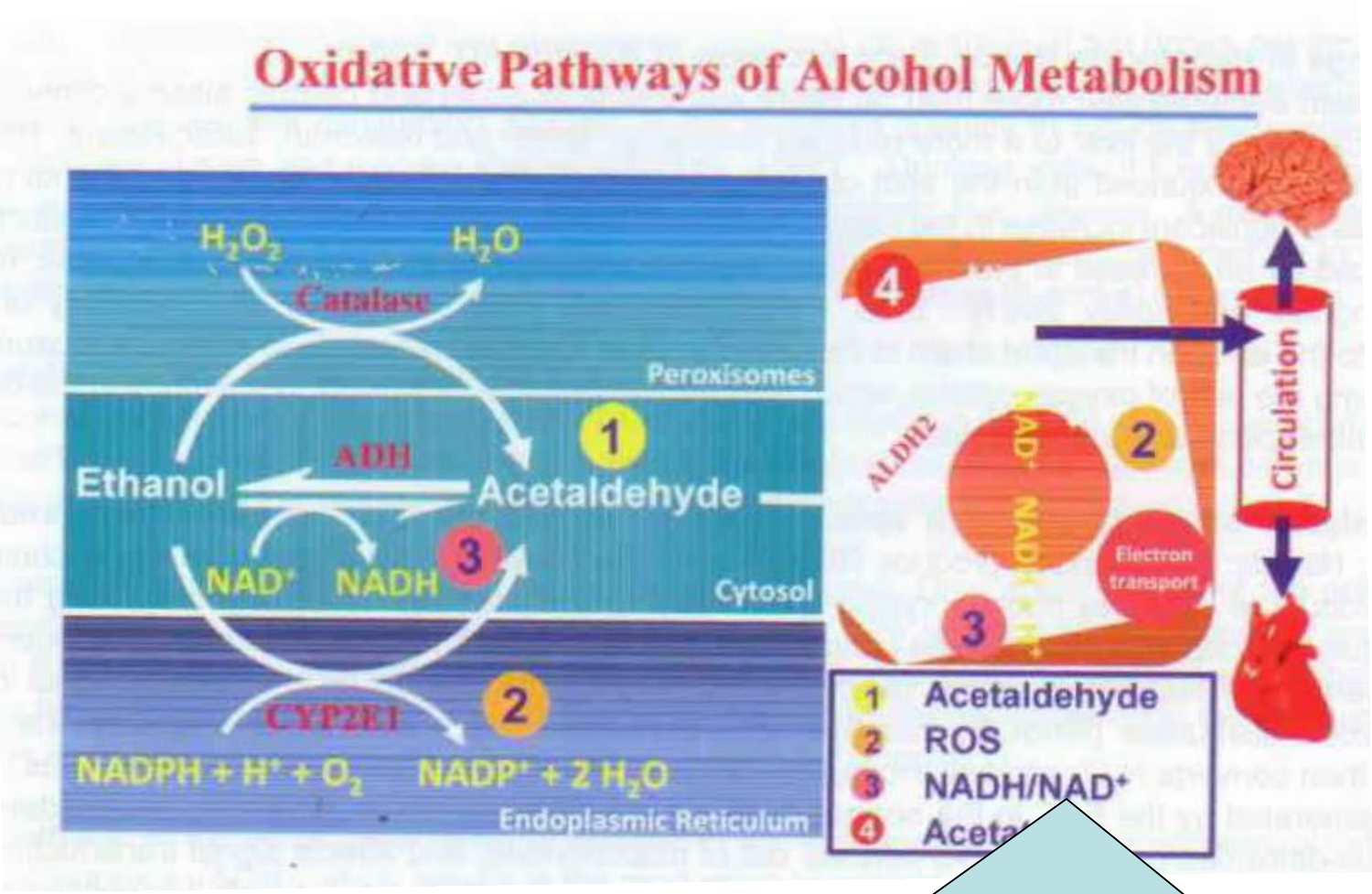

Oxidative Pathways of Alcohol Metabolism
H_2O_2
H_2O
Catalase
Peroxisomes
ADH
Ethanol
Acetaldehyde
1
NAD+
NADH
3
Cytosol
CYP2E1
2
NADPH + H+ + O_2
NADP+ + 2 H_2O
Endoplasmic Reticulum
4
2
3
Electron transport
Circulation
Asetat
1 Acetaldehyde
2 ROS
3 NADH/NAD+
4 Acetate



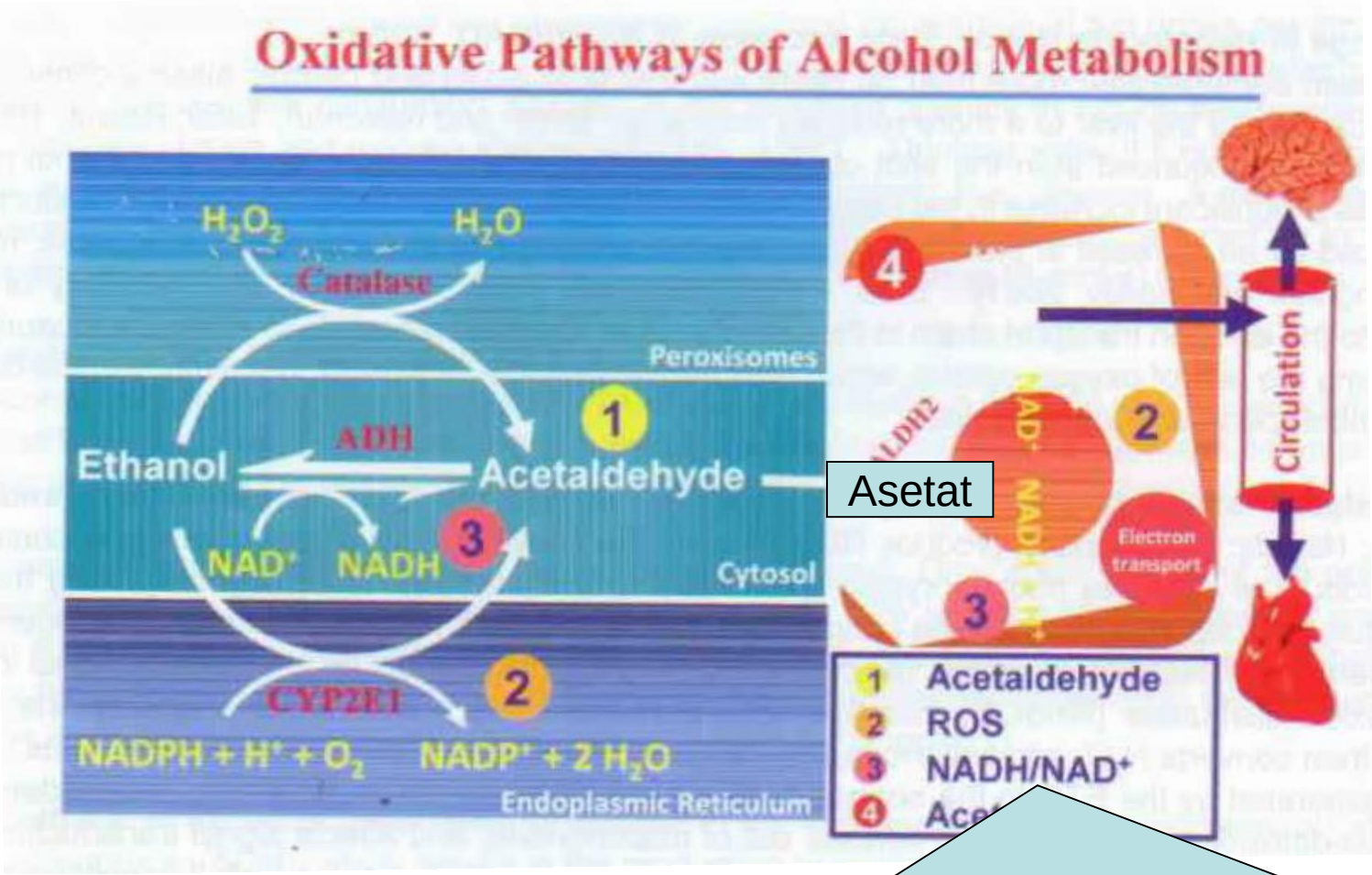
DNA, RNA ile etkileşebiliyor, DNA tamirini azaltıyor.
Enzimlerin, mikrozomal proteinlerin, mikrotübüllerin lizin rezidüleri ile reaksiyona girebiliyor, yeni protein ürünler oluşuyor.
Bu proteinlerin bazıları proinflamatuvar ve profibrojenik.
Bazıları da Immunojenik (immün aracılı karaciğer hasarı).



Sinyal yolakları ve gen ekspresyonlarına etki ediyor.
Böylece sitokinler, hormonlar, büyüme faktörlerinin sentezi artıyor.
Sonuç: Hepatik inflamasyon, nekroz, apoptosis.

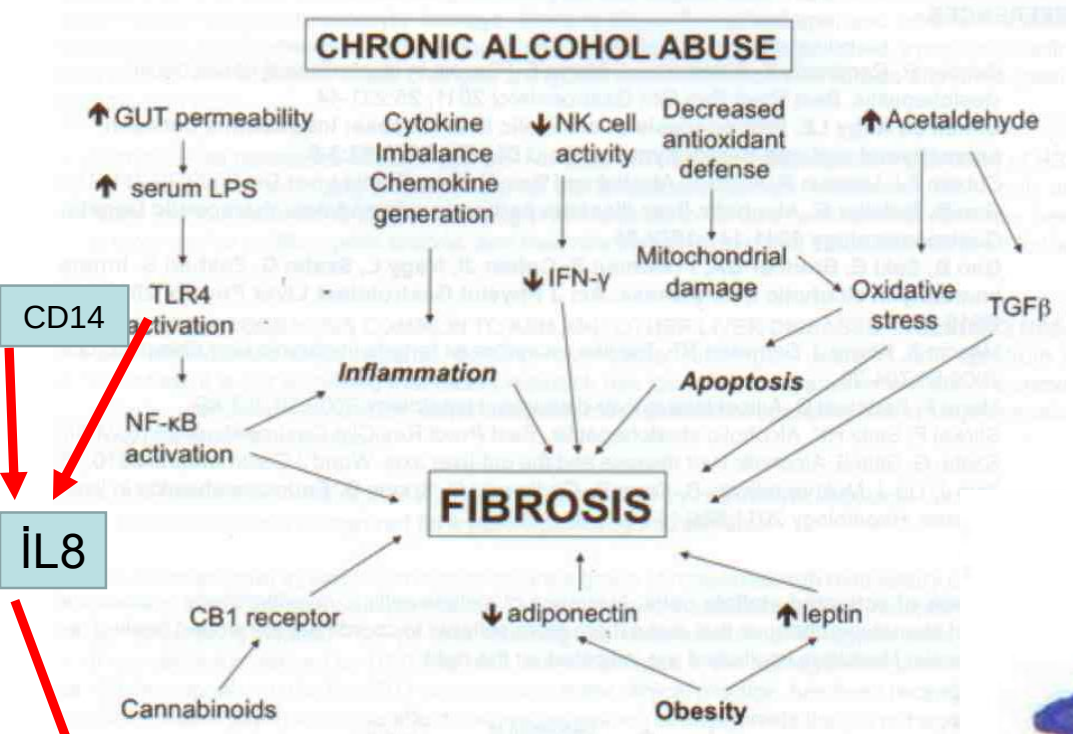


NADH'yı tekrar oksijenize etmek için karaciğer fazla oksijene gereksinim duyuyor.
Bu durum özellikle perisentral bölgelerin hipoksik periyodlara girmesine neden oluyor.



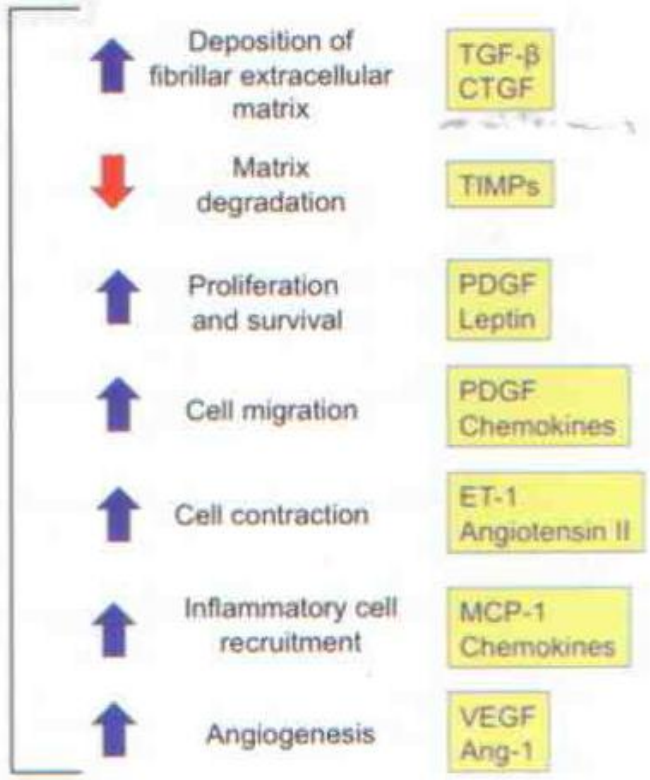
Alkolik hipoglisemi (glukoneogenesis inhibe olur) (piruvat laktata döner)
Hiperürisemi (ksantin oksidaz)
Hipertrigliseridemi (yağ asidlerinin oksidasyonu bozulur, TG sentezi artar)
Hipoksi (Etanol metabolizması çok oksijen ister, perivenöz hepatositler hipoksik kalır)
Alkolik asidoz (ketonların oluşumuna bağlı)

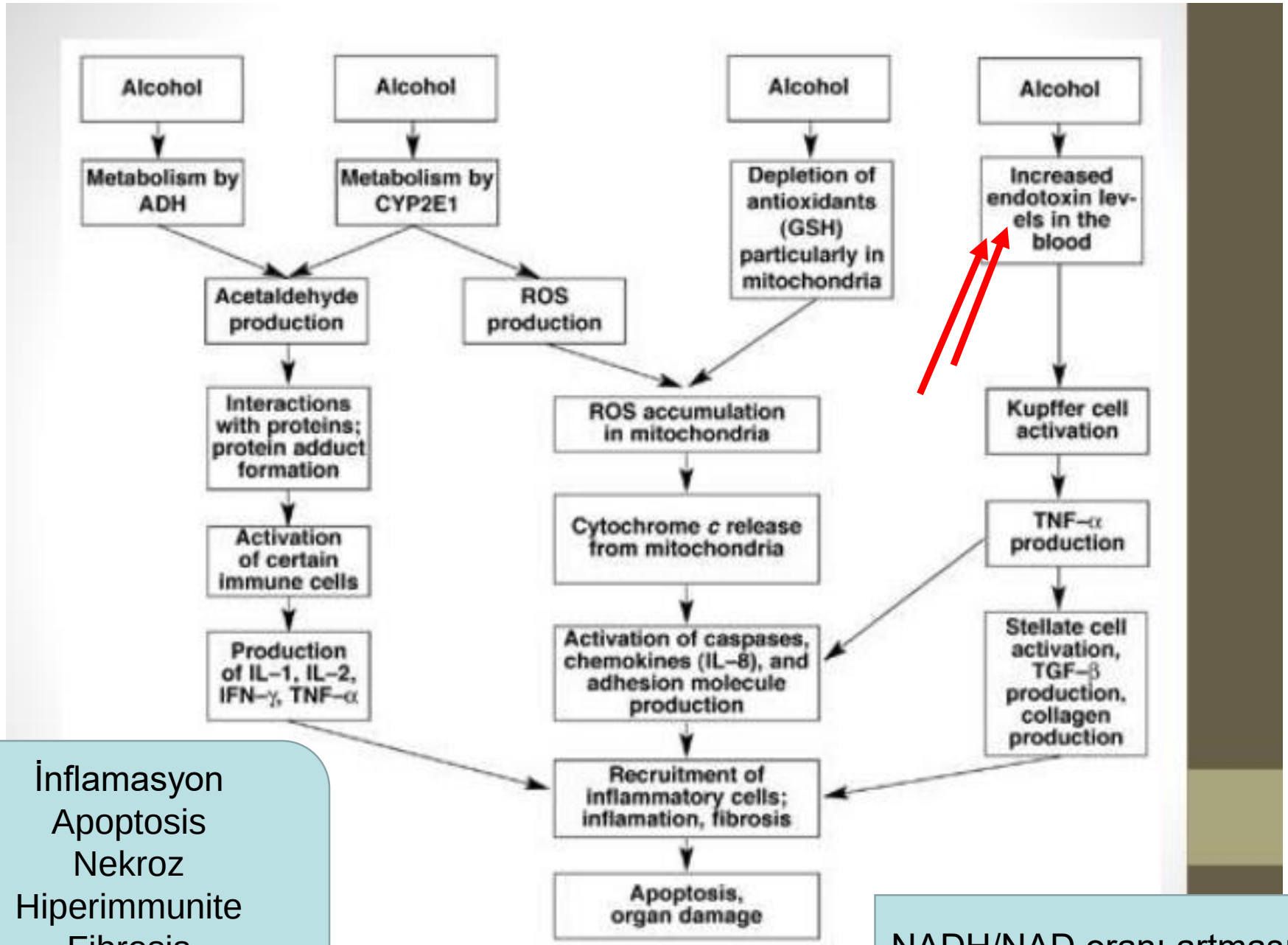
FİBROSİS



ROS: stellat hücrede intraselüler profibrojenik sinyal yolaklarını stimüle ediyor (ERK, PI3K/AKT, JNK)

ROS
Asetaldehit
Hasarlanmış hepatositler
Aktive Kuppfer hücreleri
PMN lökositler





İnflamasyon
Apoptosis
Nekroz
Hiperimmunite
Fibrosis
Hipoksi

NADH/NAD oranı artması

- ALKOLİK HEPATİT VS STEATOHEPATİT
- Steatoz.....alkolik hepatit
- Steatohepatit.....alkolik hepatit
- Siroz.....alkolik hepatit

- Alkolik hepatitlerin en az yarısında altta yatan siroz mevcut.

- Alkolik hepatite tanı koyduran spesifik bir test yok. Klinik bir tanı.
- Önemi: MORTALİTESİ YÜKSEK.

TANI???

Clinical Practical Guidelines

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

EASL Clinical Practical Guidelines: Management of Alcoholic Liver Disease

European Association for the Study of the Liver*,†

Definition, incidence, and diagnosis

Alcoholic hepatitis is a clinical syndrome, i.e. recent onset of jaundice and/or ascites in a patient with ongoing alcohol misuse. Historically, it was referred to as "acute alcoholic hepatitis". Although the clinical presentation may present abruptly, the term "acute" is not recommended, since it is an exacerbation of an underlying chronic liver disease and usually follows an extended course.

AASLD PRACTICE GUIDELINES

Alcoholic Liver Disease

Robert S. O'Shea, Srinivasan Dasarathy, Arthur J. McCullough, and the Practice Guideline Committee of the American Association for the Study of Liver Diseases and the Practice Parameters Committee of the American College of Gastroenterology

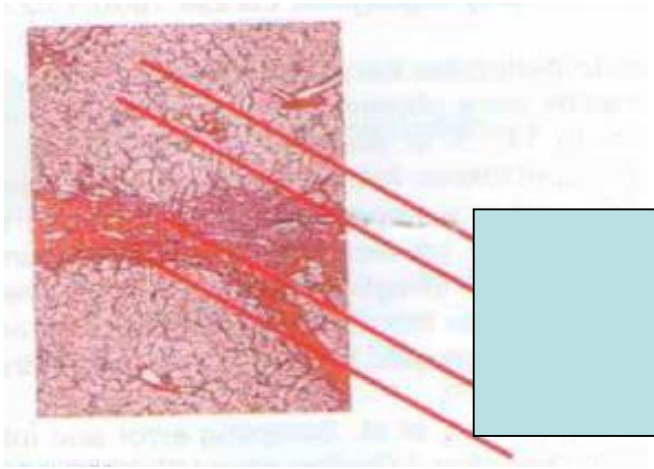
and are not individually pathognomonic of ALD. The clinical diagnosis of AH is made based on a typical presentation, with severe liver dysfunction in the context of excessive alcohol consumption, and the exclusion of other causes of acute and chronic liver disease. In the subset of

Tipik prezentasyon, ciddi karaciğer disfonksiyonu, aşırı alkol kullanımı varlığı ve diğer nedenlerin dışlanması

Tanıda önemli bir nokta:

- Örnek: alkole bağlı kompanze karaciğer sirozu olgu. Aktif içici…Son günlerde ikter farketmiş, T.bil: 17 mg/dl

- Siroz dekompanzasyonu?,
  Kompanze siroz + alkolik hepatit? (akut-on-kronik?)



BİYOPSİ??????

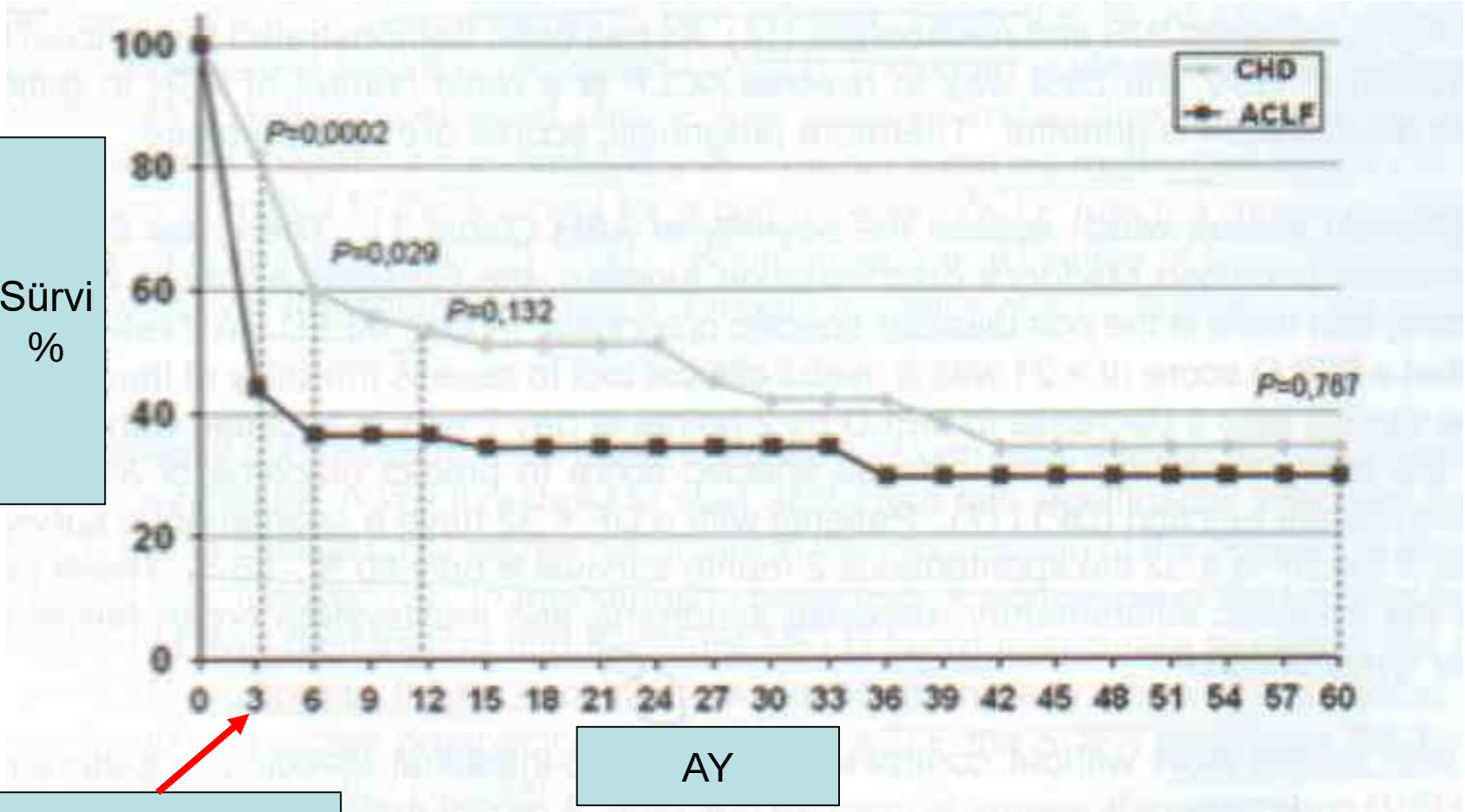
2 grubun histolojik özellikleri

Katoonizadeh et al, Gut 2010

Histological parameter	ACLF (n=54)	CHD (n=48)	P
Hepatic progenitor cells	68 ± 29	60 ± 36.5	NS
Intermediate hepatocytes/CK7	14 ± 14	11.5 ± 19.25	NS
Intermediate hepatocytes /CK19	3.5 ± 5.5	2 ± 4	0.03
Proliferating hepatocytes /mib-1	1 ± 3	1.5 ± 3.25	NS
Lobular bilirubinostasis **	67% (35/52)	15% (7/47)	0.0001
Ductular bilirubinostasis *	75% (39/52)	30% (14/47)	0.0001
Cholangiolitis*	64% (32/50)	24% (11/46)	0.0001
Mallory bodies**	70% (37/53)	40% (19/47)	0.004
Ballooning*	94% (50/53)	79% (36/46)	0.008
Inflammation/lobular	96% (49/51)	86% (40/46)	NS
Satellitosis*	63% (33/52)	32% (15/47)	0.002
ASH severe	24% (13/53)	6% (3/48)	0.01

Akut on kronik: 25 ex

Akut-on-kronik vs kronik hepatik dekompanzasyonda sürvi farklılıkları



3. Ayda belirgin farklılık

Katoonizadeh et al, Gut 2010

Akut alkolik Hepatitte KC Biyopsisi Mutlak Şart mı ?

- HAYIR

Ne zaman gerekir ?

- ✓ Tanıda kuşku olduğu zaman
- ✓ Birlikte yandaş hastalık varlığında (viral hepatit)
- ✓ Fibrozis derecesini kronisiteyi ortaya koyarak prognozu daha iyi belirlemek için
- ✓ Araştırma kapsamında

Alkolik Hepatit

- İlerleyici **sarılık**, karında rahatsızlık hissi, ateş, kilo kaybı
- Şiddetli vakalarda, assit, bakteriyel enf, hepatorenal sendrom, HE, varis kanaması
- Şiddetli olgularda sistemik inflamatuvar yanıt (Taşikardi, lökositoz, CRP)
- Sirotik bir hasta da olabilir, önceden fark edilmemiş AKH'nın ilk bulgusu da olabilir.

Tanıda yardımcı tetkikler

- ÖYKÜ********
- AST: 100-400
- ALT<100
- AST>ALT (2/1)
- ALP, GGT yüksek (değişken)
- Lökositoz
- Hiperürisemi
- INR, albumin
- Ultrasonografi

Alkolik hepatit ve prognostik skorlama sistemleri

	Bilirubin	PT/INR	Creatinine/ urea	Leucocytes	Age	Albumin	Change in bilirubin from day 0 to day 7
Maddrey score	+	+	-	-	-	-	-
MELD score	+	+	+	-	-	-	-
GAHS score	+	+	+	+	+	-	-
ABIC score	+	+	+	-	+	+	-
Lille score	+	+	+	-	+	+	+

Maddrey score, Maddrey discriminant function; GAHS, Glasgow Alcoholic Hepatitis Score; ABIC score, age, serum Bilirubin, INR, and serum Creatinine (ABIC) score; MELD score, Model-for-End-Stage-Liver-Disease score.

Tedavinin 7. gününde tedavi seçimine yönlendirebilme özelliği

Lille Model

This model has been developed by the hepatology unit of the CHRU Lille with the collaboration of 4 other French centers.

In the following model, survival probability at 6 months is defined by the 0.45-cutoff: 6-month survival probability of patients with a Lille model above 0.45 is about 25% contrary to patients with a Lille model below this cutoff (85%).
See for more details the manuscript published in Hepatology 2007.

Day 0	28 / 1 / 2013	(dd/mm/yyyy)	
Date of Birth	/ /	(dd/mm/yyyy)	
Bilirubin		µmol/L (at Day 0)	
		µmol/L **(at Day 7)**	
Creatinine		µmol/L (at Day 0)	
Albumin*		g/L (at Day 0)	
Patient's prothrombin time		sec (at Day 0)	

Compute | Reset all fields

Lille skoru > 0.45

Lillemodel.com

- Introduction
- Lille Model
- MELD Score
- Child-Pugh Score
- Maddrey Score
- Glasgow Score
- ABIC Score
- Alcoholic Hepatitis in General
- Contact

Change mg/dL for µmol/L ?

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See for more details the manuscript published in Hepatology 2007.

Day 0	3 /	2 /	2013	(dd/mm/yyyy)
Date of Birth	10 /	5 /	1972	(dd/mm/yyyy)
Bilirubin	17	mg/dL (at Day 0)		
	5	mg/dL **(at Day 7)**		
Creatinine	1	mg/dL (at Day 0)		
Albumin*	4	g/L (at Day 0)		
Patient's prothrombin time	14	sec (at Day 0)		

Compute | Reset all fields

Please note that the Lillemodel has been developed with prothrombin time in seconds.
If this variable is not avaible, use the Lillemodel-INR

** « In patients who have been treated with albumin infusions, in order to avoid the use of an artificial value, it is recommended to use the available albumin value before infusion of albumin »*

Lille Model-PT :

0,265

Tedavinin 7. gününde tedavi seçimine yönlendirebilme özelliği

Journal of Gastrointestinal & Digestive System

Tekin et al., J Gastrointest Dig Syst 2016, 6:6
DOI: 10.4172/2161-069X.1000480

Research Article OMICS International

A Comparison of Prognostic Scoring Systems in Turkish Alcoholic Hepatitis Patients

Fatih Tekin*, Zeki Karasu, Elvan Isik Erdogan, Fulya Gunsar, Galip Ersoz, Omer Ozutemiz and Ulus Akarca

Ege University Medical School, Department of Gastroenterology, Izmir, Turkey

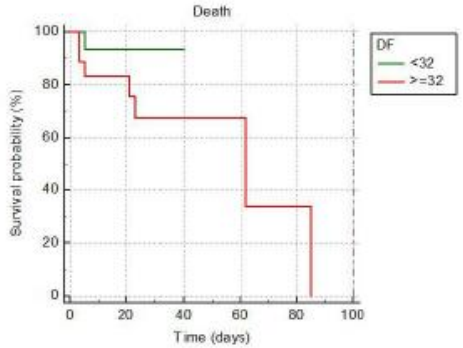


Figure 1: Comparisons of survival rates between patients with a DF score ≥ 32 versus a DF score <32.

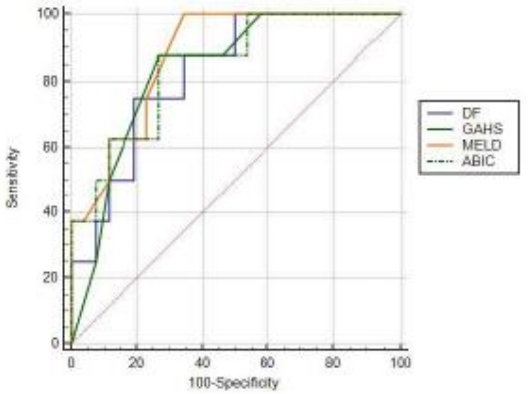


Figure 2: No statistically significant differences were found between DF, MELD, GAHS, and ABIC scores for predicting in-hospital mortality.

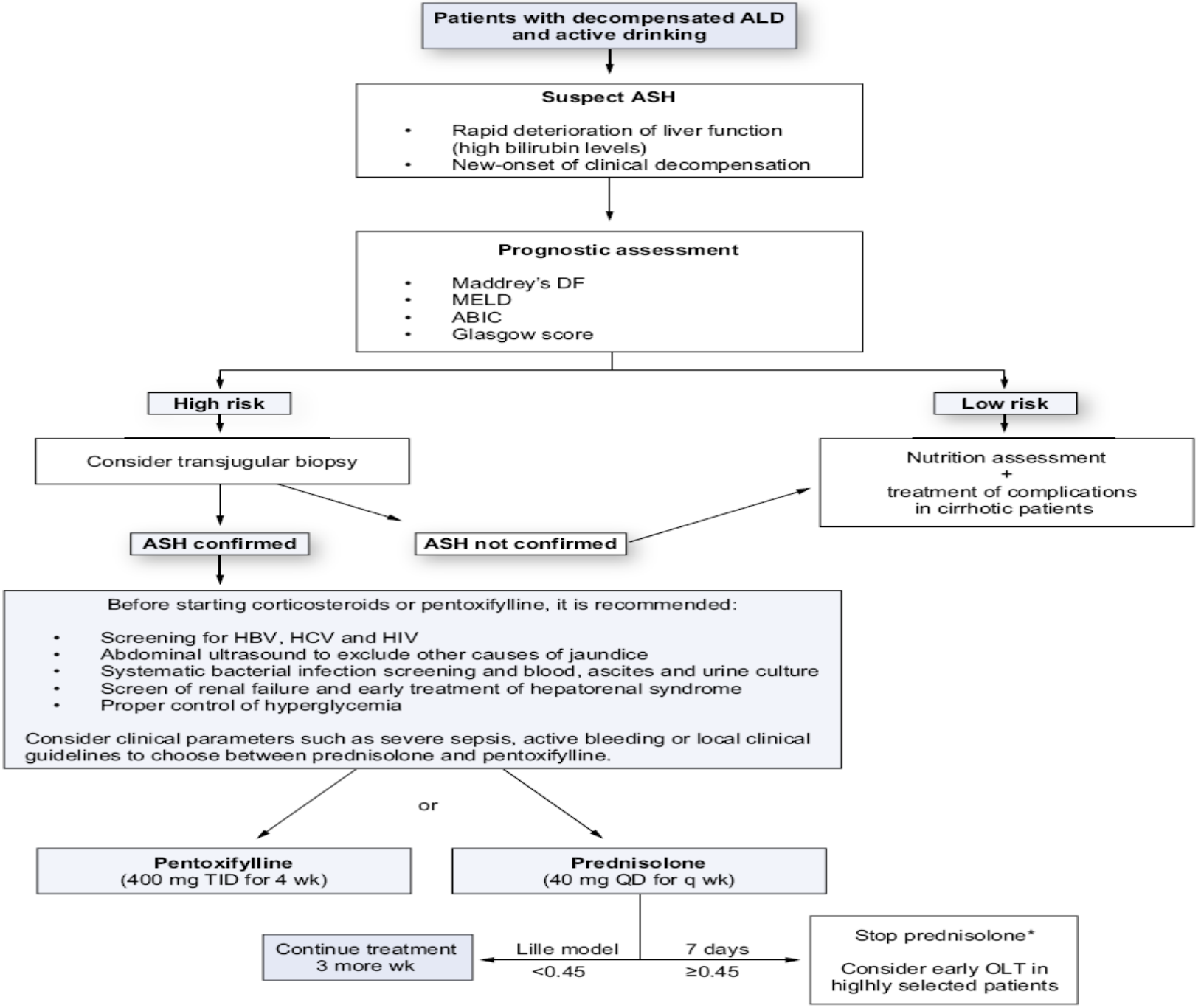
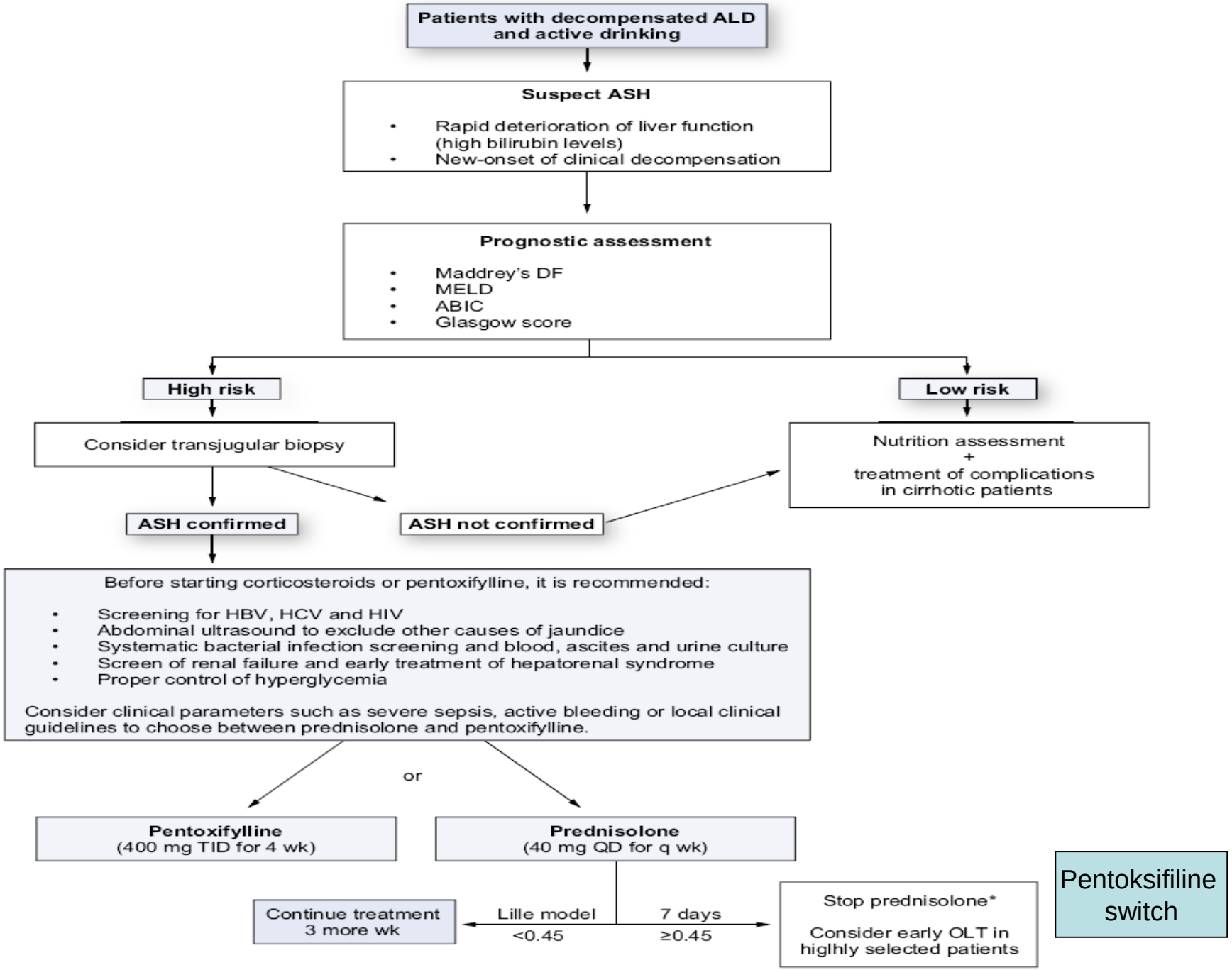


Fig. 2. Therapeutic algorithm for the treatment of patients with alcoholic steatohepatitis (ASH). *A Lille score ⩾0.45 indicating non-response and increased risks of infection and death. In non responders, the interruption of corticosteroids is recommended particularly in those classified as null responders (Lille score >0.56).



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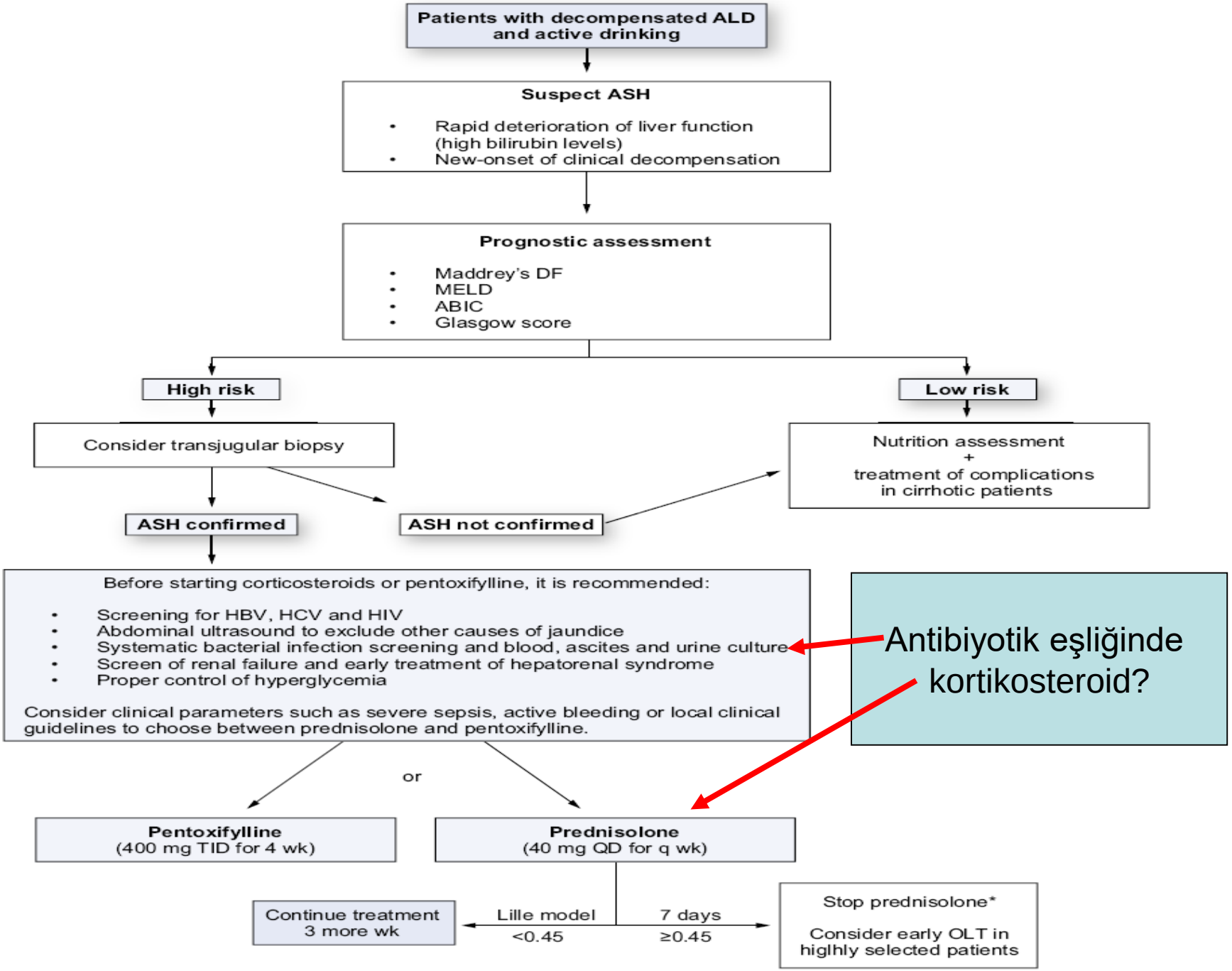

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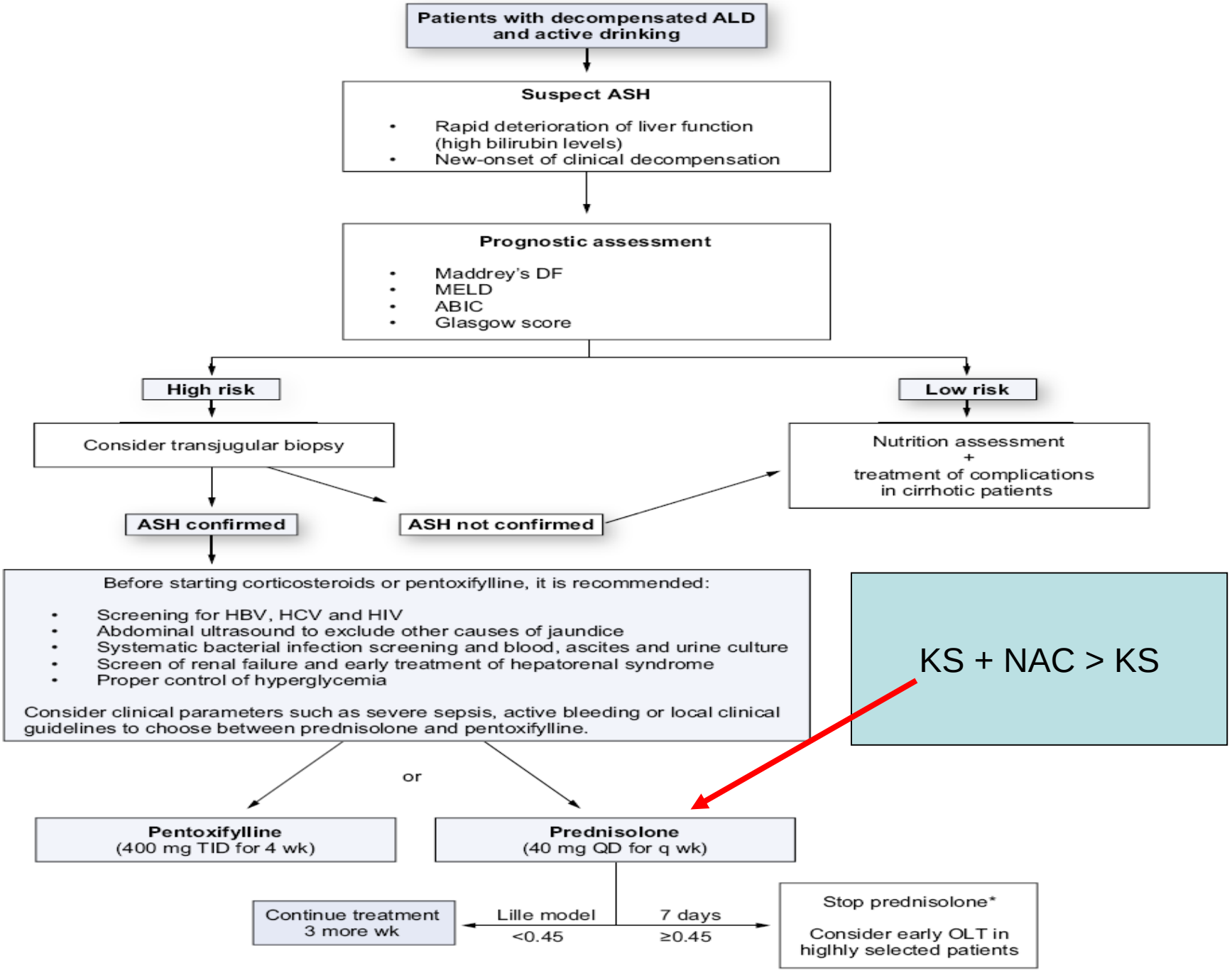

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Pentoksifilin:
1- Anti-oksidan
2- Anti-TNF-alfa

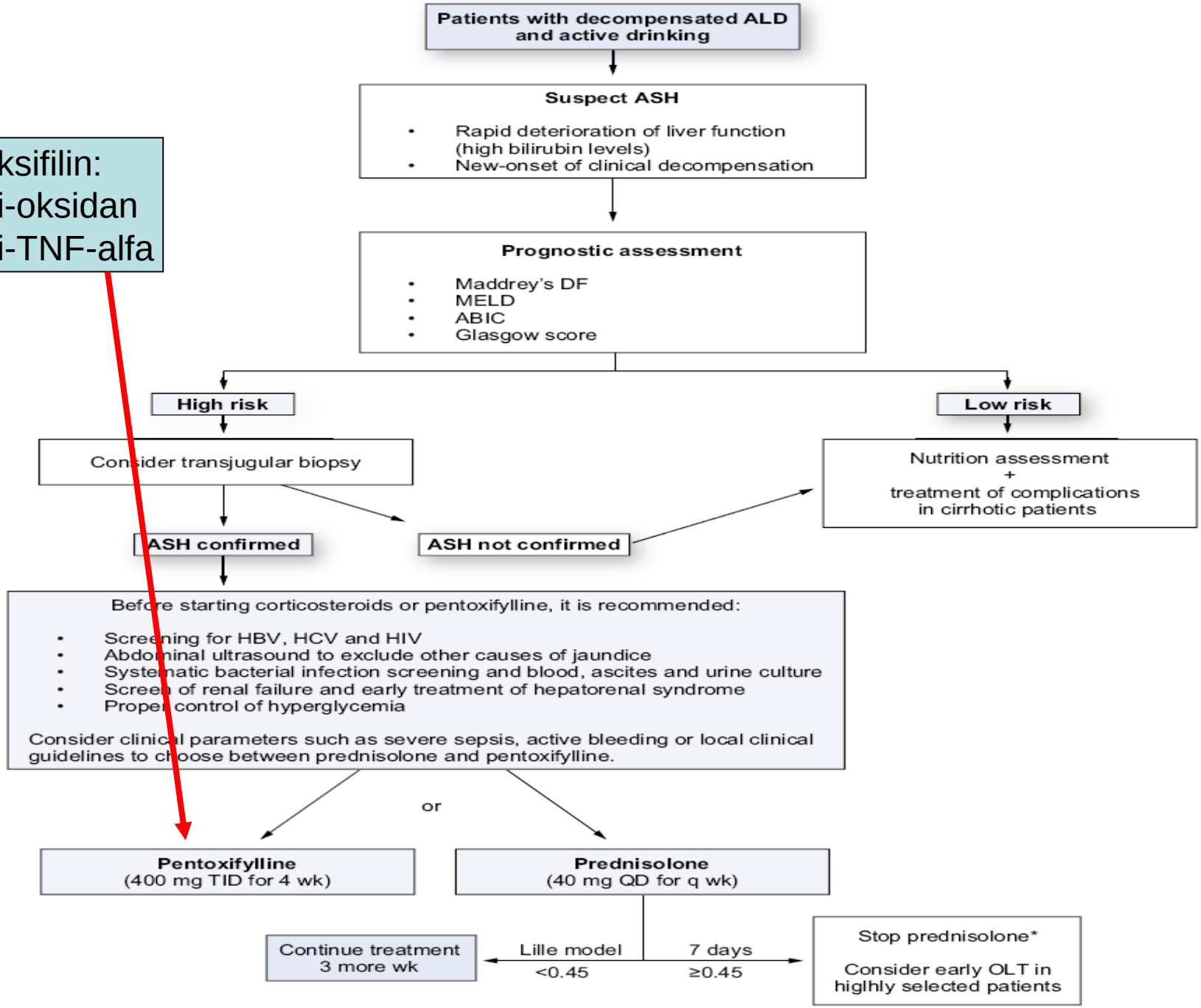
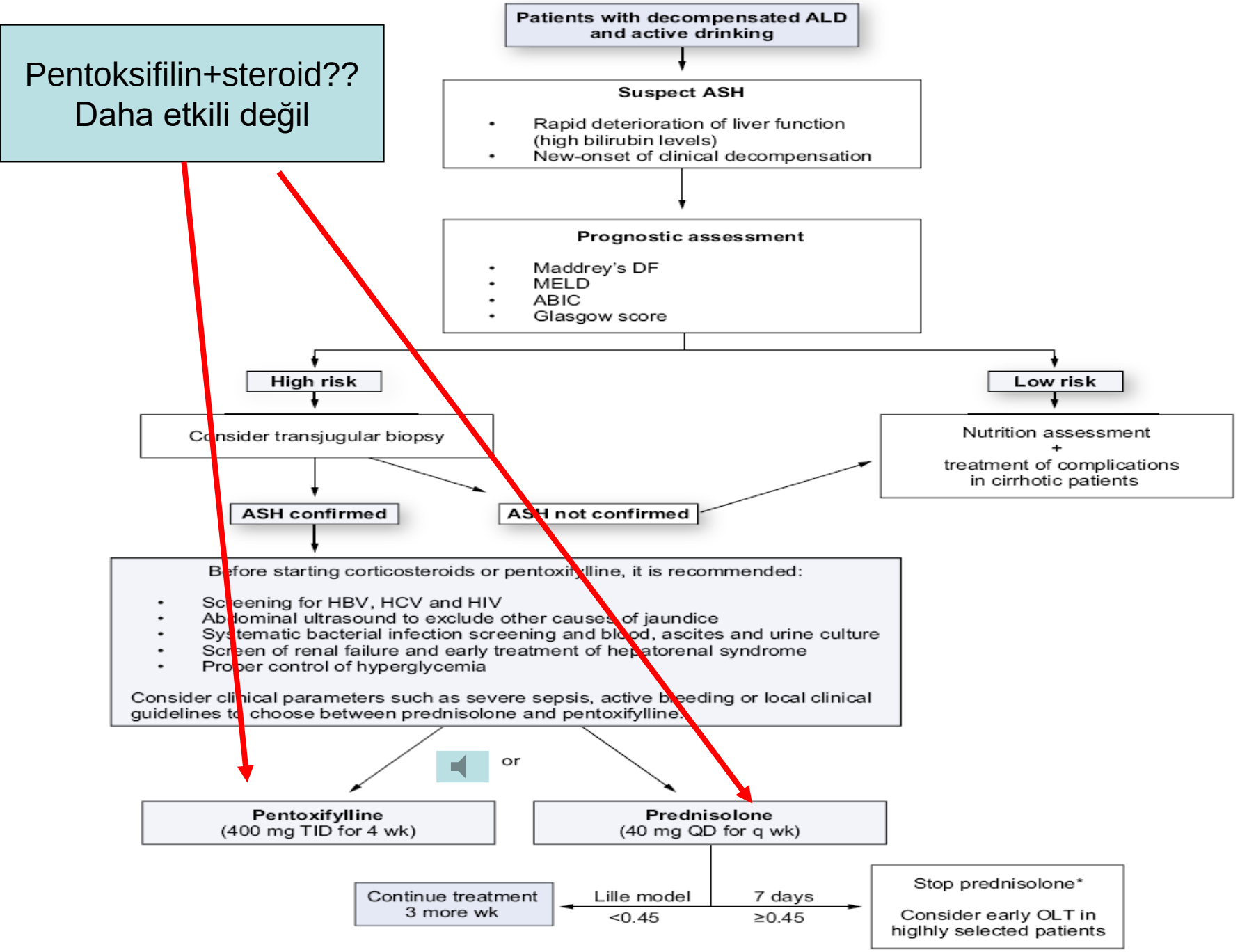


Fig. 2. Therapeutic algorithm for the treatment of patients with alcoholic steatohepatitis (ASH). *A Lille score ⩾0.45 indicating non-response and increased risks of infection and death. In non responders, the interruption of corticosteroids is recommended particularly in those classified as null responders (Lille score >0.56).

Pentoksifilin+steroid??
Daha etkili değil



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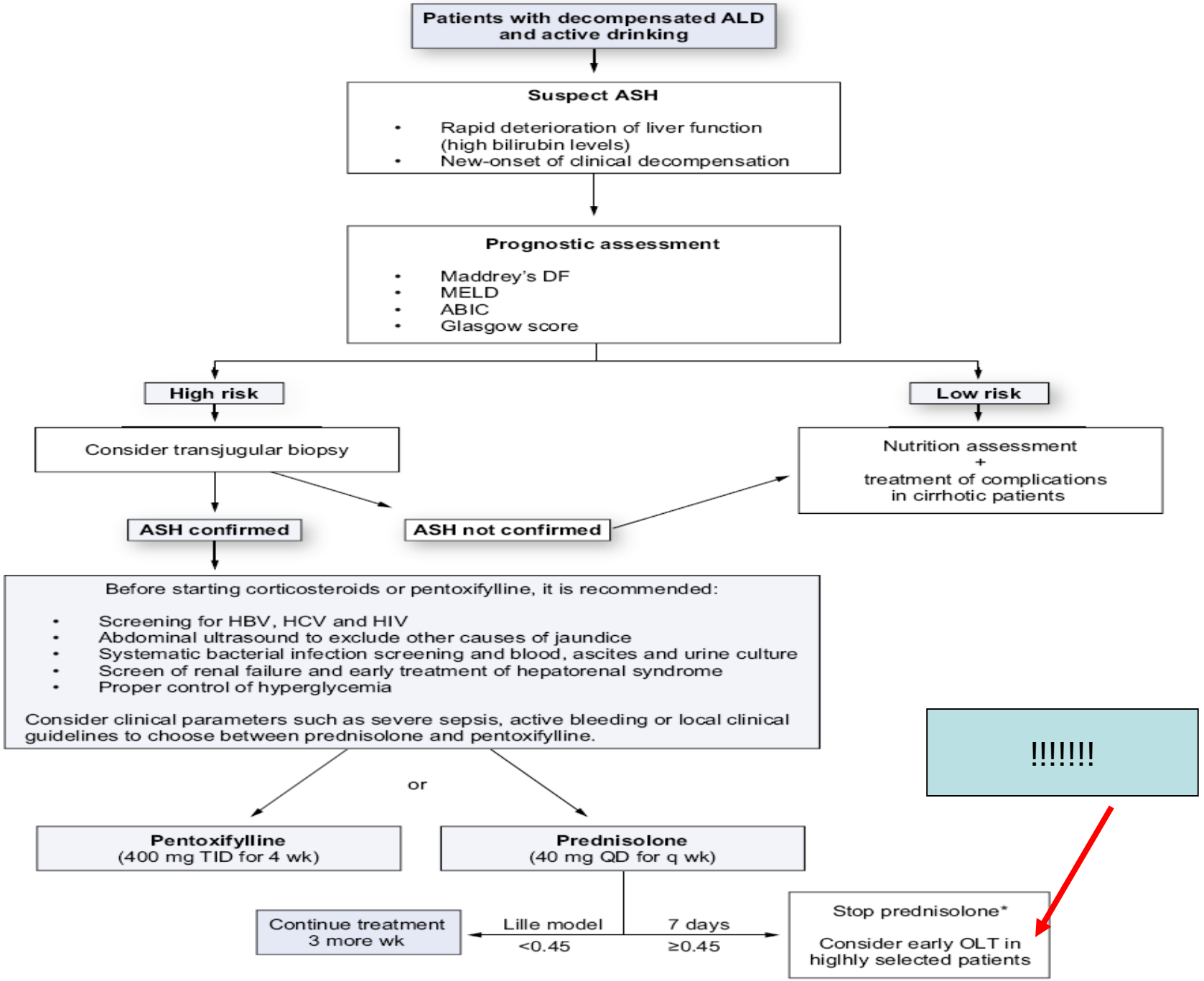

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CAN WE OFFER LIVER TRANSPLANTATION TO PATIENTS WITH ALCOHOLIC HEPATITIS? ANSWER: YES

Medikal tedaviye yanıtsız ciddi alkolik hepatitli olgularda Kc tx'in başarısı çeşitli çalışmalarda gösterildi

Jean-Charles Duclos-Vallée
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Yine çeşitli çalışmalarda 6 ay alkolü bırakma protokolünün zayıf bir gösterge olduğu da gösterildi

Mathurin'in çalışmasında başarı oranı düşük
Başarı oranı yüksek diğer hastaların kaynağı azalıyor
İleride verici havuzu çok artarsa subgruplar incelenebilir
Toplum ve aile hekimleri bu duruma karşı (gönüllü havuzu azalabilir)
Tx listesindeki hastalar alkol kullanmaya devam edebilirler

CAN WE OFFER LIVER TRANSPLANTATION TO PATIENTS WITH ALCOHOLIC HEPATITIS? ANSWER: NO

James Neuberger
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N Engl J Med. 2011 Nov 10;365(19):1790-800. doi: 10.1056/NEJMoa1105703.

Early liver transplantation for severe alcoholic hepatitis.

Mathurin P, Moreno C, Samuel D, Dumortier J, Salleron J, Durand F, Castel H, Duhamel A, Pageaux GP, Leroy V, Dharancy S, Louvet A, Boleslawski E, Lucidi V, Gustot T, Francoz C, Letoublon C, Castaing D, Belghiti J, Donckier V, Pruvot FR, Duclos-Vallée JC.

Hôpital Claude Huriez, Services Maladies de l'Appareil Digestif and INSERM Unité 995, Centre Hospitalier Universitaire, de Lille and Université Nord de France, Lille.

Abstract

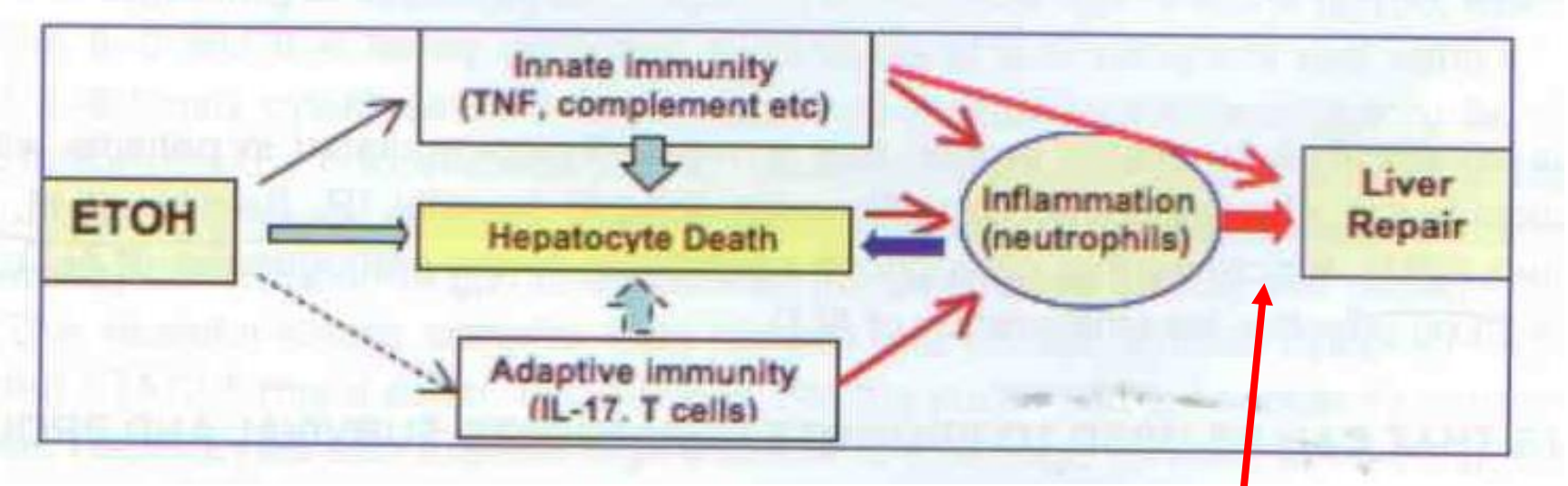
BACKGROUND: A 6-month abstinence from alcohol is usually required before patients with severe alcoholic hepatitis are considered for liver transplantation. Patients whose hepatitis is not responding to medical therapy have a 6-month survival rate of approximately 30%. Since most alcoholic hepatitis deaths occur within 2 months, early liver transplantation is attractive but controversial.

METHODS: We selected patients from seven centers for early liver transplantation. The patients had no prior episodes of alcoholic hepatitis and had scores of 0.45 or higher according to the Lille model (which calculates scores ranging from 0 to 1, with a score ≥ 0.45 indicating nonresponse to medical therapy and an increased risk of death in the absence of transplantation) or rapid worsening of liver function despite medical therapy. Selected patients also had supportive family members, no severe coexisting conditions, and a commitment to alcohol abstinence. Survival was compared between patients who underwent early liver transplantation and matched patients who did not.

RESULTS: In all, 26 patients with severe alcoholic hepatitis at high risk of death (median Lille score, 0.88) were selected and placed on the list for a liver transplant within a median of 13 days after nonresponse to medical therapy. Fewer than 2% of patients admitted for an episode of severe alcoholic hepatitis were selected. The centers used 2.9% of available grafts for this indication. The cumulative 6-month survival rate (±SE) was higher among patients who received early transplantation than among those who did not (77 ± 8% vs. 23 ± 8%, P<0.001). This benefit of early transplantation was maintained through 2 years of follow-up (hazard ratio, 6.08; P = 0.004). Three patients resumed drinking alcohol: one at 720 days, one at 740 days, and one at 1140 days after transplantation.

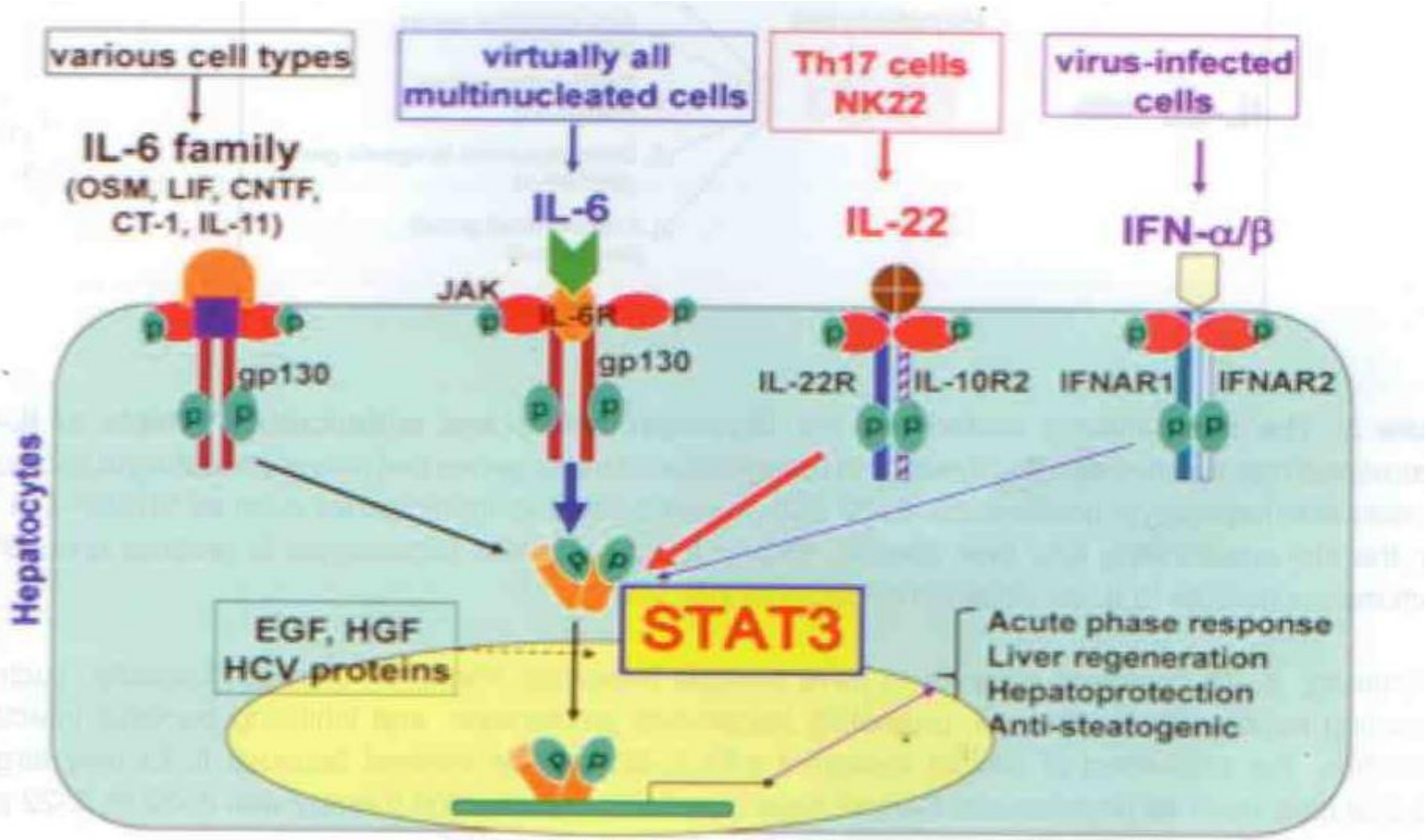
CONCLUSIONS: Early liver transplantation can improve survival in patients with a first episode of severe alcoholic hepatitis not responding to medical therapy. (Funded by Société Nationale Française de Gastroentérologie.).

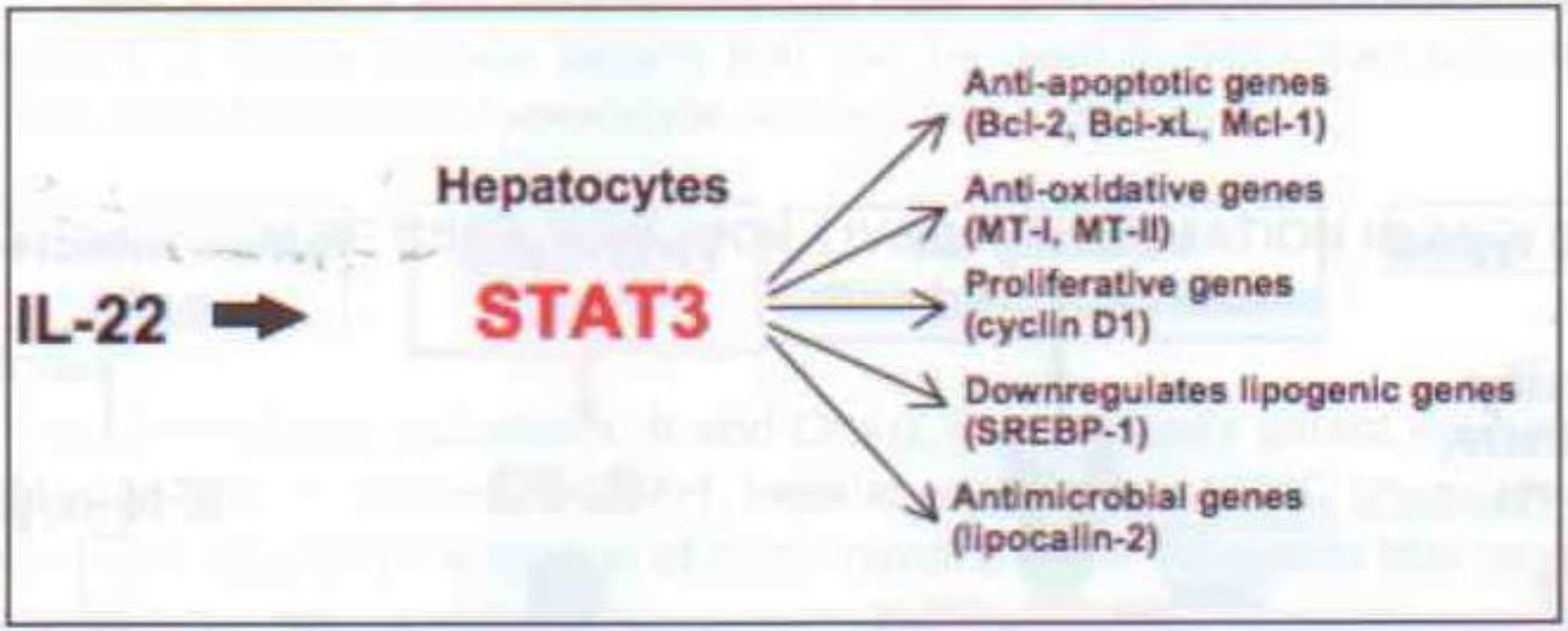
ALKOLİK HEPATİTDE TEDAVİDE YENİ HEDEFLER (OLMALI!) İL-22



*IL1b reseptör antagonistleri
*Apoptosis inhibitörleri=kaspas inhibitörleri
*Farnesoid X reseptör analogları-obetikolikasit
*Stem cell ile tedavi

KORTİKOSTEROİDLER


various cell types
virtually all multinucleated cells
Th17 cells NK22
virus-infected cells
IL-6 family (OSM, LIF, CNTF, CT-1, IL-11)
IL-6
IL-22
IFN-α/β
JAK
IL-6R
gp130
gp130
IL-22R
IL-10R2
IFNAR1
IFNAR2
Hepatocytes
EGF, HGF
HCV proteins
STAT3
Acute phase response
Liver regeneration
Hepatoprotection
Anti-steatogenic


Hepatocytes
IL-22
STAT3
Anti-apoptotic genes
(Bcl-2, Bcl-xL, Mcl-1)
Anti-oxidative genes
(MT-I, MT-II)
Proliferative genes
(cyclin D1)
Downregulates lipogenic genes
(SREBP-1)
Antimicrobial genes
(lipocalin-2)

ÇIKARIMLAR

- Alkolik hepatit mortalitesi yüksek bir hastalık…
- Tanısı için tipik-kesin kriterler yok, klinik bir tanı….
- Akut-on-kronik hastalar…mortalitesi yüksek…
- Kime kortikosteroid tedavisi verileceği iyi karar verilmeli..
- Maddrey skoru pratik ve kullanışlı.....
- Lille skoru-modeli……..
- Alkolik hepatitlerde erken tx?.....
- 6 ay alkolü bırakma kuralı…….
- Yeni tedavi: IL-22?……

NOTES

SABRINIZ İÇİN
TEŞEKKÜR EDERİM…