Antibiyotikler ve GIS

DR. TARIK AKAR

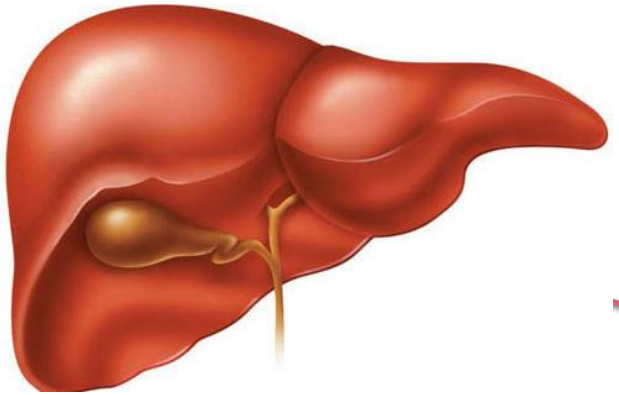
Antibiyotikler ve GIS

Pek çok antibiyotiğin **prospektüs** bilgisinin **en sık görülen yan etkiler** başlığında **GIS** ile ilgili semptomlar (bulantı, kusma, dispeptik yakınmalar) bulunur.

Fakat bunların yönetimi çoğu zaman ufak tefek önlemler (doz azaltımı, yemekten sonra alma) ile mümkündür.

Problemli konuların başında;

- Çoklu antibioyotik kullanımı (HP eradikasyonu gibi nedenler ile)
- Uzun süre antibiotik kullamı (Akne vulgaris ve tekrarlayan GÜS enfeksiyonları)
- Proflaktik antibiyotik kullanımı (Bakteriyal peritonit, kolanjit, pankreatit, IBS, bakteri aşırı çoğalma sendromu)



Karaciğer Toksistesi

PİLL ÖZOFAJİT

ÖNEMLİ GİS YAN ETKİLER

Akut Pankreatit

Mikrobiyota

Antibiyotik ilişkili Diyare

Pill Özofajitis

İlk 1970 de Pemberton tarafından **POTASYUM CLORİDE** alımı sonrası tanımlanmış.

Genelde kendi kendini sınırlayan şiddetli göğüs ağrısı ve ağrılı yutma (**ODİNOFAJİ**) sorunu ile kendini belli eder.

Olduğundan daha az vaka bildirildiğinde inanılıyor. Çoğu hasta başvurmuyor veya hafif semptomları olanlar ilacı keserek çözmeye çalışıyor.

**Ama günümüzde bu konudaki farkındalık artmış durumda, daha az hasta bu konuda Gastroenteroloji'ye başvuruyor.

Pill Özofajitis Risk ?

Spesifik bazı ilaçların ***su içmeden*** kullanımı en önemli risk faktörü…

- Antibiotikler (**Tetrasiklin, Doksisiklin**), Ostooporoz ilaçları (Alendronate) vs ….Kapsüllü, Asidik özellikli, BÜYÜK Boyut

Orta Yaş hastalar (20-40)—Daha sık antibiotik kullanıyorlar

Bayan cinsiyet (GÜS enfeksiyonlar sık)

Postüler Bozukluklar

- Özofagustaki anatomik veya motilite bozukluklar (Akalazya, Skleroderma, Reflü sekonder darlık, Özofagial Web, Zenker divertikülü, Epifrenik divertikül)
- Özofagusa dıştan bası durumu (AC Ca, Kalp yetmezliği, Perikart hastalıkları ve Sol Atrium basısı)

Tükrük salgısının azalmasına bağlı hastalıklar (Sjögren Sendromu)

Pill Özofajitis Risk ?

İlaçlar;

- **Asidik formulasyon** ---Demir preparatları, **Ascorbic Asid**
- **Alkali özellikli**--- Alendronate
- **Hiperosmolar solüsyon** ---Potasyum Kloride
- **Direkt Toksik etki-**--Doksisiklin ve Tetrasiklin
- **Kapsül formu-**- Clindamisin

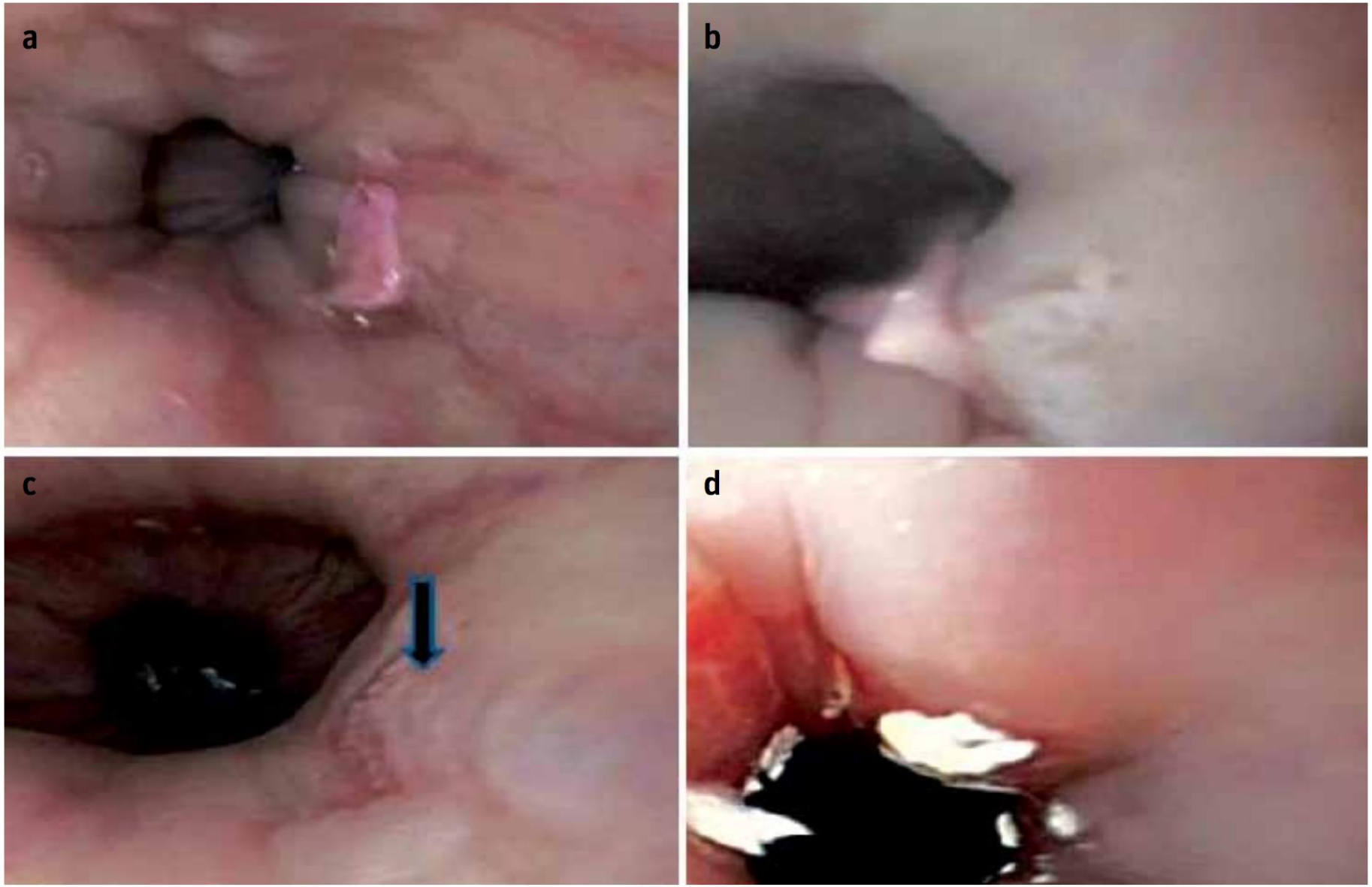
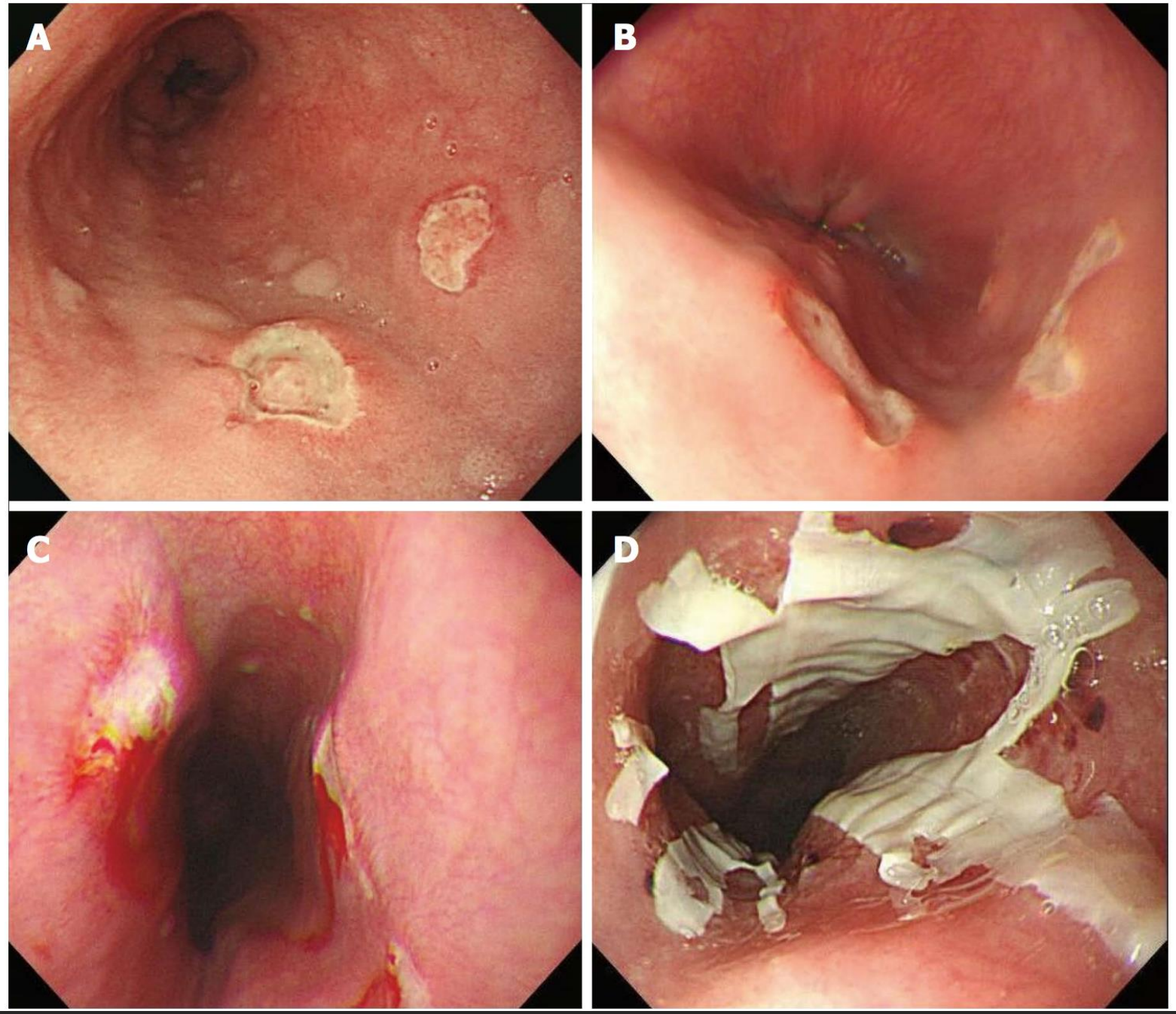


Figure 2. a-d. Clindamycin in gelatin capsule form adhering to distal esophagus **(a)**. Washing the capsule with water during endoscopy **(b)**. The superficial ulcerous area under the capsule (arrow) **(c)**. The white colored content of the drug's capsule adhering to mucosa in the distal esophagus **(d)**.


A
B
C
D

Pill Özofajitis
Antibiotikler (Bildirilenler)

Doksisiklin

Tetrasiklin

Cloxacillin

Clindamycin

Ciprofloxacin

Amoxicilin

Metranidazole

Pill Özofajitis
Klinik

Göğüs ağrısı

Yutma güçlüğü

Ağrılı yutma

15-20 güne kadar sürebilir

Oral alımda azalma, besleme sorunları

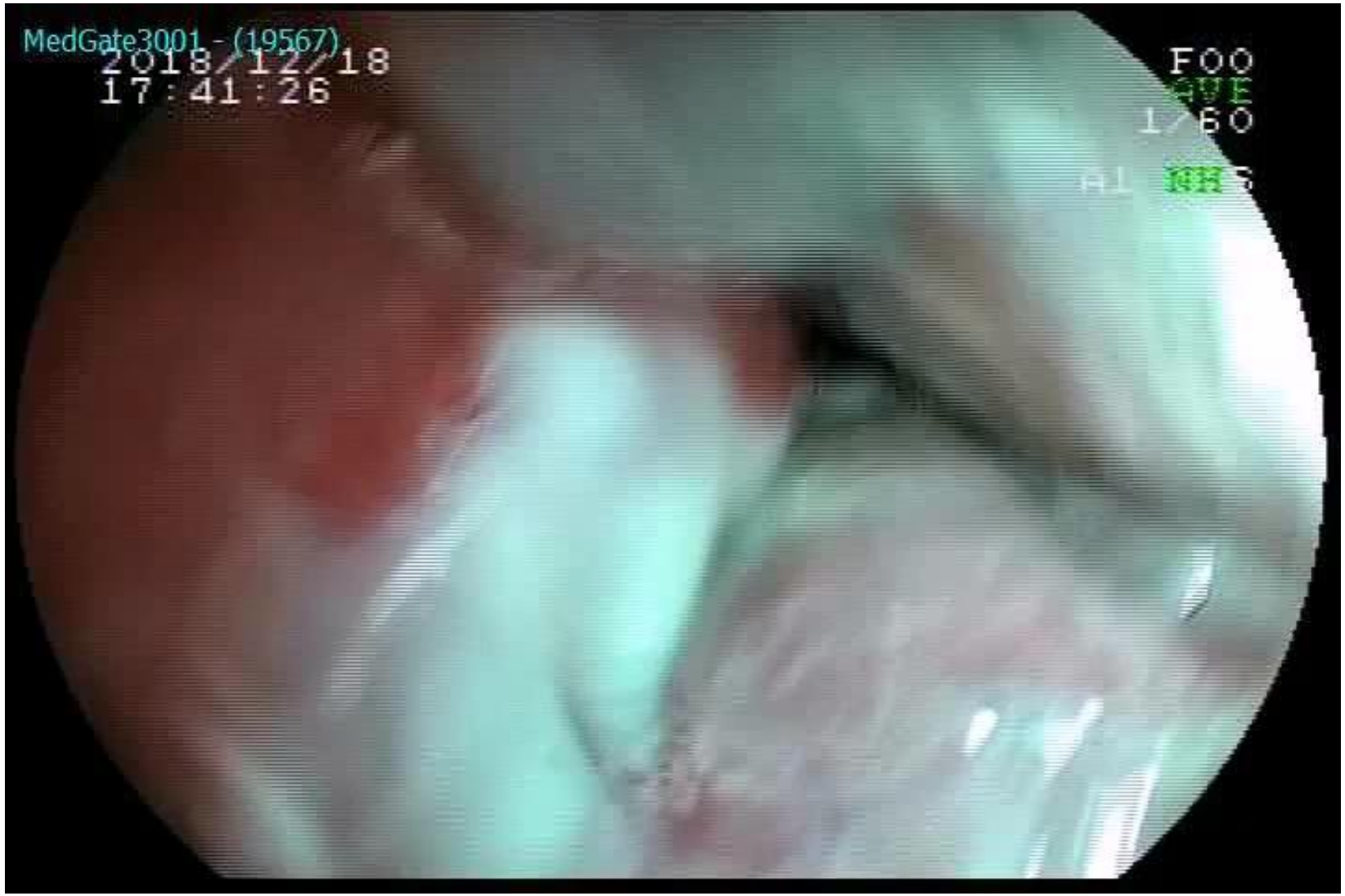
Pill Özofajitis
TANI

Bu semptomları olan hastaların en kısa sürede Gastroenteroloji' ye Endoskopi yapılması sevki gerekir.

Endoskopide çoğu kez Özofagus' un orta kısmında yüzeyel ülserler görülür.

Biyopsi potansiyel bir ilaç söz konusu ise gereksizdir.

ENDOSKOPİ



Pill Özofajitis Komplikasyonlar

Darlık (Antibiotiklerde sık görülmez, **Alendronate** kullanında sık)

Kanama (Antibiotiklerde az, **NSAİ** bağlı sık)

Perforasyon bildirilmemiş.

Drug-induced esophageal ulcers: Case series and the review of the literature

Muhammed Sait Dağ1 , Zeynel Abidin Öztürk2 , İrem Akın3 , Ediz Tutar4 , Öztekin Çıkman5 , Murat Taner Gülşen

Table 1. Etiological agents causing esophageal ulcer

Etiological Agents	Number
Doxycycline	24
Tetracycline	1
Cyproterone acetate, ethinylestradiol	3
Escitalopram	2
Citalopram HBr	1
Ibuprofen	2
Naproxen	2
Aspirin	1
Ciprofloxacin	2
Alendronate sodium	1
Ornidazole	1
Dobesilate calcium	1
Methylprednisolone	1
Ferrous glycine sulfate	1
Phenytoin sodium	1
Clindamycin	1
Rifampicin	1
Radioactive I^{131}	1
Lansoprazole	1

Table 2. Primary diseases requiring treatment

Primary Diseases	Number
URD (vaginitis, cervicitis, endometritis, salpingitis, urethritis)	13
Acne vulgaris	11
Menstrual disorders, contraception	3
Depressive disorder, anxiety	3
Migraine	2
Sinusitis	2
Urinary system infection	2
Osteoporosis	1
Brucellosis	2
Seborrheic dermatitis	1
Hemorrhoids	1
Pemphigus vulgaris	1
Anemia	1
Epilepsy	1
Gingivitis	1
Tuberculosis	1
Papillary thyroid Ca	1
Gastritis	1

Turk J Gastroenterol. 2014 Apr;25(2):180-4. doi: 10.5152/tjg.2014.5415.

Clinical and endoscopic characteristics of drug-induced esophagitis

Kim SH, Jeong JB, Kim JW, Koh SJ, Kim BG World J. Gastroenterol. 2014 Aug 21;20(31):10994-9.

Table 1 Demographic features and clinical symptoms of patients diagnosed with drug-induced esophagitis *n* (%)

Characteristics		
Age(yr)	mean ± SD	43.9 ± 18.9
Sex	Male/female	28/50
Symptom	Chest pain	56 (71.8)
	Odynophagia	30 (38.5)
	Dysphagia	23 (29.5)
	Vomiting	6 (7.7)
	Melena	2 (2.6)

Table 2 Endoscopic features of patients diagnosed with drug-induced esophagitis

Feature		*n* (%)
Location	Proximal	3 (3.8)
	Middle	61 (78.2)
	Distal	14 (17.9)
Endoscopic findings	Ulcers	64 (82.1)
	Bleeding	19 (24.4)
	Erosions	14 (17.9)
	Coating	4 (5.1)
	Pill	3 (3.8)
	Stricture	2 (2.6)
	Kissing ulcers	34 (43.6)

Pill Özofajitis
Tedavi

Potansiyel suçlu antibiyotik hemen kesilir.

Şiddetli göğüs ağrısı için NSAİ veya Narkotik ağrı kesiciler kullanılmalı.

- **NSAİ'ler Intra musküler kullanılmalı. (oral alınmamalı)

Beslenme Ağrı kesici verildikten 30 dak sonra soğuk gıdalar alınmalı.

Mukoza koruyucu Sükralfat (Antepsin), PPI iyileşmeyi hızlandırabilir.

Ağır vakalarda **Nütrisyonel** destek sağlanmalı.

Pill Özofajitis
KORUNMA

Bu tür ilaçları alacaklar en az **200-250 ml su** ile almalı.

Mümkünde **ilaç alımından hemen sonra yemek yenmeli**.

Pron pozisyonda alınmamalı.

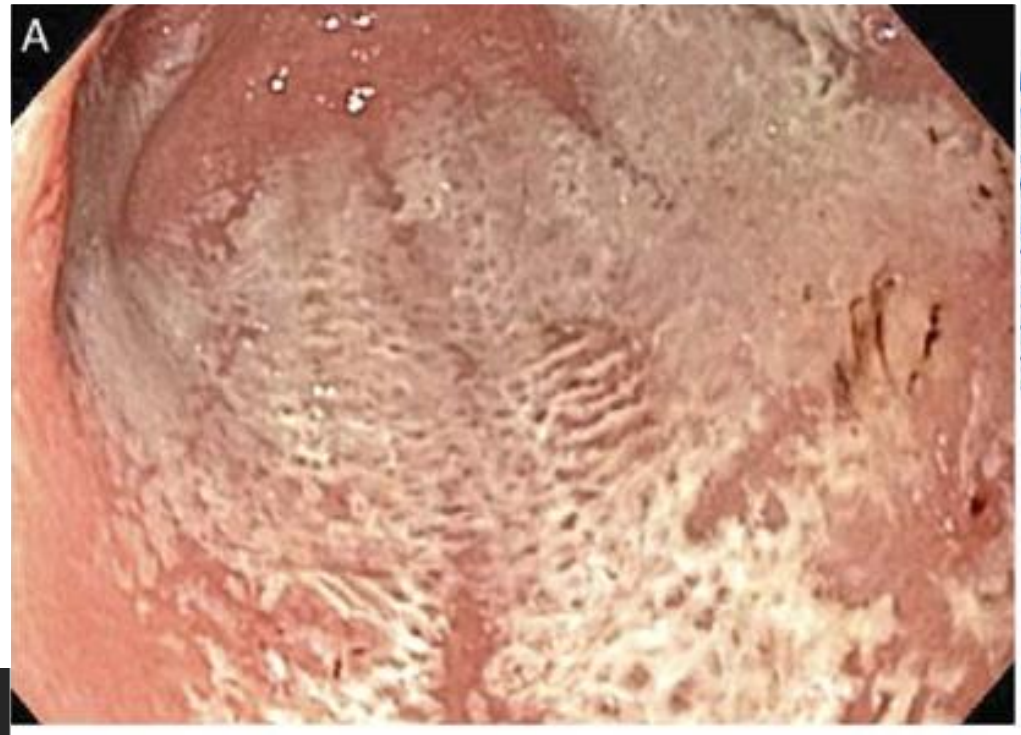
Alındıktan En az 30 dakika sonra yatılmalı.

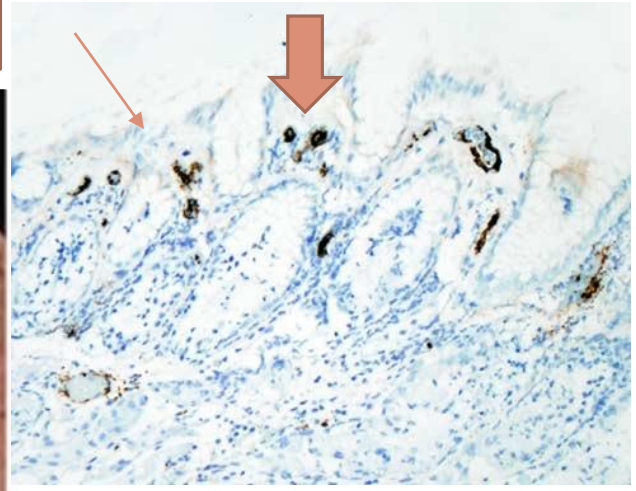
Bu tür ilaçların kullanacak hastalara mutlaka bu uyarılar yapılmalı. Vakaların çoğunda ilgili doktorun bu konuda yeterli uyarı yapmadığına şahit oluyoruz!!!

Gastric Mucosal Necrosis With Vascular Degeneration Induced by Doxycycline

Shu-Yuan Xiao, MD,* Lei Zhao, MD, PhD,* John Hart, MD,* and Carol E. Semrad, MD…..Am J Surg Pathol Volume 37, Number 2, February 2013

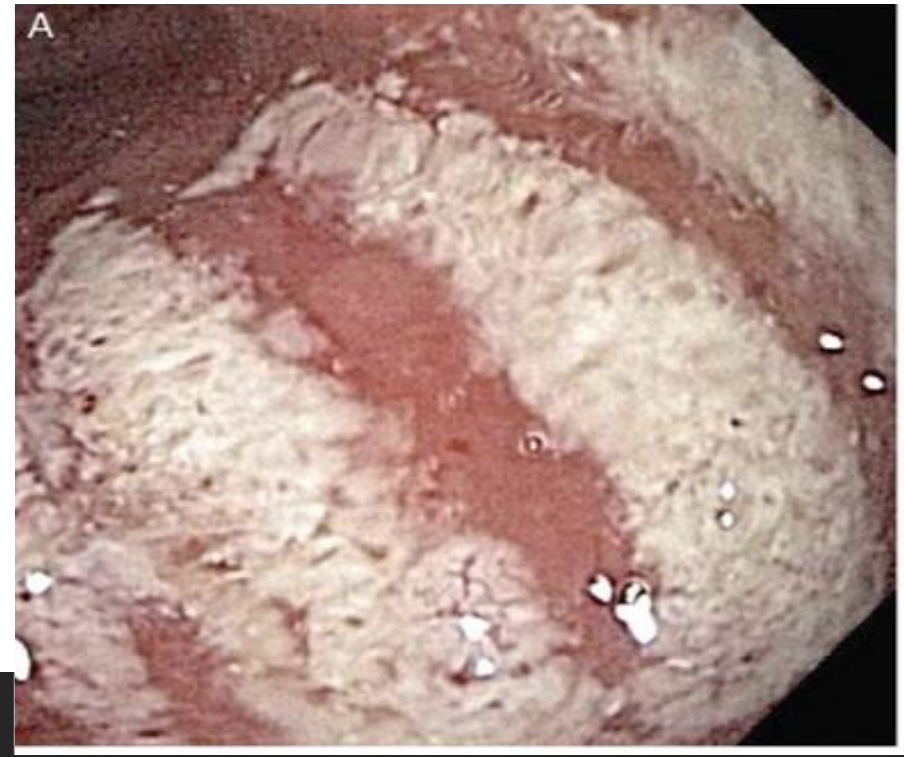
Case 1: 65 yaş bayan





Mukoza altında Trombüsler
Vasküler değişiklikler

Case 2: 82 yaş bayan



Doxycycline-induced gastrointestinal injury

Kajsa Affolter MDa,*, Wade Samowitz MDb, Kathleen Boynton MDc, Erinn Downs Kelly DO.
Human Pathology (2017) 66, 212–215

Case 1: 53 yaş bayan, yatalak, çoklu hastalıklı.. 54 gündür Doksisilin 2x1 almakta iken dispepsi, kanama bulguları oluşmuş. Endoskopide mide ülseri mevcut

Case 2: 80 yaş erkek, çoklu hastalıklı ve siroz, 37 gündür Doksisiklin 2x1 almakta. Endoskopide ciddi mide erozyonlar görülmüş.

Case 3: 39 yaş bayan hasta. 5 gündür Doksisiklin 2x1 almakta. Mide ve bulbusta **ciddi erozyonlar** izlenmiş.

Sonuç: Bu tür ilaçların uzun süre kullanımı Mide mukoza hasarı, ülser ve kanamaya neden olabilir. **Mutlaka PPI ile birlikte ve süre kısa tutulmalıdır**.

Antibiotik ilişkili PANKREATİT

Akut pankreatit (Atalanta kriterleri); <(Aşağıdaki 3 kriterden en az 2 si olmalı)

- Tipik pankreatit ağrısı (kuşak tarzı, sırta vuran)
- Amilaz ve Lipaz da 3 kat artış
- USG, CT veya MRI pankreatit ile uyumlu bulgular (pankreas ödemi, sıvı, nekroz)
- **DİKKAT EDİLMESİ GEREKENLER**

--Tedavi sırasında pankreatit gelişmiş olmalı

--Diğer nedenler ekarte edilmeli (Taş, alkol, Trigliserit, Hiperkalsemi)

--Klinik ve lab bulguları ilaç geri çekildiğinde düzelmeli.

--Potansiyel suçlu ilaç tekrar verildiğinde semptomlar ve lab bozukluk yeniden gelişmeli

Antibiotik ilişkili PANKREATİT

Class I (> 20 den fazla vaka bildirilmiş)→ azathioprine, valproic acid, mesalamine, estrogen, opiates, tetracycline, steroids, trimethoprim/sulfamethoxazole, sulfasalazine, furosemide

Class II (>10 dan fazla vaka)→Metranidazol, **rifampin**, octreotide, carbamazepine,bacetaminophen, interferon alfa-2b, enalapril, hydrochlorothiazide, cisplatin, ve erythromycin

Class III (Nadir vaka)—>ciprofoxacin, levofoxacin, and azithromycin

Metronidazole-Induced Pancreatitis: Is There Underrecognition? A Case Report and Systematic Review of the Literature

Ibrahim Youssef, Naba Saeed Mohammad El Abdallah Kara Huevelhorst and Kais Zakharia.. Case Reports in Gastrointestinal Medicine Volume 2019, Article ID 4840539, 6 pages
https://doi.org/10.1155/2019/4840539

Table 1: Metronidazole-induced pancreatitis case reports in the English literature.

First author, year of study	Gender	Age	Number of Episodes	Indication for use of metronidazole (with each episode)	Interval between metronidazole administration and onset of pancreatitis' symptoms (per episode)	Serum amylase, level after the onset of pancreatitis' symptoms (per episode)	Serum lipase level after the onset of pancreatitis' symptoms (per episode)	Imaging findings for acute pancreatitis (per episode)
Plotnick BH, 1985	F	29	1 2	Vaginal discharge	1 day 38 days	1182 U/dL 1727 U/dL	50 U/dL 64 U/dL	N/A N/A
Sanford KA, 1988	F	23	1 2 3 4	Gardnerella vaginalis	9 days 3-7 days 3-7 days 3-7 days	19.07 μkal/L Elevated Elevated Elevated	N/A Elevated Elevated Elevated	Positive N/A N/A N/A
Celifarco A, 1989	F	22	1 2 3	Vaginal infection	24 hours 24 hours 12 hours	250 U/L 280 U/L 1657 U/L	N/A N/A 52.2 U/L	N/A N/A Positive
Corey WA, 1991	F	63	1	Crohn's recurrent rectovaginal fistula	7 days	906 U/L	2148 U/L	Negative
de Jongh FE, 1996	F	45	1 2 3	Vaginitis	N/A N/A 1 day	N/A N/A 120 U/L	N/A N/A N/A	N/A N/A Negative
Sura ME, 2000	F	61	1	Aspiration pneumonia	4 days	566 U/L	245 U/L	Negative
Feola DJ, 2002	F	49	1 2	Trichomoniasis	3-5 days 12 hours	N/A 1397 U/L	N/A 6916 U/L	N/A Negative
Nigwekar SU, 2004	F	46	1 2	Bacterial vaginosis	8 days 8 days	N/A 398 U/L	N/A 2543 U/L	N/A Negative
Tsesmeli NE, 2007	M	31	1	Bloody diarrhea with a history of IBD	3 days	581 U/L	N/A	Positive
Loulergue P, 2008	M	25	1	Pseudomembranous colitis	5 days	317 U/L	665 U/L	N/A
O'Halloran E, 2010	F	25	1 2	Periodontal abscess	3 doses (1 day) 5 doses (2 days)	N/A 810 U/L	N/A N/A	N/A N/A
Cabrera R, 2011	M	74	1	Acute diverticulitis	12 hours	729 U/L	2250 U/L	Negative
Yousaf H, 2012	F	23	1	Trichomoniasis	1 hour	327 IU/mL	876 IU/mL	Positive
Yilmaz M, 2016	M	22	1 2 3	Ulcerative colitis C. *difficile* colitis	3 days 2 days 3 days	N/A 387 IU/L 427 IU/L	N/A 400 IU/L 429 IU/L	N/A N/A Positive
Our case	F	60	1 2	C. *difficile* colitis	4 days 3 days	N/A N/A	808 IU/L 396 IU/L	Positive Positive

Beraberinde PPI kullanımı Pankreatit artıran bir neden olabilir.

ANTİBİYOTİKLER & HEPATİK TOKSİSİTE

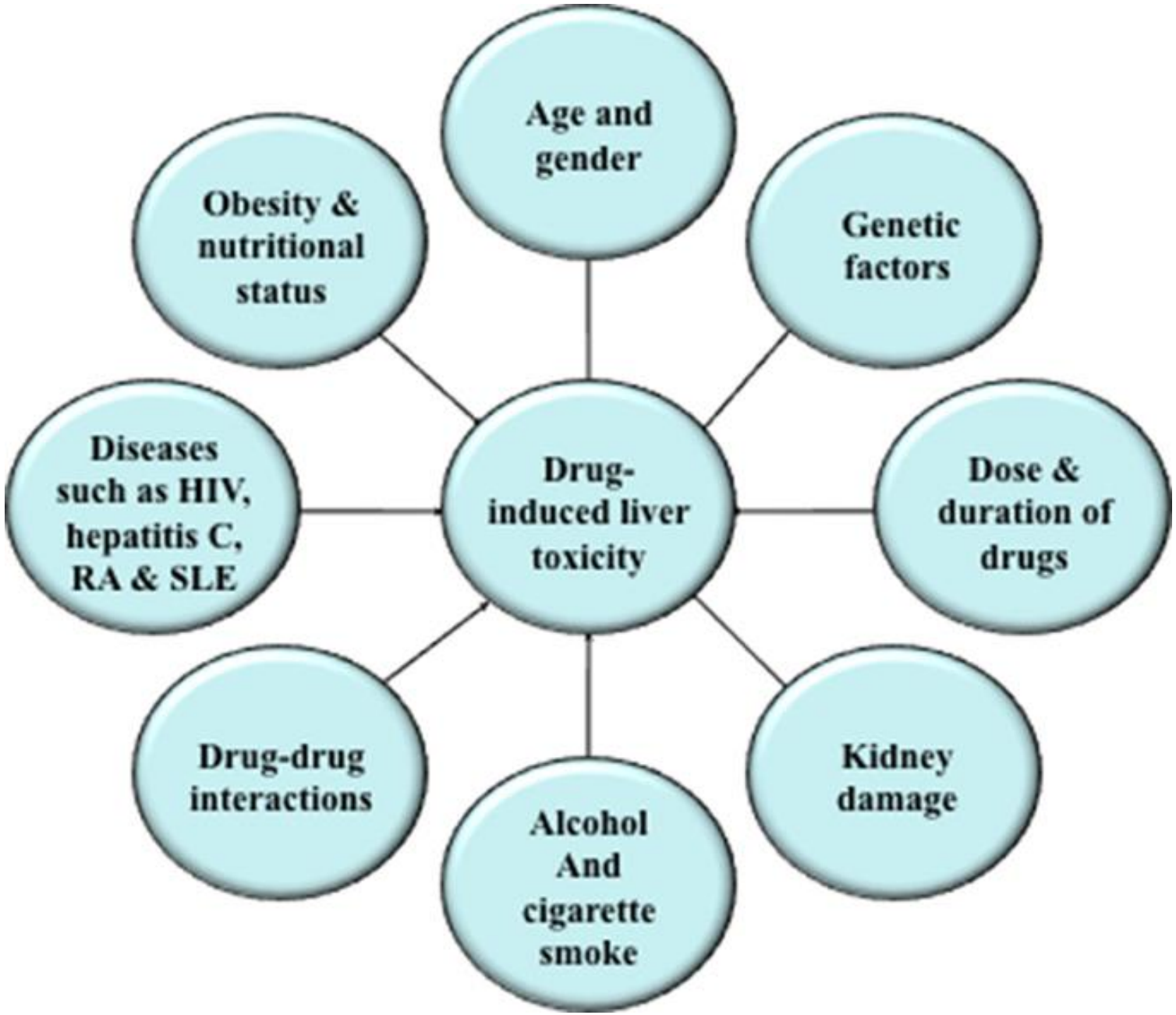
Antibiyotikler ve Hepatik Toksisite

Pek çok antibiyotiğin Karaciğer toksisitesi mevcut.

Bunları çoğu hafif ve asemptomatik enzim yüksekliği şeklindedir ve buna 'ilaç toleransı' veya 'ilaç adaptif cevap' deniliyor.

. Ama Sarılıkla seyreden ağır hepatit formları da görülebilir. (**BİLİRUBİN >3 mg/dl**)

%90 ilaç kesildiğinde toksisite tamamen düzelirken %10 kc yetmezliği, kc nakli ve ölüme giden bir tablo oluşabilir.


Age and gender
Obesity & nutritional status
Genetic factors
Diseases such as HIV, hepatitis C, RA & SLE
Drug-induced liver toxicity
Dose & duration of drugs
Drug-drug interactions
Alcohol And cigarette smoke
Kidney damage

Hepatik Toksisite Risk ?

Yaşlı

Bayan

Kronik KC hastalığı

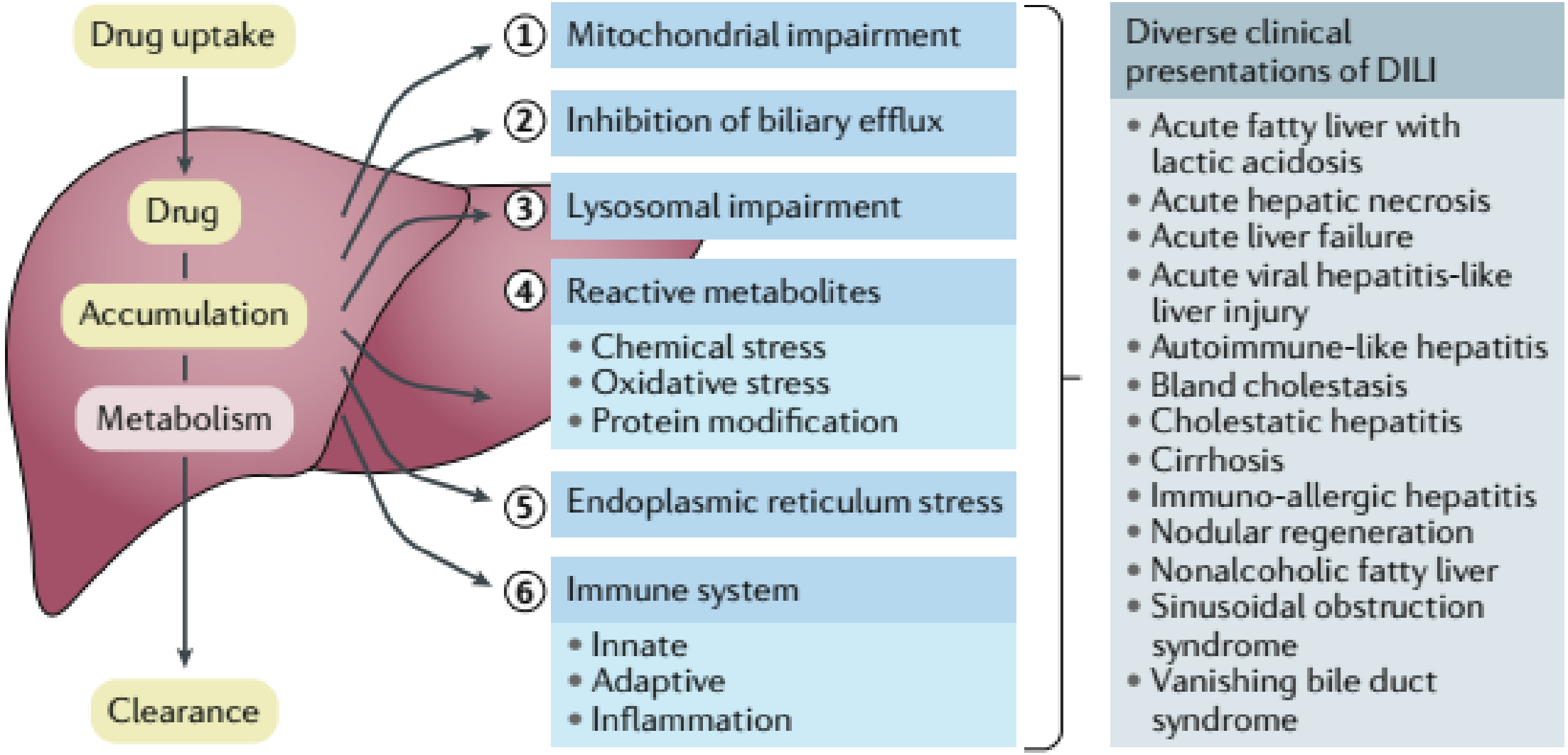
Obezite

Yağlı Karaciğer

Metabolik Sendrom

Yüksek doz LİPOFİLİK ilaç kullanımı

Genetik Varyasyonlar (HLA ve Sitokrom P 450)



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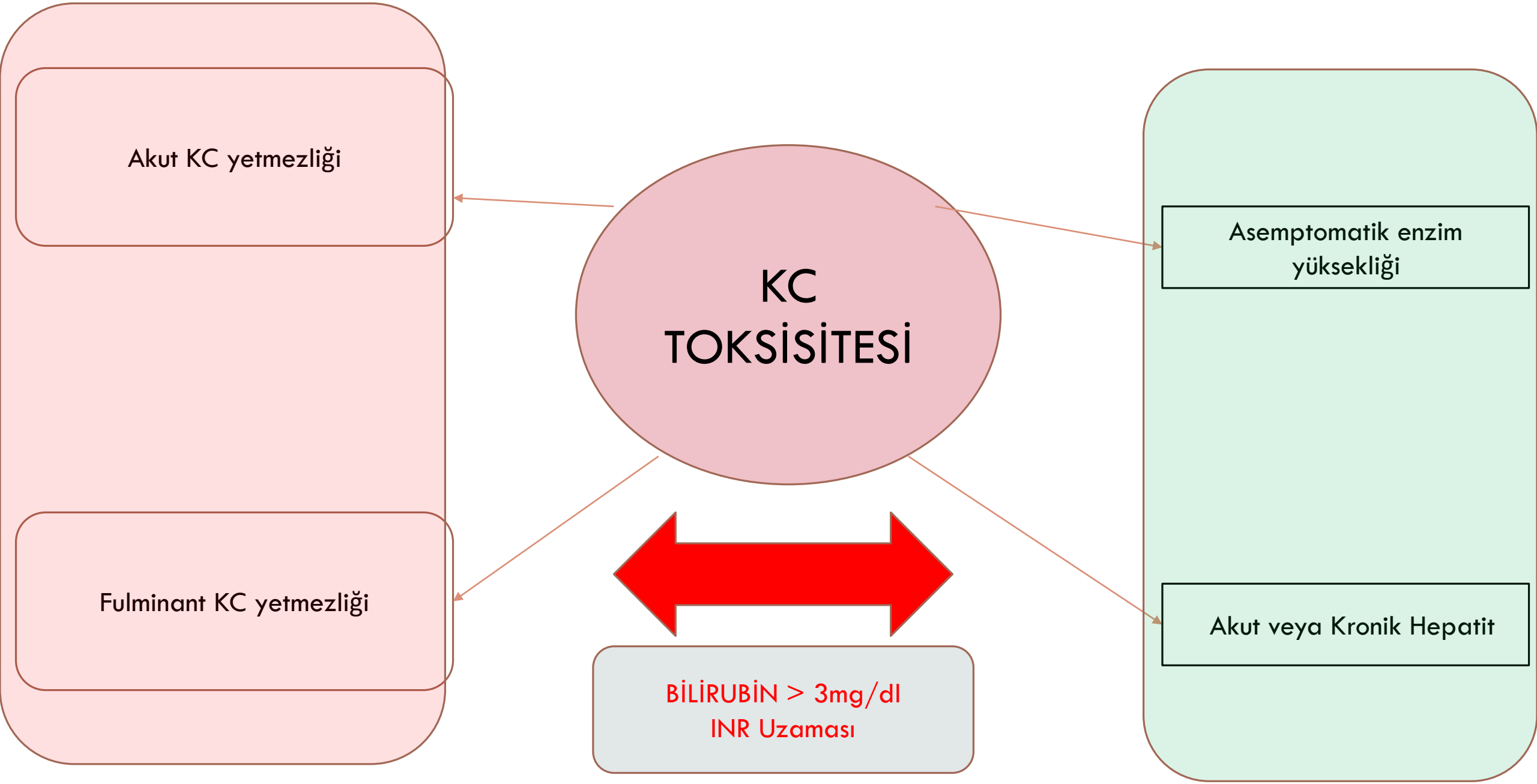
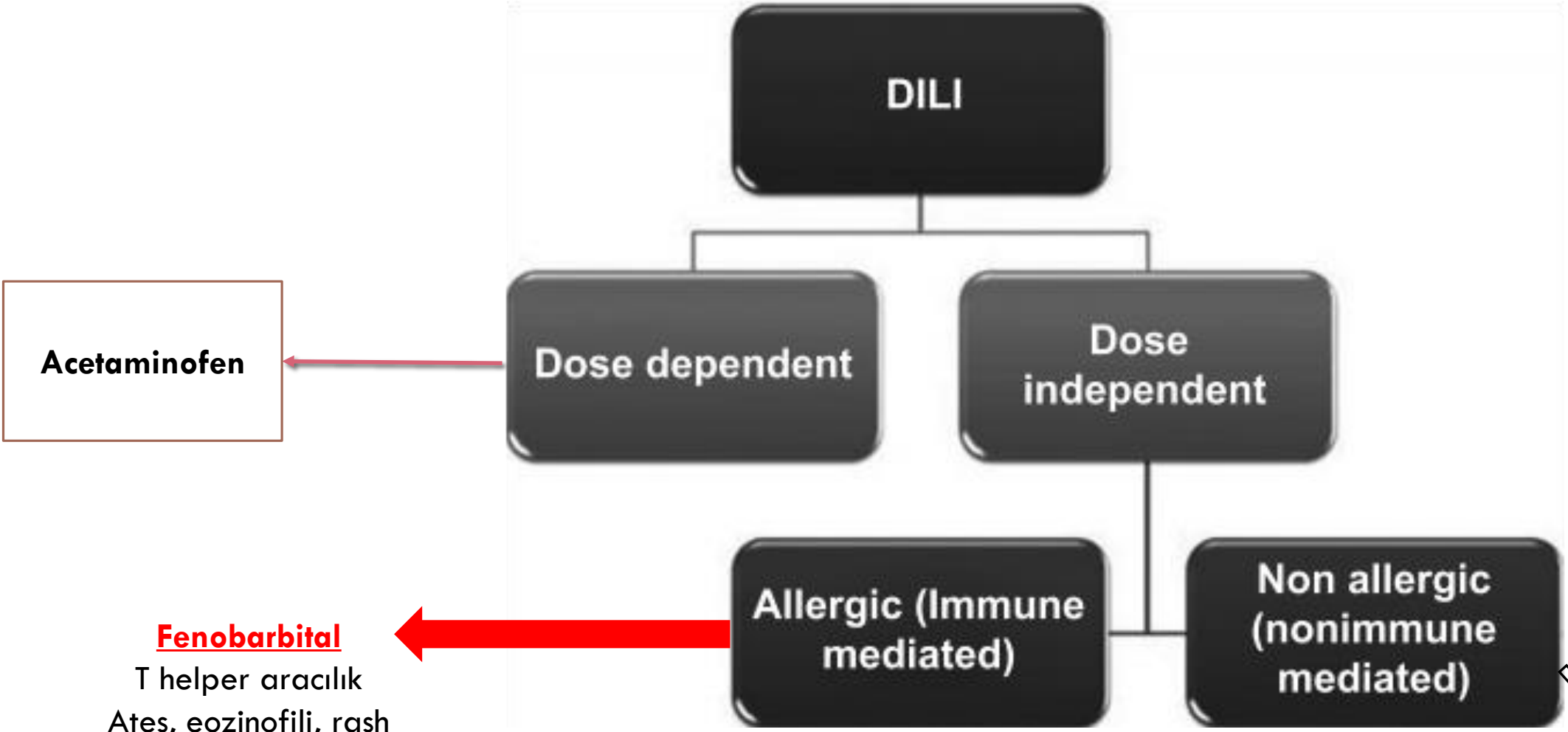

Akut KC yetmezliği
Fulminant KC yetmezliği
KC
TOKSİSİTESİ
Asemptomatik enzim yüksekliği
Akut veya Kronik Hepatit
BİLİRUBİN > 3mg/dl
INR Uzaması



Acetaminofen

Fenobarbital

T helper aracılık

Ateş, eozinofili, rash

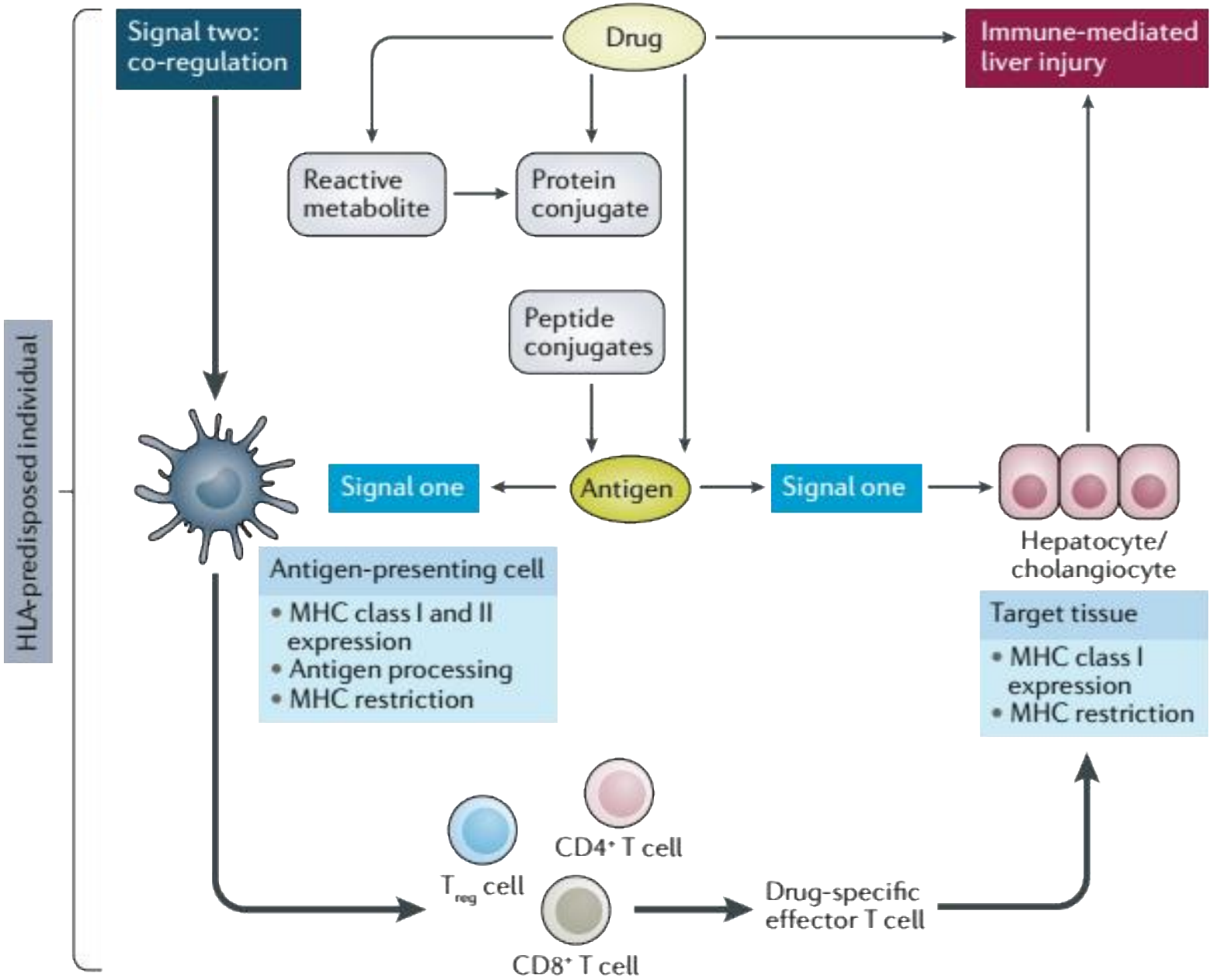
İlk temasta antijen ile uyarılma

Yeniden karşılaşmada Hızlı ve Şiddetli toksisite

Reaktif Metabolit

Mitokondrial Toksisite

Models of Drug Induced Liver Injury (DILI) – Current Issues and Future Perspectives. Lucija Kunac,Ivana Bozic, Current Drug Metabolism, 2018, Vol. 19, No. 10 831



Managing the challenge of drug-induced liver injury: a roadmapfor the development and deployment of preclinical predictive models. Nature reviews | Drug Discovery 2019

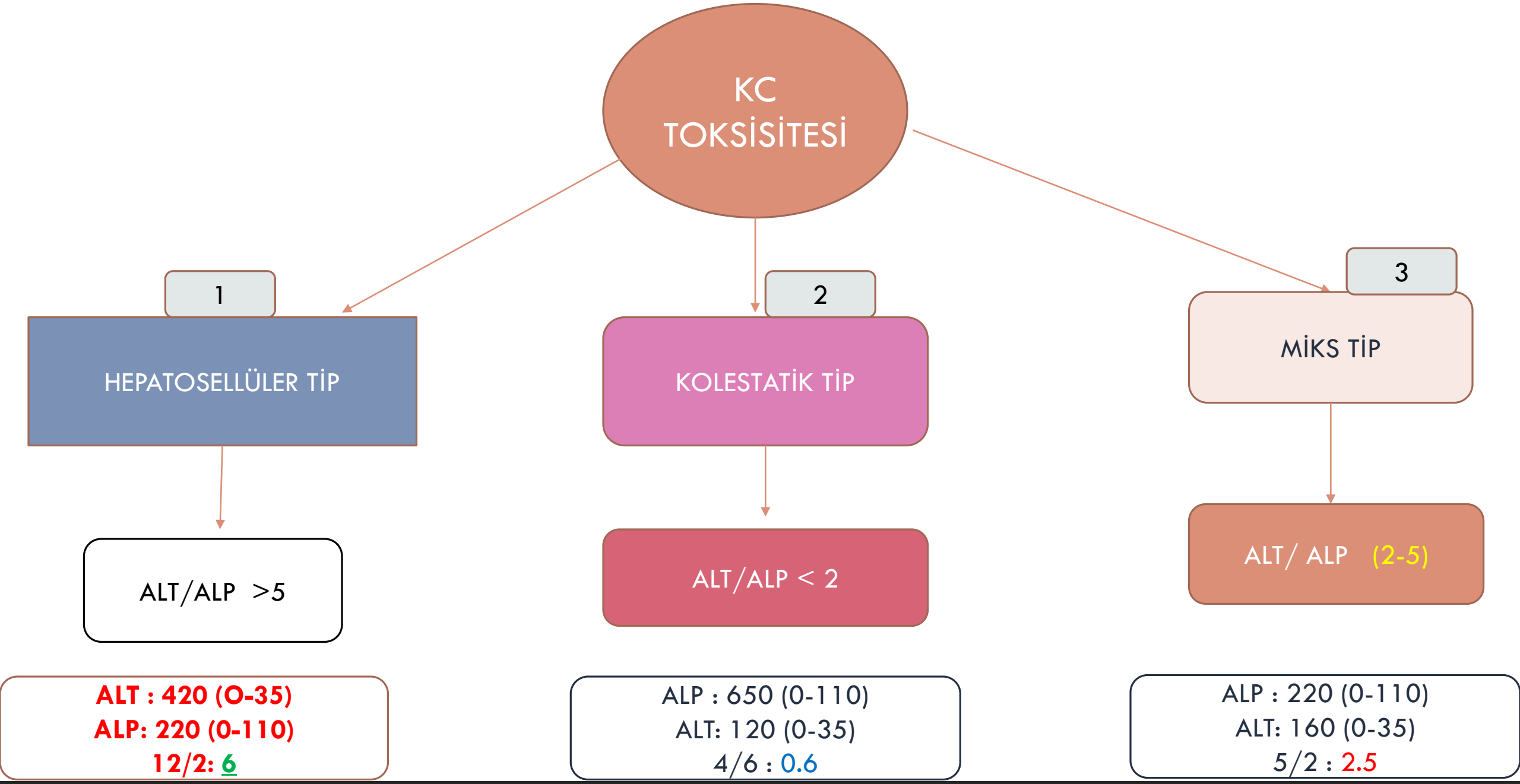
HLA ---Antibiyotik toksisitesi

HLADRB1*15:01-------→ Amoksisilin Clavulanat toksisitesi.

HLA-B*35:02 allele---→ Minosiklin toksisitesi.

HLA-B*57:01 allele---→ Floclaxacin toksisitesi ile ilişkili.

HLA tespiti ile toksisite ihtimali azaltmak mümkün.


KC
TOKSİSİTESİ
1
HEPATOSELLÜLER TİP
ALT/ALP >5
ALT : 420 (O-35)
ALP: 220 (0-110)
12/2: 6
2
KOLESTATİK TİP
ALT/ALP < 2
ALP : 650 (0-110)
ALT: 120 (0-35)
4/6 : 0.6
3
MİKS TİP
ALT/ ALP (2-5)
ALP : 220 (0-110)
ALT: 160 (0-35)
5/2 : 2.5

Hepatik Toksisite Nasıl anlaşılır?

Şüphe ettiğimiz ilaç ile ilgili **LiverTox, U.S. DILI Network** gibi sitelerden toksisite ile ilgili geçmiş vaka raporları hakkında bilgi alabiliriz.

TOKSİSİTE GÖSTERGELERİ; Hala en iyi markırlar ALT, GGT, Alkalen Fosfataz ve Bilirubin. Sarılık (Bilirubin >3 mg/dl) olduğu vakalar **mortal** seyretmesi daha muhtemel.

KC işlevselliği; Albumin ve Protrombin zamanı (INR).

KC NAKLİ gereksimi olup olmadığı; MELD, Child-Pugh, King's College Kriterleri ile belirlenir

MELD = 3.78 x $\log_e$ serum bilirubin (mg/dL) +
11.20 x $\log_e$ INR +
9.57 x $\log_e$ serum creatinine (mg/dL) +
6.43 (constant for liver disease etiology)

NOTES:
If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0

Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8, a value of 1.0 is used) to prevent the occurrence of scores below 0 (the natural logarithm of 1 is 0, and any value below 1 would yield a negative result)

→ >20 KC Nakli adayı

Chlid Pugh Sınıflaması >9 Kötü

Parameter	Assign 1 point	Assign 2 points	Assign 3 points
Ascitis	Absent	Slight	Moderate
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (second over control) or INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3
Encephalopathy	None	Grade 1-2 (Mild to moderate)	Grade 3-4 (Severe)

King's College Criteria

TABLE 6

Acetaminophen

- Lactate >3.5
  or
- pH < 7.3 or lactate >3
  or
- Grade III or IV HE and
  - INR > 6.5
  - Creatinine > 300

Non-acetaminophen

- INR > 6.5 with HE
  or
- Any 3 of 5 with HE
  - Age <10 or >40 yrs
  - Bili > 300
  - Coag: INR > 3.5
  - Duration jaundice to HE > 7 days
  - Etiology: Non A-E, other drug

King's College Criteria remain the most clinically useful with sensitivity of 68-69% and specificity of 82-92%

Lee WM, et al. AASLD Practice Guidelines. Hepatology 2011

Table 2 The most common individual drugs and classes responsible for idiosyncratic drug-induced liver injury according to various Global Registries

	Iceland[78], *n* = 96	India[79], *n* = 313	Spain[76], *n* = 446	Sweden[77], *n* = 784	United States DILIN[72], *n* = 899
Individual drugs (%)					
	Amoxicillin-clavulanate 22.9	INH + anti-TB 57.8	Amoxicillin-clavulanate 13.2	Flucloxacillin 16.5	Amoxicillin-clavulanate 10%
	Diclofenac 6.3	Phenytoin 6.7	INH + anti-TB 6.9	Erythromycin 5.4	INH 5.3%
	Nitrofurantoin 4.2	Dapsone 5.4	Ebrotidine 4.9	Disulfiram 3.4	Nitrofurantoin 4.7%
	Infliximab 4.2	Olanzapine 5.4	Ibuprofen 4	TMP-SMX 2.7	SMX-TMP 3.4%
	Azathioprine 4.2	Carbamazine 2.9	Flutamide 3.8	Diclofenac 2.6	Minocycline 3.1%
	Isotretinoin 3.1	Cotrimoxazole 2.2	Ticlopidine 2.9	Carbamazepine 2.2	Cefazolin 2.2%
	Atorvastatin 2.1	Atorvastatin 1.6	Diclofenac 2.7	Halothane 1.9	Azithromycin 2%
	Doxycycline 2.1	Leflunamide 1.3	Nimesulide 2	Naproxen 1.4	Ciprofloxacin 1.8%
		Ayurvedic 1.3	Carbamazepine 1.8	Ranitidine 1.3	Levofloxacin 1.4%
Drug classes (%)					
Antibiotics	37	65	32	27	45.4
HDS	16	1.3	2	NS	16.1
CNS	7	12	17	3	9.8
Hypolipidemic	3.1	1.6	5	1	3.7
Others	37	20	44	69	25.7

Drug-induced liver injury: Do we know everything?. Tamara Alempijevic, Simon Zec, Tomica Milosavljevic. World J Hepatol 2017 April 8; 9(10): 491-502

Table 4. Clinical Features of DILI in Our Study vs Reported From 7 Other Countries

Study	Iceland[8]	France[9]	United States[23]	Spain[21]	Sweden[24]	India[25]	Japan[26]	China (current study)
Study design	Prospective	Prospective	Prospective	Prospective	Retrospective	Retrospective	Retrospective	Retrospective
Duration (*y*)	2010–2011	1997–2000	2004–2013	1994–2004	1970–2004	1997–2008	1997–2006	2012–2014
Incidence per year	19.1 per 100,000 inhabitants	13.9 per 100,000 inhabitants	2.7 per 100,000 adults in Delaware[10]	3.42 per 100,000 inhabitants[22]	2.4 per 100,000 person[29]	N/A	N/A	23.80 per 100,000 inhabitants (estimated)
No. of cases	96	34	899	461	784	313	1676	25,927
% Female	56.25	64.70	59	48.65	57.7	42	57	49.17
Dominated age range	40–59 Y/O	≥50 Y/O	N/A	≥60 Y/O	N/A	N/A	50–69 Y/O	40–59 Y/O
% Chronic	7	N/A	18	10.31	N/A	0.32	N/A	13.00
% HC, % Chol, % Mix	42, 32, 26	47.1, 20.6, 26.5	54, 23, 23	57.8, 20.0, 22.2	52.2, 26,3, 21.5	N/A	59, 20, 21	51.39, 20.31, 28.30
Fatality (%)	1.04	5.88	6	5.38	9.18	17.3	0.4	0.39
Top implicated drugs (%)	Antimicrobials (37.0), HDS (16.0), NSAIDs (6)	Anti-infectious (25.0), psychotropic (22.5), hypolipidemic (12.5), and NSAIDs (10.0)	Antimicrobials (45.4), HDS (16.1), CVS drugs (9.8), CNS drugs (9.1)	Amoxicillin/ clavulanate (13.23), TB drugs (6.95), ebrotidine (4.93)	Antibiotics (27.04), NSAIDs (4.85), anesthetics (1.91)	TB drugs (57.8), phenytoin (6.7), olanzapine (5.4), dapsone (5.4)	Antibiotics (14.3), psychotropics and neurological drugs (10.1), dietary supplements (10.0)	TCM or HDS (26.81), tuberculostatics (21.99), antineoplastic or immunomodulators (8.34) and anti-infectious (6.08)

Rank	West	No. of studies	DILI event	Total DILIs	Prevalence	East	No. of studies	DILI event	Total DILIs	Prevalence
1	Antibiotics	15	1,167	3,613	34.9% (25.4%, 45.1%)	Anti-TB	4	563	2,340	26.6% (13.1%, 42.9%)
2	CVD agents	6	392	2,868	17.3% (7.8%, 29.5%)	Herbal and sup	8	914	4,164	25.3% (12.5%, 40.6%)
3	Psychotropic	7	161	1,512	13.1% (6.8%, 21.0%)	Antibiotics	9	554	4,380	15.7% (9.0%, 23.9%)
4	NSAIDs	10	307	3,252	12.5% (6.8%, 19.8%)	Psychotropic	5	251	2,665	8.2% (4.4%, 12.8%)
5	Herbal and sup	4	184	2,094	6.7% (1.2%, 16.0%)	NSAIDs	5	256	3,666	4.8% (2.2%, 8.2%)

DILI, drug induced liver injury; TB, tuberculosis; CVD, cardiovascular; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 3. Summary of ranks by class and single agents by single agents

Rank	West	No. of studies	DILI event	Total DILIs	Prevalence	East	No. of studies	DILI event	Total DILIs	Prevalence
1	Amoxicillin-clavulanate	15	356	2,977	11.3% (8.4%, 14.8%)	INH_RIF_PZA	4	348	1,270	25.4% (8.3%, 47.7%)
2	Nimesulide	4	77	1,485	6.3% (0.87%, 15.9%)	Phenytoin	4	25	1,270	3.5% (0.6%, 8.2%)
3	Ibuprofen	5	68	1,389	6.1% (2.8%, 10.4%)	Cephalosporin	3	17	1,241	2.9% (0.0%, 10.1%)
4	INH_RIF_PZA	8	109	2,027	4.6% (3.2%, 6.2%)	Carbamazepine	3	61	1,241	1.3% (0.4%, 2.7%)
5	Diclofenac	8	75	2,588	3.7% (1.8%, 6.2%)	Valproate	3	37	909	0.3% (0.0%, 1.8%)

Drug induced liver injury: East versus West, a systematic review and meta-analysis. En Xian Sarah Low et al. Clin Mol Hepatol 2019 Dec 10.

Table 4 Classic Clinical Syndromes of drug-induced liver injury and the drugs most commonly associated[6,7,117]

Acute viral hepatitis-like: *e.g.*, INH: Absence of hypersensitivity symptoms; present with malaise, fatigue, anorexia, nausea, vomiting, right upper quadrant pain
Hypersensitivity syndrome: Fever, rash, and/or eosinophilia seen in 25%-30% of DILI cases, usually with short latency and prompt rechallenge response (*e.g.*, amoxicillin-clavulanate, phenytoin, carbamazepine, SMX-TMP, halothane)
Sulfone syndrome: *e.g.*, dapsone: Fever, exfoliative dermatitis, lymphadenopathy, atypical lymphocytosis, eosinophilia, hemolytic anemia, methemoglobinemia
Pseudomononucleosis syndrome: *e.g.*, phenytoin, dapsone, sulfonamides: Hypersensitivity syndrome with atypical lymphocytosis, lymphadenopathy, and splenomegaly
DILI associated with severe skin injury: Stevens-Johnson syndrome, toxic epidermal necrolysis, *e.g.*, beta-lactam antibiotics, allopurinol, carbamazepine
Autoimmune hepatitis associated with positive autoantibodies: *e.g.*, nitrofurantoin, minocycline, methyldopa
Immune-mediated colitis with autoimmune hepatitis: *e.g.*, ipilimumab
Acute cholecystitis-like: *e.g.*, erythromycin estolate
Reye syndrome-like: *e.g.*, valproic acid: Hepatocellular injury, acidosis, hyperammonemia, encephalopathy, abdominal pain, nausea, vomiting, paradoxical worsening of seizure activity, microvesicular steatosis on biopsy

Drug-induced liver injury: Do we know everything?. Tamara Alempijevic, Simon Zec, Tomica Milosavljevic. World J Hepatol 2017 April 8; 9(10): 491-502

Features and Outcomes of 899 Patients with Drug-induced Liver Injury: The DILIN Prospective Study

N Chalasani, HL Bonkovsky, R Fontana et al. Gastroenterology. 2015 June ; 148(7): 1340–1352

Demographic and Selected Clinical Features for the 899 Subjects Studied. Comparisons by Pat

	Entire cohort (N=899) 100%	HC* (n=484) 53.8%	Chol* (n=210) 23.4%	Mixed (n=205) 22.8%	P value†
Age (years, mean [SD])	49 [17]	45 [17]	54 [16]	50 [17]	< 0.001
Females (%)	59	65	51	52	<0.001
Self-reported race (%)					
White	79	74	84	84	0.003
Black or African-American	12	13.5	11	8	
Other/Multiracial	10	12	5	8	
BMI (kg/m^2, mean [SD])	27 [6.5]	28 [6..8]	27 [6.3]	27 [6.1]	0.2
Prior drug allergies (%)	44	44	47	42	0.6
Immuno-allergic features (%)	15	12	17	21	0.018
Preexisting Liver Disease (%)	9.9	9.9	13.3	6.3	0.059
Diabetes mellitus (%)	25	23	33	20	0.004
Latency (days in median, IQR)	36 [19–88]	46 [22–104]	31 [16–72]	31 [18–51]	<0.001
Jaundice (%)	70	65	78	75	<0.01
Liver Biochemistries –DILI recognition					
ALT (U/L, mean [SD])	825 [1105]	1275 [1329]	202 [160]	379 [226]	<0.001
AP (U/L, mean [SD])	288 [254]	187 [110]	497 [371]	306 [206]	<0.001
Total bilirubin (mg/dl, mean [SD])	6.7 [6.6]	6.3 [6.6]	7.8 [7.3]	6.4 [6.0]	0.005
INR	1.4 [1.0]	1.6 [1.2]	1.2 [0.5]	1.3 [0.6]	<0.001
Liver Biochemistries – Peak values					
ALT (U/L, mean [SD])	1008 [1221]	1510 [1431]	339 [445]	506 [439]	<0.001
AP (U/L, mean [SD])	406 [388]	271 [252]	682 [532]	440 [317]	<0.001

%10 Ölüm veya KCTx
%17 Kronik Hepatit

	Entire cohort (N=899) 100%	HC* (n=484) 53.8%	Chol* (n=210) 23.4%	Mixed (n=205) 22.8%	P value†
Total bilirubin (mg/dl, mean [SD])	13 [12]	12 [11.3]	15 12.5]	13.3 [12.1]	<0.001
INR	1.7 [1.5]	1.8 [1.8]	1.6 [1.15]	1.5 [1.1]	0.007
Peripheral eosinophilia (>500/µL) (%)	11	7.2	14.6	15.8	<0.001
Improvement in liver tests – median days					
Peak ALT to below ULN	71	79	113	59	0.01
Peak AP to below ULN	96	48	183	90	<0.001
Peak bilirubin to ≤ 1 mg/dL	70	66	77.5	74	0.3
Causality Assessment (%)					
Definite/ Highly likely/ Prob, n	235 / 466 / 198	120 /255 / 109	47/109/54	68/102/35	
%	26 / 52 / 22	25 / 53 / 22	22 / 52 / 26	33 / 50 / 17	0.056
Severity of Liver Injury (%)					
Mild	24	29	15	20	<0.001
Moderate	21	15	27	29	
Moderate-hospitalized	29	26	33	34	
Severe	19	21	21	13	
Fatal	7	9	4	4	
Death, at any time point (%)	6.2	5.4	9	5.4	0.17
- Percent Liver –related (%)	49	58	56	18	0.079
Liver Transplantation (%)	4	6.2	2.9	0	<0.001
Chronic DILI (%)	17	13	31	14	<0.001

>65 yaş ile <65 yaş Karşılastırma

>65 Kolestatik daha sık (p<0.001)

Klinik sonuçlar, ölüm ve Kc Tx benzer.

	≥ 65 years (n=149)	< 65 years (n=750)	P value
Age (years, mean [SD])	73 [6]	44 [14]	
Females (%)	60	59	0.8
Self-reported race (%)			0.12
White	85	77	
Black or African-American	7	13	
Other/Multiracial	8	10	
BMI (kg/m^2, mean [SD])	27 [5]	28 [6.8]	0.4
Prior drug allergies (%)	54	42	0.015
Preexisting Liver Disease (%)	10.1	9.9	0.9
Concomitant medicines (%)			
0–2 / 3–5 / >5	16/26/58	26/26/48	0.03
Diabetes mellitus (%)	30	24	0.1
Top 5 implicated classes of agents (%)	Antimicrobials (57.7%)	Antimicrobials (43%)	<0.001
	Cardiovascular (14.8%)	HDS (17.7%)	
	HDS (8.1%)	CNS agents (10.4%)	
	Antineoplastic (4%)	Cardiovascular (8.8%)	
	Analgesics (3.4%)	Antineoplastic (5.7%)	
Latency (days in median , IQR)	35 [18–99]	36 [19–84]	0.8
Jaundice (%)	67	71	0.4
Pattern of liver injury			
HC/Chol/Mixed (%)	39/36/25	57/21/22	<0.001
Severity of Liver Injury (%)			
Mild	31	22	0.08
Moderate	19.5	22	
Moderate-hospitalized	29	29.5	
Severe	13	20	
Fatal	8	6.7	
Death, at any time point (%)	8.7	5.7	0.2
- Proportion of Liver –related (%)	54	48	0.8
Liver Transplantation (%)	2	4.4	0.25
Chronic DILI (%)	11.4	18.7	0.04

DILI in Subjects with and without Known Pre-existent Liver Disease

	Known pre-existent liver disease (n=89)	No known pre existent liver disease (n=810)	P value
Age (years, mean ± SD)	52± 12.4	48 ±17.4	0.08
Females (%)	54	59	0.4
Self-reported race (%)			0.35
White	73	79	
Black or African-American	13.5	11.5	
Other/Multiracial	13.5	9	
BMI (kg/m^2, mean ± SD)	28± 6.9	27 ± 6.5	0.72
Prior drug allergies (%)	46	44	0.7
Diabetes mellitus (%)	38	23	0.004
Top 5 implicated classes of agents (%)	Antimicrobials (51%)	Antimicrobials (45%)	0.2
	HDS (13.5%)	HDS (16%)	
	Cardiovascular (6.7%)	Cardiovascular (10.1%)	
	Antineoplastic (6%)	CNS agents (9.6%)	
	CNS agents (4.5%)	Antineoplastic (5.4%)	
Latency (days in median , IQR)	34 (20–63)	36 (19–89)	0.3
Jaundice (%)	70	70	0.9
Pattern of liver injury			
HC/Chol/Mixed (%)	54/31/15	54/22/24	0.058

Kc hastalığının var olması Klinik Sonucu etkiliyor mu ?

Severity of Liver Injury (% of column total)			
Mild	29	23	0.09
Moderate	15	22	
Moderate-hospitalized	27	30	
Severe	17	19	
Fatal	12.4	6.3	
Death, at any time point (%)	16	5.2	<0.001
- Percent Liver –related	57	46	0.5

Features and Outcomes of 899 Patients with Drug-induced Liver Injury: The DILIN Prospective Study

N Chalasani, HL Bonkovsky, R Fontana et al. Gastroenterology. 2015 June ; 148(7): 1340–1352

Top ten therapeutic classes and individual agents to cause DILI in the DILIN Prospective Study

	Therapeutic classes	n		Individual agents¶	n
1	Antimicrobials	408	**1**	Amoxicillin-Clavulanate	91
2	Herbal and dietary supplements	145	**2**	Isoniazid	48
3	Cardiovascular agents	88	**3**	Nitrofurantoin	42
4	Central nervous system agents	82	**4**	Sulfamethoxazole/Trimethoprim	31
5	Anti-neoplastic agents	49	**5**	Minocycline	28
6	Analgesics	33	**6**	Cefazolin	20
7	Immunomodulatory	27	**7**	Azithromycin	18
8	Endocrine	20	**8**	Ciprofloxacin	16
9	Rheumatologic	13	**9**	Levofloxacin	13
10	Gastrointestinal	12	**10**	Diclofenac	12

	Short latency (≤ 7 days) (n=41)	Long latency (>365 days) (n=60)	P value
Liver Tests – Peak values			
ALT (U/L, mean± SD)	1008± 1648	863± 791344±338	0.6
AP (U/L, mean± SD)	335± 234.5	8.9±9.3	0.6
Total bilirubin (mg/dL, mean± SD)	8± 9.2	1.8± 1.9	0.8
INR	1.8± 1.7		0.5
Peripheral eosinophilia (>500/μL) (%)	7.7	8.6	1.0
Improvement in liver tests –median d			
- Peak ALT to below ULN	68	98	0.07
- Peal AP to below ULN	84	129	0.99
- Peak total bilirubin to ≤ 1 mg/dL mg/dL	36	76	0.3
Causality Assessment			
Definite/ Highly likely/ Probable	10/54/37	15/62/23	0.3
Severity of Liver Injury (%)			
Mild	32	37	0.17
Moderate	27	15	
Moderate-hospitalized	22	12	
Severe	12	28	
Fatal	7.3	8.3	
Death, at any time point (%)	4.9	13.3	0.2
-Percent Liver –related	50	71	1.0
Liver Transplantation (%)	2.4	3.3	1.0
Chronic DILI (%)	12.5	31	0.07
Causative agents	Moxifloxacin (4) Azithromycin (3) Ciprofloxacin (3) HDS (3) Rifampicin (2) Levofloxacin (2) Nitrofurantoin (1), Azathioprine (1), Amoxicillin (1), Amox-clavulanate (1), Antithymocyte globulin (1), Cefaclor (1), Cefazolin (1), Cefotaxime (1), Ceftriaxone (1), Dalteparin (1), Diclofenac (1), Erythromycin (1), Fluconazole (1), Meropenam (1), Methylprednisolone (1), Micafungin (1), Nicotinic acid (1), Oxaprozin (1), Phenytoin (1), Piperacillin-tazobactam (1), Ranitidine (1), TMP-SMX (1), Telithromycin (1),	Nitrofurantoin (16) Minocycline (10) Amiodarone (3) Mercaptopurine (3) Atomoxetine (2) Atorvastatin (2) Rosuvastatin (2) Tamoxifen (2) Oxaliplatin (2) Buproprion (2), Nicotinic acid (1), Azathioprine (1), Diclofenac (1), Etravirine (1), Imatinib (1), Interferon-beta(2), Fluoxetine (1), Metformin (1), Methotrexate (1), Methylphenidate (1), Promethazine (1), Tacrolimus(1), Testosterone (1), Topiramate (1), HDS (1)	

İlaç alımı ile KCFT bozukluğu arası süre

Kısa <7 gün Uzun >365 gün

Antibiyotiklerin çoğu kısa (<7 gün) süre içersinde hepatik sorun ortaya çıkarıyor

Uzun süren toksisite de iyileşme daha uzun sürede oluyor.

Mortalite ve klinik sonuçlar benzer.

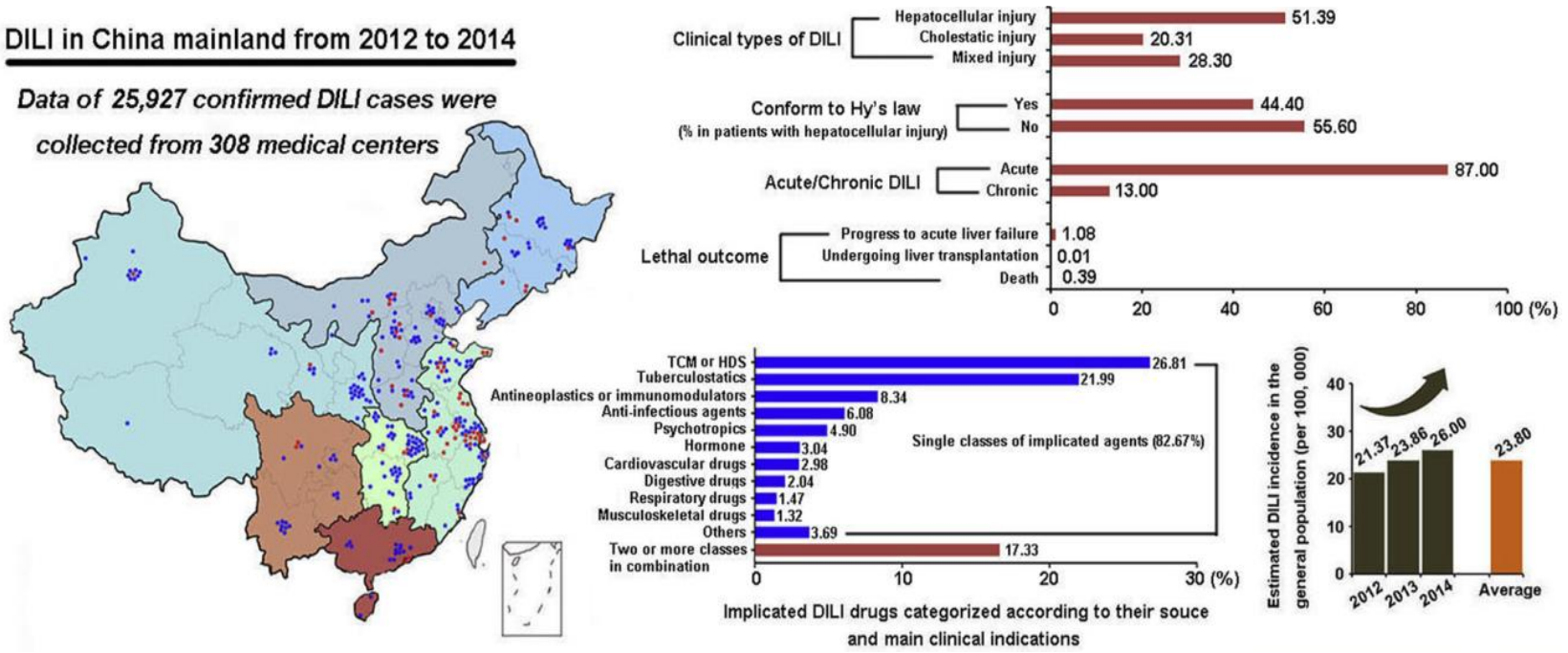
Incidence and Etiology of Drug-Induced Liver Injury in Mainland China

Tao Shen et al.

Gastroenterology 2019;156:2230–2241

Table 1. Demographic and Clinical Features of 25,927 DILI Cases From 308 Centers Nationwide

	Number	%	95% CI
Gender[a]			
Male	12,930	50.83	[50.22–51.45]
Female	12,507	49.17	[48.55–49.78]
Age[b]			
≥60	5694	22.09	[21.58–22.60]
40–59	11,015	42.73	[42.13–43.34]
18–39	7962	30.89	[30.33–31.45]
<18	1105	4.29	[4.04–4.54]
Ethnicity[c]			
Han	25,113	96.93	[96.72–97.14]
Non-han	795	3.07	[2.86–3.29]
Department of diagnosis			
Internal medicine	10,822	41.74	[41.14–42.34]
Infectious diseases	8450	32.59	[32.02–33.16]
Hepatology	3738	14.42	[13.99–14.85]
Oncology	869	3.35	[3.13–3.57]
Others	2048	7.90	[7.57–8.23]
Preexisting liver diseases			
Yes	6061	23.38	[22.86–23.90]
No	19,866	76.62	[76.10–77.14]
Initial serum ALT values[d]			
≥ 5×ULN	12,826	49.47	[48.86–50.08]
≥3×ULN and <5×ULN	4335	16.72	[16.27–17.17]
< 3×ULN	8766	33.81	[33.23–34.39]
Clinical types of DILI[e]			
Hepatocellular injury (R ≥5)	12,298	51.39	[50.76–52.03]
Conform to Hy's law	5460	44.40	[43.52,45.28]
Others	6838	55.60	[54.72,56.48]
Cholestatic injury (R ≤2)	4860	20.31	[19.80–20.82]
Mixed injury (2 < R < 5)	6771	28.30	[27.73–28.87]
Acute/chronic DILI			
Acute DILI	22,556	87.00	[86.55–87.38]
Chronic DILI	3371	13.00	[12.44–13.25]
Life-threatening outcomes			
Progress to acute liver failure[f]	280	1.08	[0.95–1.21]
Undergoing liver transplantation	2	0.01	[0.00–0.02]
Death	102	0.39	[0.32–0.47]
DILI had primary role	72	70.59	[61.75–79.43]
DILI had contributory role	21	20.59	[12.74–28.44]
DILI had no role	9	8.82	[3.32,14.33]



Hepatik TOKSİSİTE
Yapılan yanlışlar

Kc toksisitesini geç farketmek. Toksik olabilecek bir ilaç kullanımı varken KCFT kontrolü yapmamak

Sadece AST ve ALT bakılması Kolestatik enzim yüksekliğinin atlanmasına neden olabilir. Mutlaka GGT, Alkalen Fosfataz ve Bilirubin düzeyleri de bakılmalı.

Yanlış teşhis. KCFT bozukluk Safra kesesi taşı ve tümörlerde de yükselebilir.

Yanlış ilacı kesmek. Etkili bir ilacın yanlışlıkla KC toksisitesi olabilir diye kesmek.

NAC, Steroid ve Ursodeoksi kolik asit işe yarar mı?

Kolestatik tip toksisite Hepatosellüler tipe göre daha az MORTAL dir.

Süreci kısaltan ve düzelmeyi hızlandıran bir tedavi için yeterli kanıt yok.

NAC (72 saat) evre hastalarda verildiğinde AST ve Bilirubinde iyileşme sağlayabilir.

Vaka raporlarında, UDCA Amoxicilin-Clavulanat toksisitesinde süreci kısaltabilir ve *vanishing bile duct syndrome* gelişimini engelleyebilir.

Bazı otörler Ciddi Vakalarda (Wree et al) → Prednisone 15–20mg/kg/gün başlanıp haftalık 2–5mg/kg/gün azaltılarak ve UDCA 750–1500mg/gün kullanılmasını önermişler.

İlaca bağlı Otoimmun Hepatit olgularında Steroid verilmesi faydalı. Bunun için ANA, IgG bakılmalı.

Current and future directions in the treatment and prevention of drug-induced liver injury: a systematic review. Jonathan G. Stine et al. Expert Rev Gastroenterol Hepatol. 2016 ; 10(4): 517–536

İLACI NE ZAMAN KESELİM ?

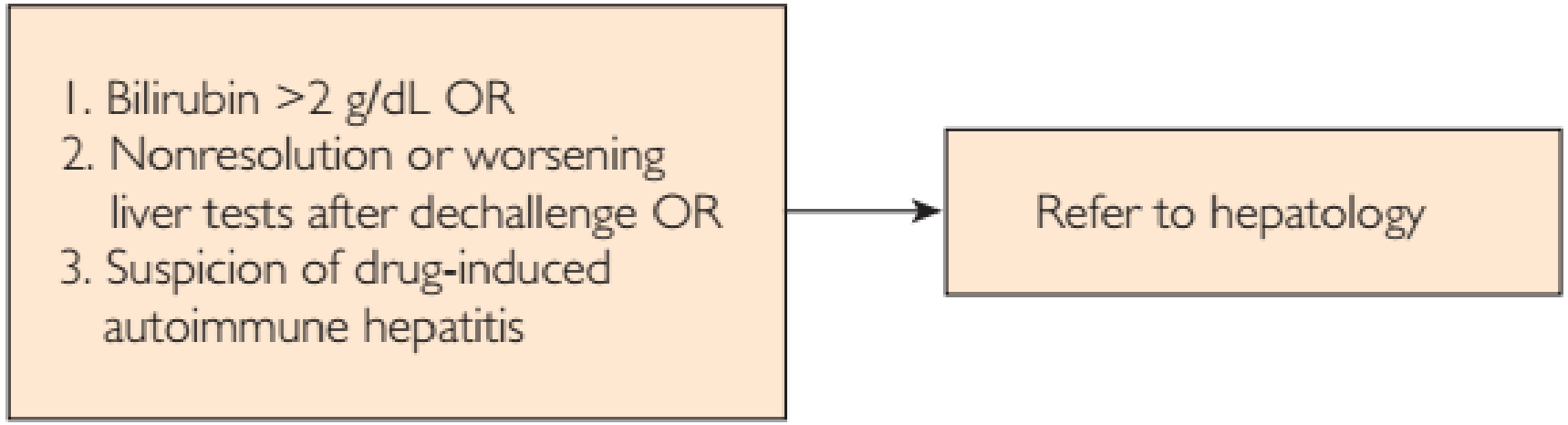
FDA Stopping Rules to Prevent Serious DILI in Clinical Trials[29]

For an increase in ALT/AST >3X ULN - repeat testing in 48–72 hr to determine if these enzymes are increasing or decreasing and an inquiry should be made about hepatitis-related symptoms
If repeat testing shows ALT/AST remain >3X ULN or if symptoms are present, close observation is appropriate to determine the trend of the injury
Treatment should be discontinued when: - ALT/AST exceed 8 X ULN - ALT/AST exceed >5X ULN for more than 2 weeks' duration - ALT/AST are >3X ULN and total bilirubin exceeds 2X ULN or INR is >1.5 - ALT/AST are >3X ULN with the appearance of fatigue, nausea, vomiting, RUQ pain or tenderness, fever, rash and/or eosinophilia (>5%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR= international normalized ratio; RUQ = right upper quadrant; ULN= upper limit of normal

Ne zaman Hepatoloğa refere edilmeli ?

Step 4: Severity assessment



Drug-Induced Liver Injury. Michael D. Leise, MD; John J. Poterucha, MD; and Jayant A. Talwalkar, MD. Mayo Clin Proc. n January 2014;89(1):95-106

Alternatif ilaç yoksa ne yapılmalı?

Two Desensitization-rechallenge strategies for isoniazid (INH) and other anti-TB medications

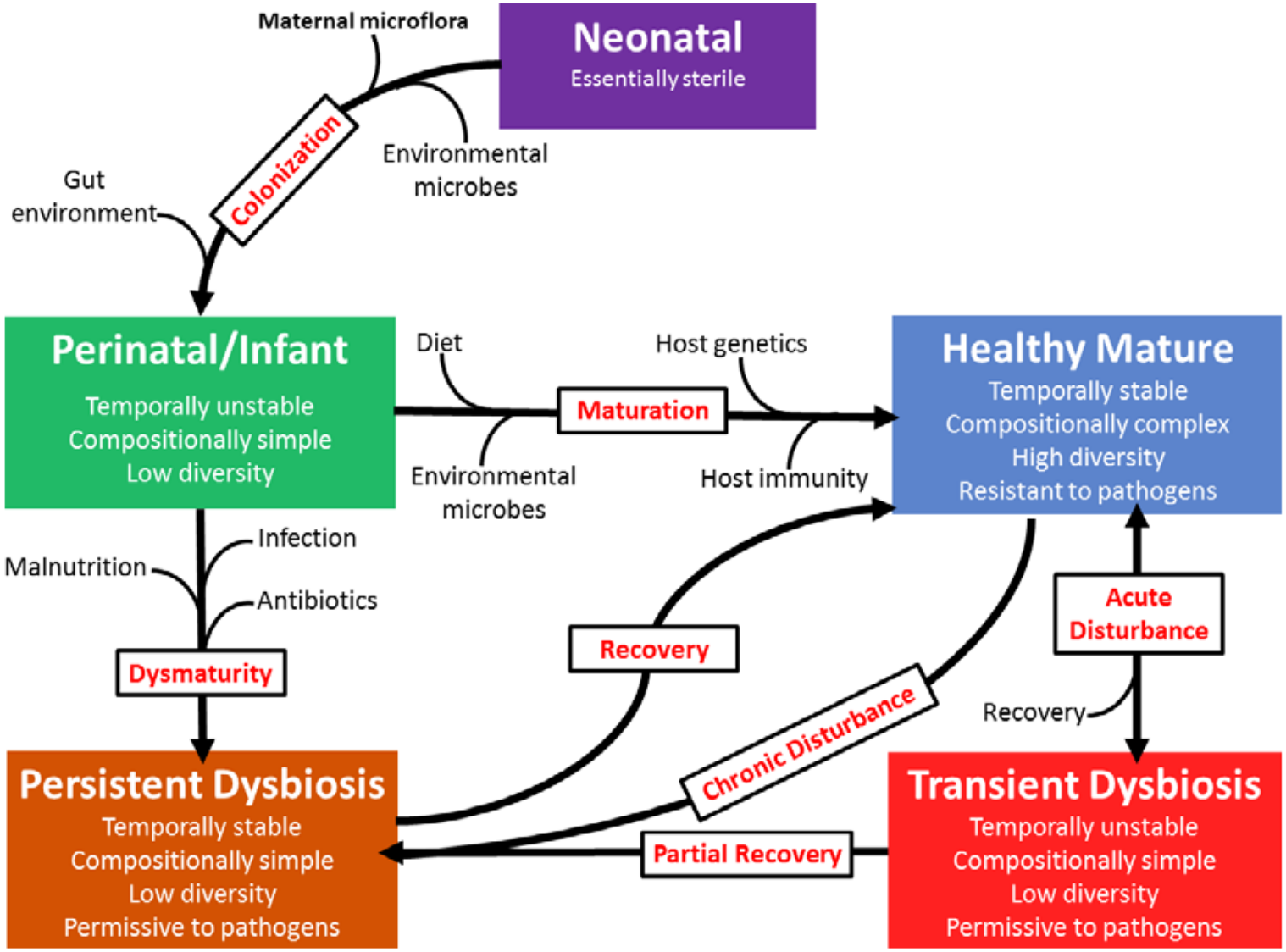
Author(ref)	Recommendations
American Thoracic Society (ATS)[15, 38]	Rechallenged patients who reach a treatment-limiting threshold should have clinical and biochemical monitoring performed at 2- to 4-week intervals. After ALT returns to less than two times the ULN, rifampin may be restarted with or without ethambutol After 3 to 7 days, INH may be reintroduced, subsequently rechecking ALT If symptoms recur or ALT increases, the last drug added should be stopped For those patients who have experienced prolonged or severe hepatotoxicity, but tolerate reintroduction with rifampin and INH, rechallenge with pyrazinamide may be hazardous. In this circumstance, pyrazinamide may be permanently discontinued, with treatment extended to 9 months Although pyrazinamide can be reintroduced in some milder cases of hepatotoxicity, the benefit of a shorter treatment course likely does not outweigh the risk of severe hepatotoxicity from pyrazinamide rechallenge.
Senousy et al[41]	Reintroduction should not be attempted until liver function is normal, liver tests as less than two times the ULN and more than 2 weeks since the disappearance of jaundice Staged reintroduction starting with Rifampin, then INH then pyrazinamide, unless patients had severe liver dysfunction, then pyrazinamde should be avoided Each drug should be given for 3–7 days before the next medication is added Medications should be reintroduced at doses lower than what was used in initial therapy and doses should be gradually up titrated to the therapeutic range

Current and future directions in the treatment and prevention of drug-induced liver injury: a systematic review. Jonathan G. Stine et al. Expert Rev Gastroenterol Hepatol. 2016 ; 10(4): 517–536

ANTİBİYOTİK &

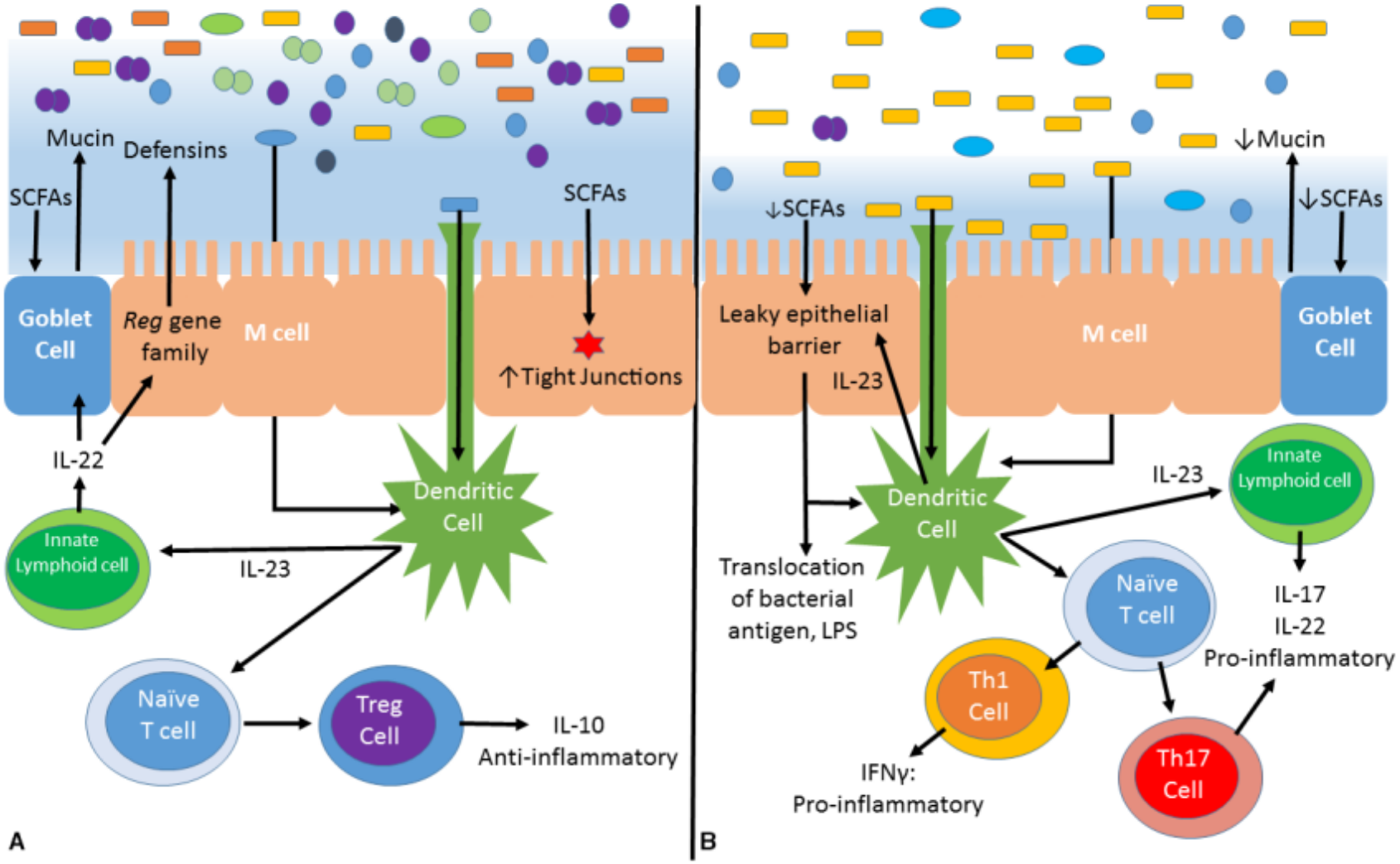
&MİKROBİYOTA

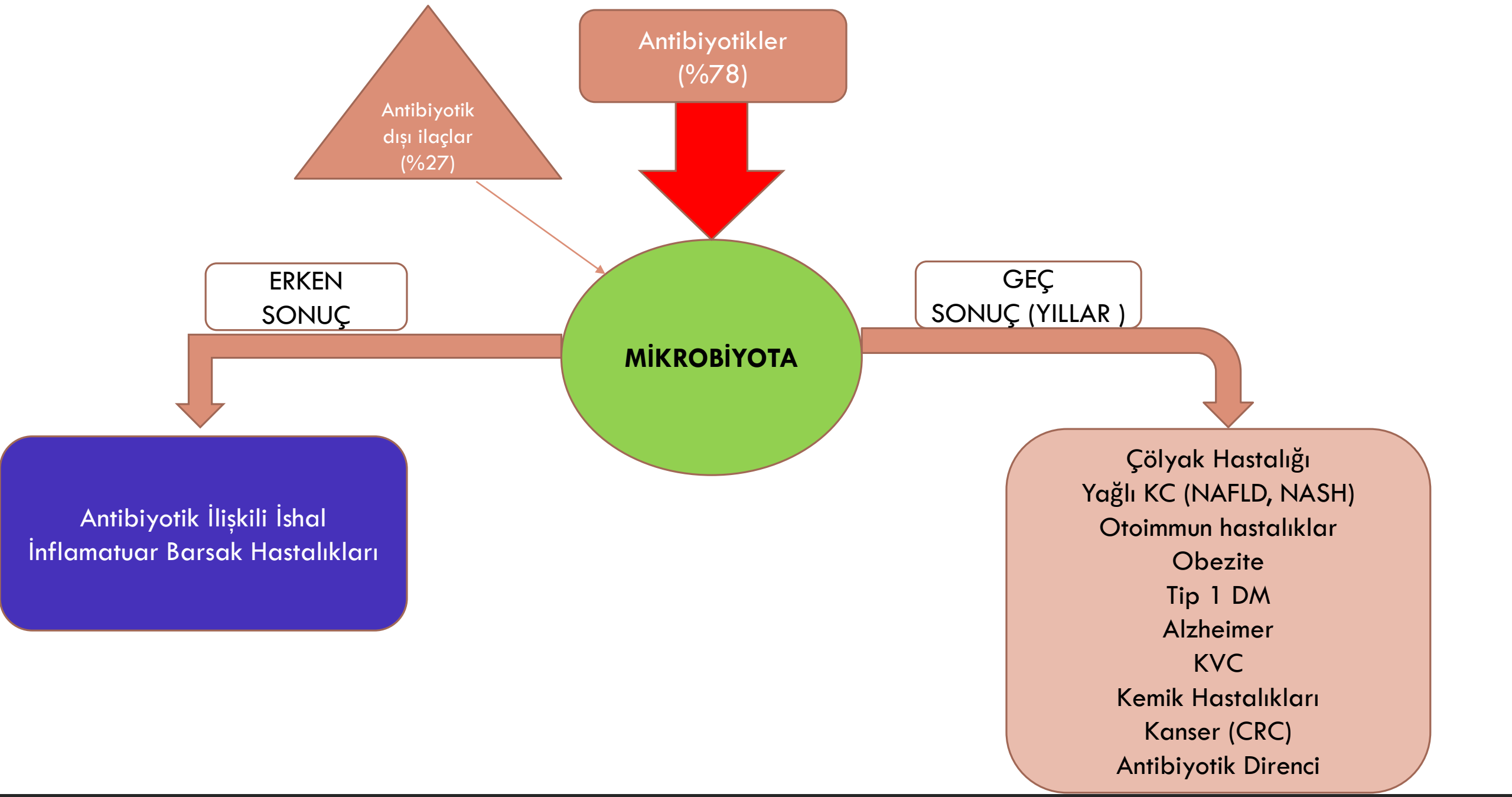
&İLİŞKİLİ DİYARE

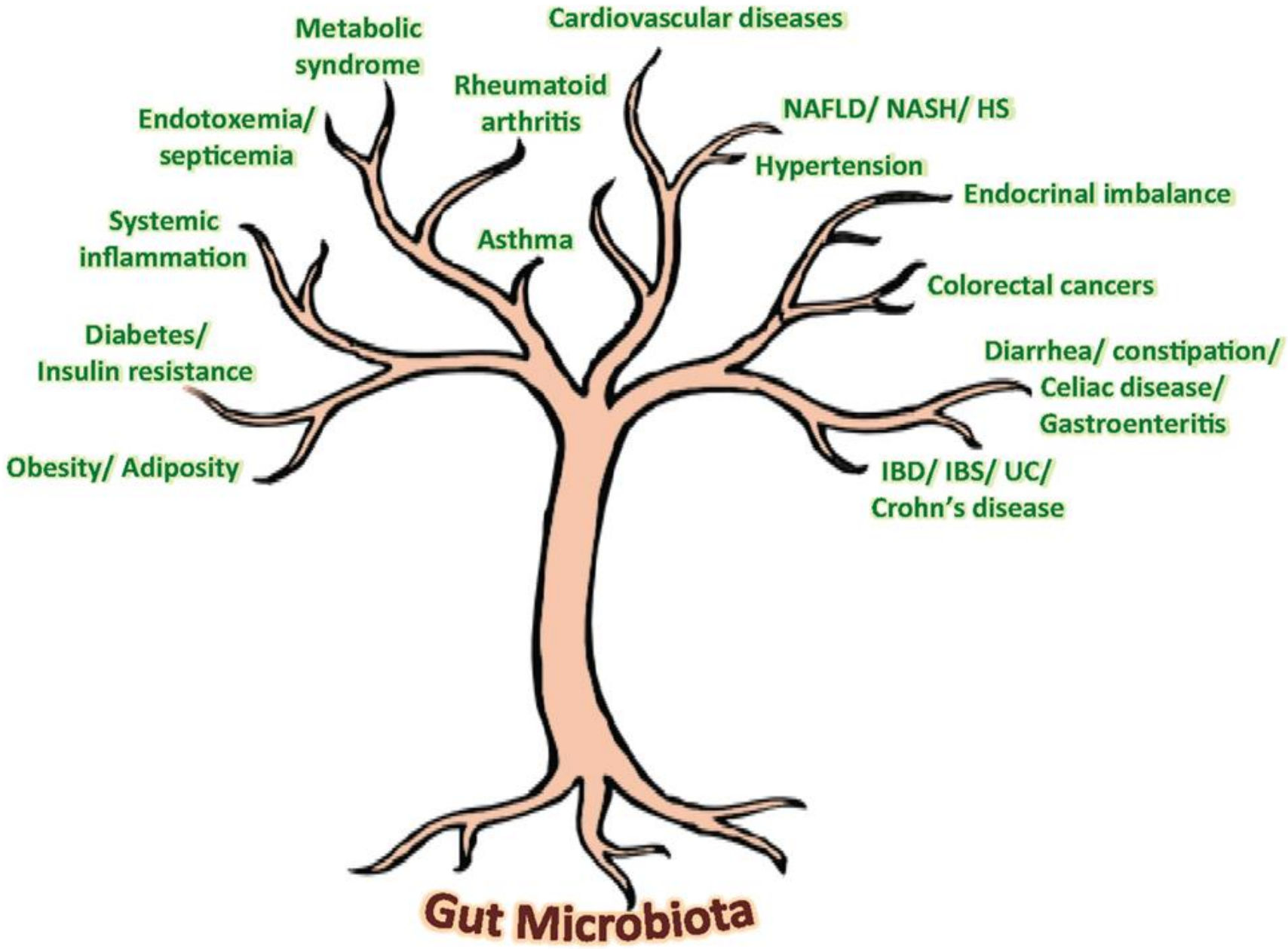

Maternal microflora
Neonatal
Essentially sterile
Colonization
Environmental microbes
Gut environment
Perinatal/Infant
Temporally unstable
Compositionally simple
Low diversity
Diet
Host genetics
Maturation
Environmental microbes
Host immunity
Healthy Mature
Temporally stable
Compositionally complex
High diversity
Resistant to pathogens
Malnutrition
Infection
Antibiotics
Dysmaturity
Recovery
Acute Disturbance
Recovery
Chronic Disturbance
Persistent Dysbiosis
Temporally stable
Compositionally simple
Low diversity
Permissive to pathogens
Partial Recovery
Transient Dysbiosis
Temporally unstable
Compositionally simple
Low diversity
Permissive to pathogens

SİMBİYOZİS

DİSBİYOZİS




Antibiyotikler
(%78)
Antibiyotik
dışı ilaçlar
(%27)
ERKEN
SONUÇ
MİKROBİYOTA
GEÇ
SONUÇ (YILLAR)
Antibiyotik İlişkili İshal
İnflamatuar Barsak Hastalıkları
Çölyak Hastalığı
Yağlı KC (NAFLD, NASH)
Otoimmun hastalıklar
Obezite
Tip 1 DM
Alzheimer
KVC
Kemik Hastalıkları
Kanser (CRC)
Antibiyotik Direnci


Metabolic syndrome
Cardiovascular diseases
Rheumatoid arthritis
Endotoxemia/ septicemia
NAFLD/ NASH/ HS
Hypertension
Endocrinal imbalance
Systemic inflammation
Asthma
Colorectal cancers
Diabetes/ Insulin resistance
Diarrhea/ constipation/ Celiac disease/ Gastroenteritis
Obesity/ Adiposity
IBD/ IBS/ UC/ Crohn's disease
Gut Microbiota

Ne zaman Disbiyosis den şüphelenmeliyiz?

Sık Gaz ve Şişkinlik hissi

Kramp ve gaitada MUKÜS çıkması

Bilinç bozuklukları, anksiyete, depresyon gelişimi (beklenmeyen durumlarda)

Gıda Hassasiyeti

Kronik Kötü Kokulu Nefes

Diyare ve Konstipasyon atakları

İrritable Barsak Sendromu (IBS)

Uzun Antibiyotik kullanımı hikayesi

Karbonhitrat intoleransı

Otoimmun hastalıklara sahip olmak

BUNLAR 5 TANESİNE SAHİPSENİZ sizde **DİSBİYOSİS** olabilir.

Antibiyotik ilişkili diyare

En sık etken C. Difficile

Neredeyse her türlü antibiyotik (SS, Penisilin (Co-Amoksilav)m, Florokinolon, klindamisin bunu yapabilir.

Geniş spektrumlu antibiyotiklerde daha sık.

Tedavi sırasında 8-10 kat, tedaviden 1 ay sonra 4 kat, tedaviden 2 ay sonra 3 kat görülme riski var.

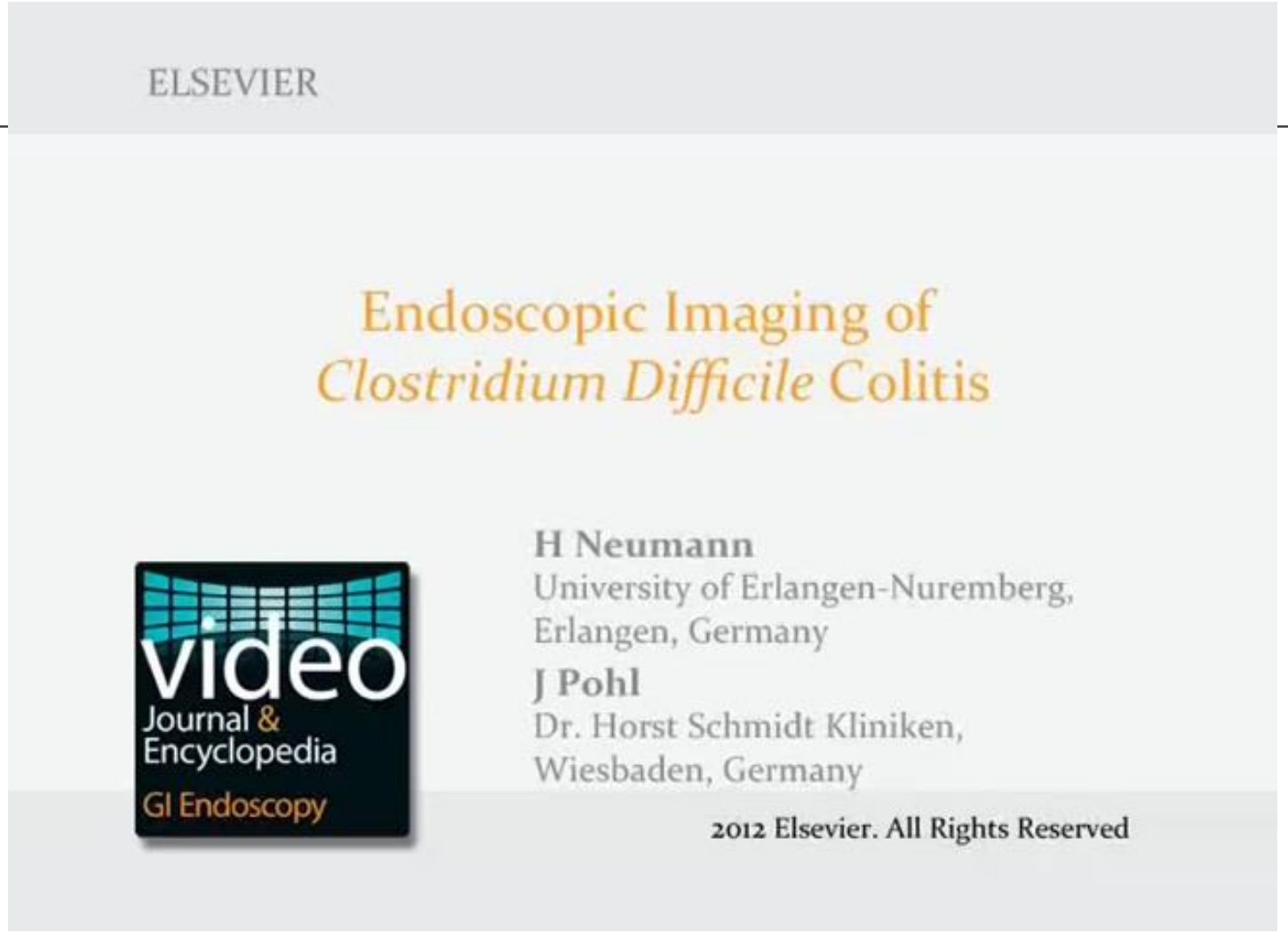
>65 yaş daha riskli

Uzun süre hastanede yatışlarda risk fazla

İmmünsüpresif ilaç kullanımı

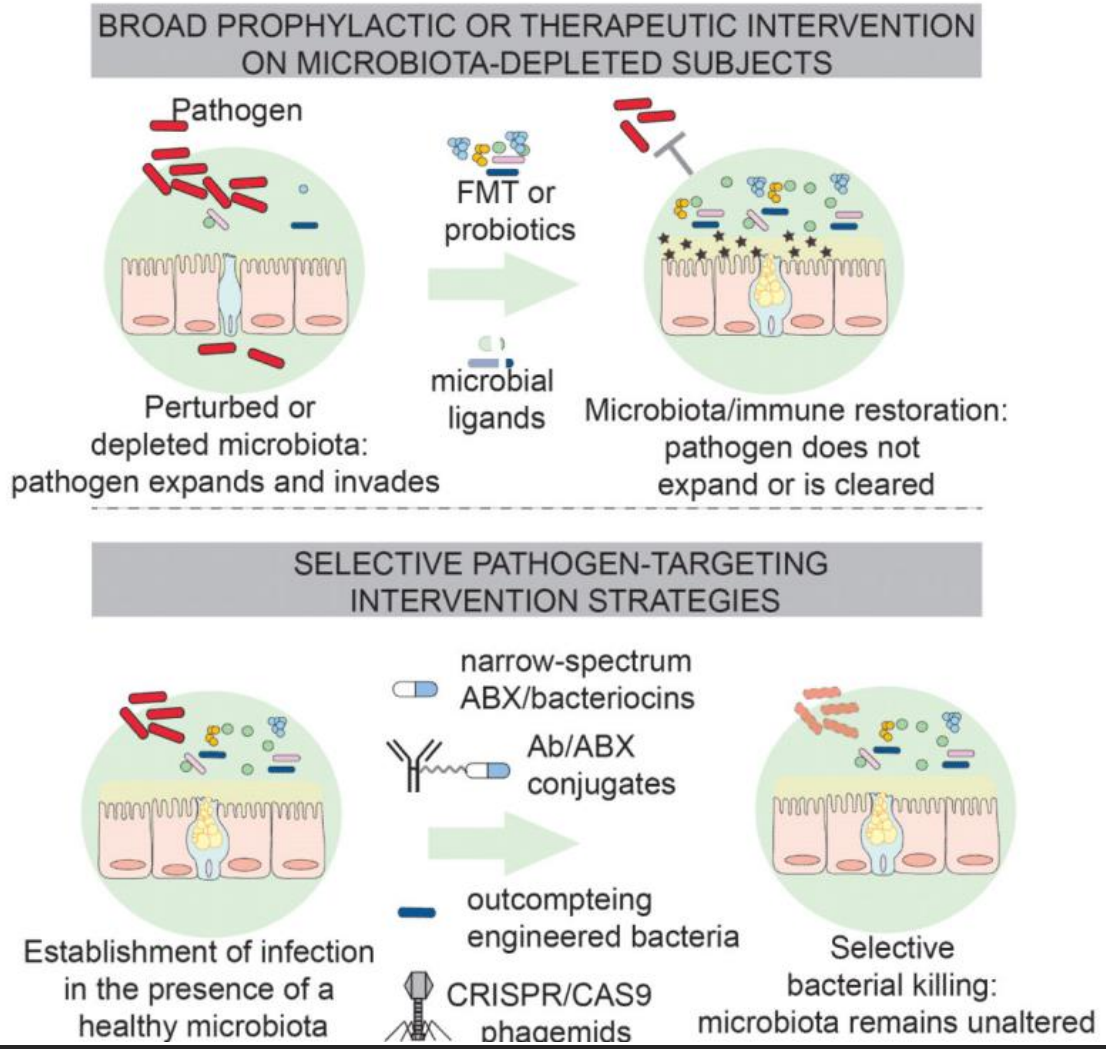
PPI alımı

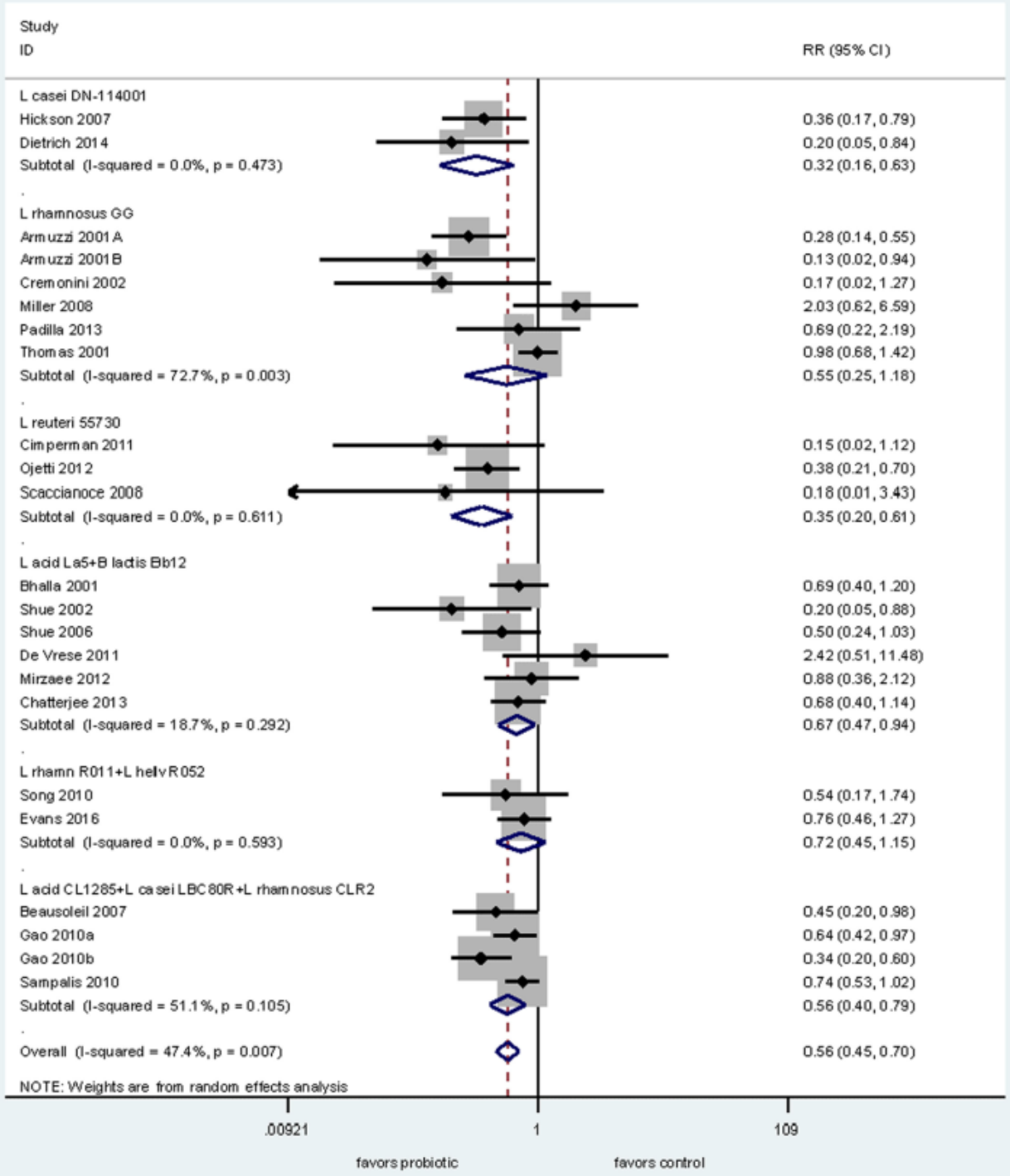
KOLONOSKOPİ



KORUNMA

Geniş Spektrumlu Antibiyotik kullanılmamalı





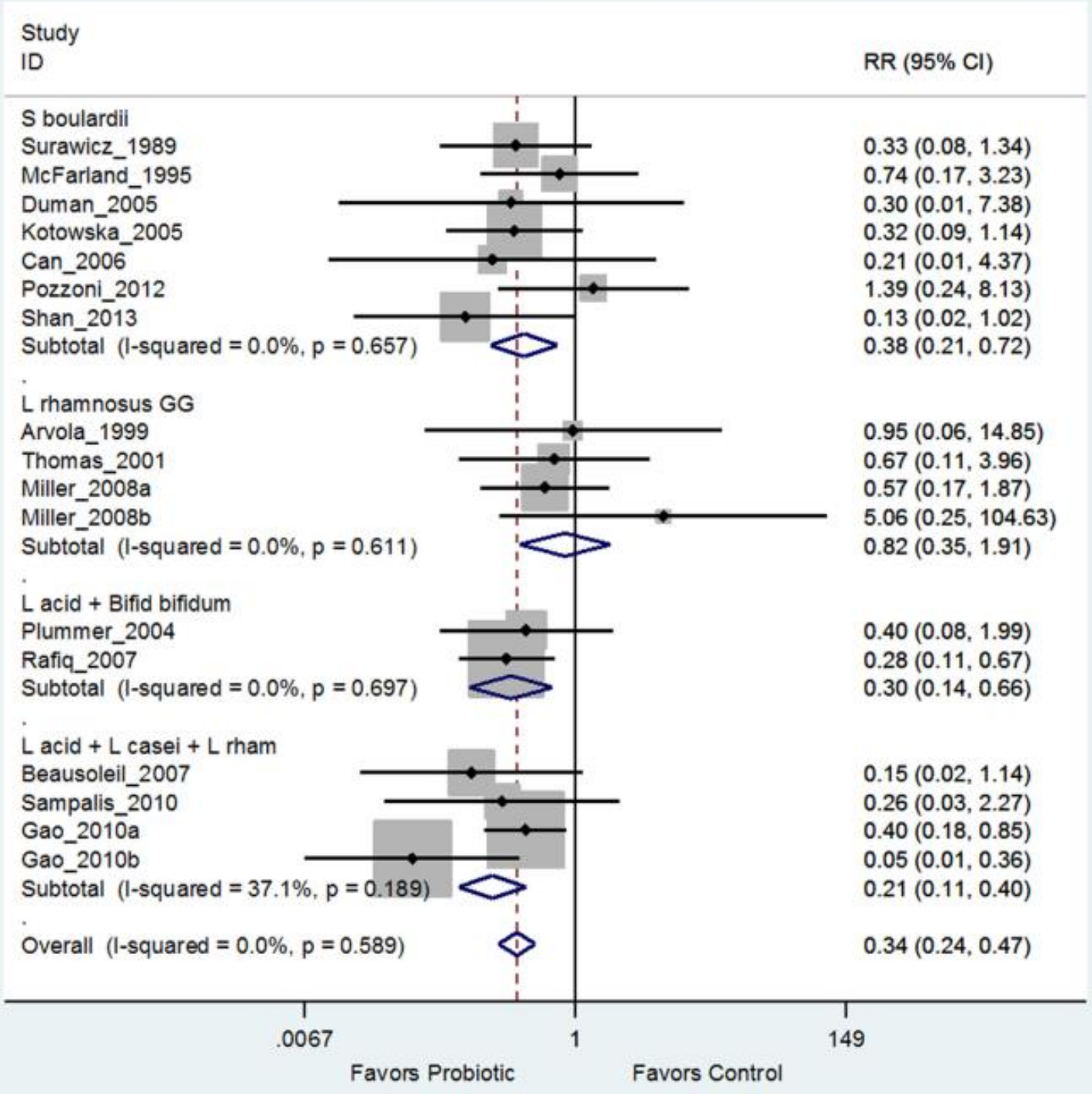
KORUNMA PROBİYOTİKLER

Strain-Specificity and DiseaseSpecificity of Probiotic efficacy: a Systematic Review and meta-analysis

Lynne V. McFarland et al. Frontiers in Medicine published: 07 May 2018

22 Çalışmanın Meta analizinde;

Lactobacillus Türlerinin bazı suşlarının Antibiyotik ilişkili diyare önlemede etkili bulunmuş.



S. Boulardi etkili

Lactobacillus acid, casei etkili

Lactobcillus Rhamnosus etkisiz

Disease indication	Net ≥ 2 significant randomized clinical trials (RCTs) (number of significant RCTs/non-significant RCTs)	At least two RCTs with significant efficacy (number of significant RCTs/non-significant RCTs)
Prevention		
Adult AAD	*Saccharomyces boulardii* I-745 (11+/6–) *Lactobacillus acidophilus* CL1285+ *Lactobacillus casei* LBC80R+ *Lactobacillus rhamnosus* CLR2 (4+/0)[a] *L. casei* DN114001 (2+/0–)	*Enterococcus faecalis* SF68 (2+/1–) *L. rhamnosus* GG (2+/4–) *Lactobacillus reuteri* 55730 (2+/1–)
Pediatric AAD	*S. boulardii* I-745 (7+/3–)	*L. helveticus* R52 + *L. rhamnosus* R11 (2+/1–)
CDI-primary	None	*L. acidophilus* CL1285 + *L. casei* LBC80R + *L. rhamnosus* CLR2 (2+/2–)[a]
Nosocomial infections	None	*L. rhamnosus* GG (2+/2–)
Travelers' diarrhea	*S. boulardii* I-745 (2+/0–)	
Treatment		
Pediatric acute diarrhea	*S. boulardii* I-745 (25+/4–) *L. rhamnosus* GG (12+/3–) *L. reuteri* DSN 17938 (3+/0–) *L. acidophilus* LB (3+/1–) *L. casei* DN114001 (3+/0–) VSL#3[b] (2+/0–) *Bac. clausii* OC/SN/R (3+/1–)	*L. helveticus* R52 + *L. rhamnosus* R11 (2+/1–)
Irritable bowel syndrome	*B. infantis* 35624 (2+/0–) *L. plantarum* 299v (4+/1–) *L. rhamnosus* GG+ *L. rhamnosus* LC705 + *B. breve* Bb99 + *Prop. freudenreichii shermanii* Jc (2+/0–)	*L. rhamnosus* GG (2+/2–) *S. boulardii* I I-745 (2+/2–) VSL#3[b] (2+/2–)
Helicobacter pylori eradication	*L. helveticus* R52 + *L. rhamnosus* R11 (4+/1–)	*S. boulardii* I-745 (5+/11–) *L. reuteri* 55730 (2+/2–) *L. acidophilus* La5 + *B. animalis* spp. *lactis* Bb12 (3+/2–)
Inflammatory bowel disease	VSL#3[b] (8+/2–)	*S. boulardii* I-745 (2+/1–)
CDI-recurrences	*S. boulardii* I-745 (2+/0–)	

Strain-Specificity and DiseaseSpecificity of Probiotic efficacy: a Systematic Review and meta-analysis

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TEDAVİ

First episode of the infection	
Non-severe disease	• Vancomycin 125 mg orally four times a day for 10 days OR • Fidaxomicin 200 mg orally twice a day for 10 days • If above agents are unavailable: metronidazole 500 mg orally three times a day for 10 days
Severe disease	• Vancomycin 125 mg orally four times a day for 10 days OR • Fidaxomicin 200 mg orally twice a day for 10 days
Fulminant disease (previously referred as severe complicated)	• Vancomycin 500 mg orally or via nasogastric tube four times a day AND • Metronidazole 500 mg IV 3 times a day + alternatively If ileus is present: vancomycin per rectum (vancomycin 500 mg in 100 ml saline as enema) four times a day* (10–14 days)

Fekal Transplantayon Kimlere ?

Dirençli ve tekrarlayan ağır C Difficile enterokoliti

İnflamatuar Barsak Hastalıkları (Ülseratif Kolit)

İrritable Barsak Sendromu (IBS)

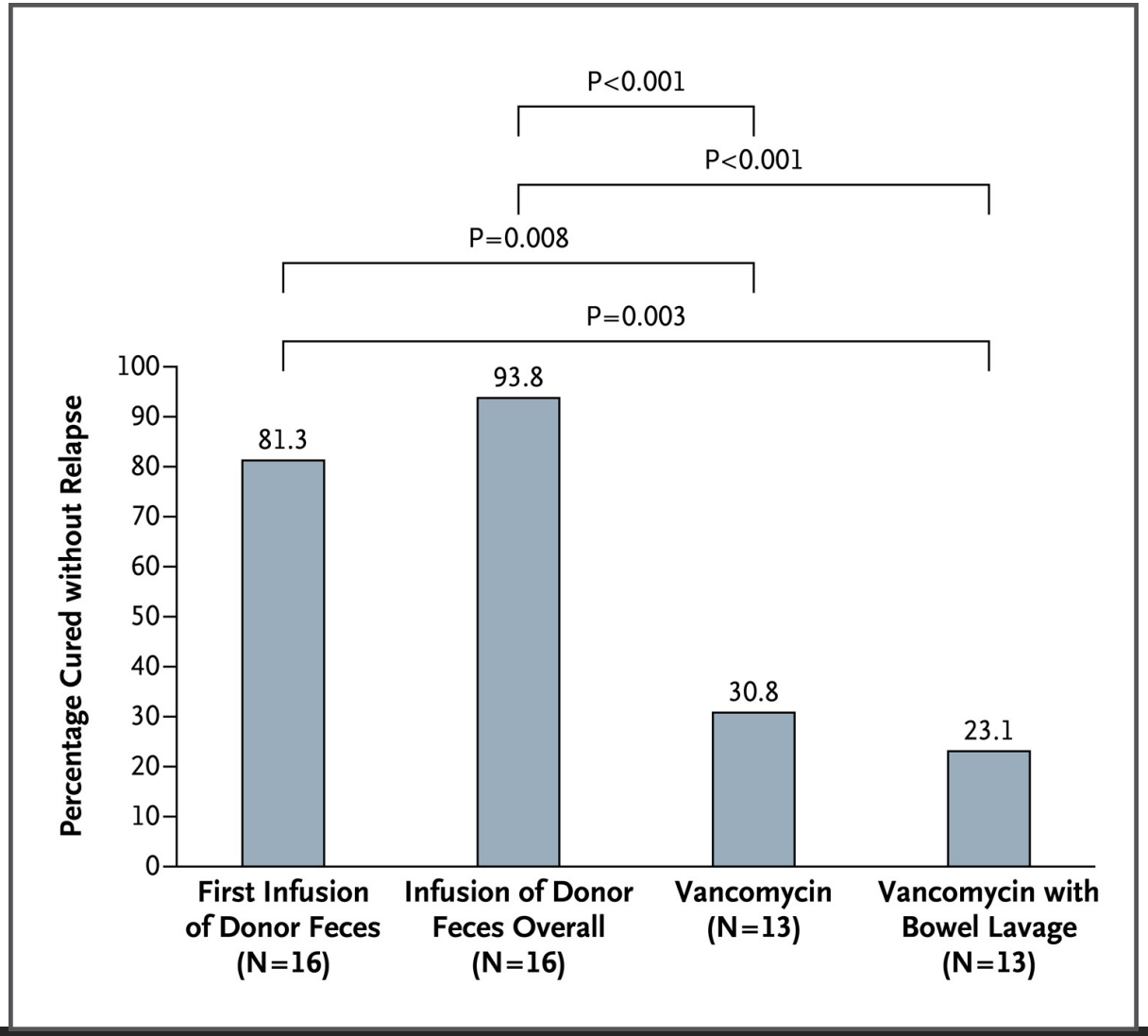
Obezite

Depresyon

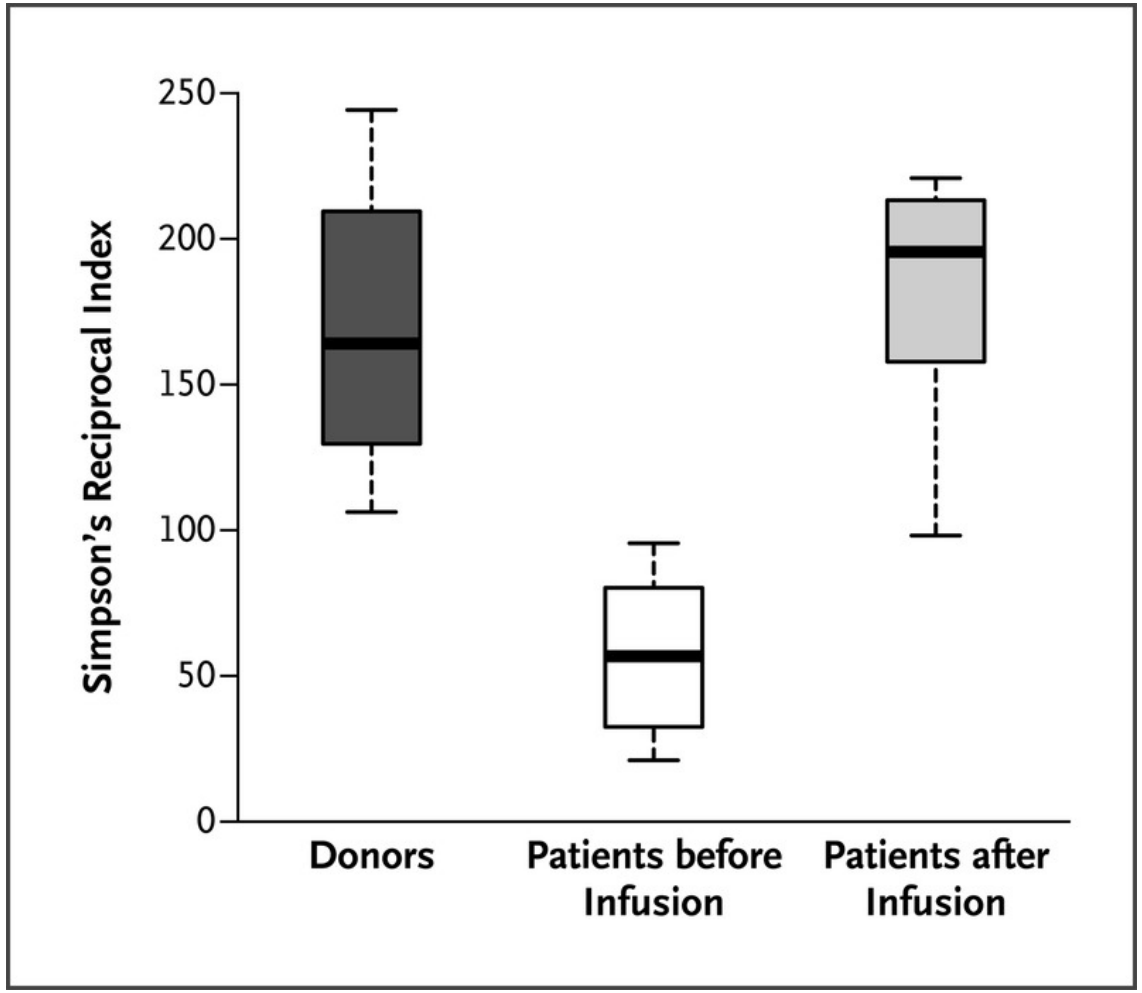
Kronik Yorgunluk

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

van Nood E Vrieze A , Nieuwdorp M et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med 2013 ; 368 : 407 – 15 .



FMT
Mikrobiyotaki Restore Eder



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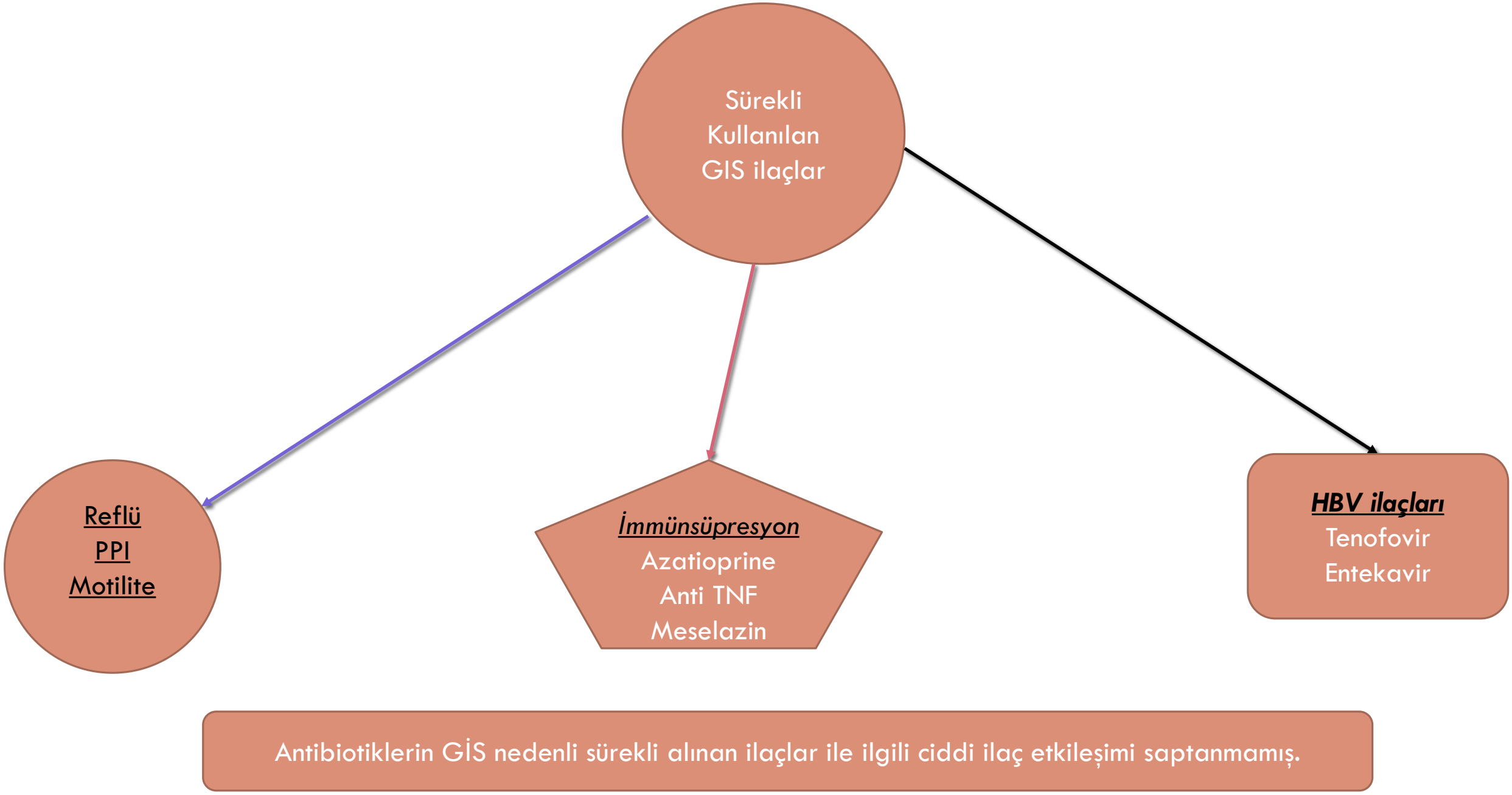

Antibiotiklerin GİS nedenli sürekli alınan ilaçlar ile ilgili ciddi ilaç etkileşimi saptanmamış.

TEŞEKKÜRLER