KOÇ ÜNİVERSİTESİ HASTANESİ

KLİMİK

Biyolojik Ajan Kullanan Hastada Aşılama

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Sunum İçeriği

- Biyolojik ajanlar
- Biyolojik ajanları kullananlarda infeksiyon riski
- Tedavi öncesi hastanın değerlendirilmesi
- Aşılamanın yönetimi
- Sonuç ve beklentiler

Biyolojik Ajan

- Kullanıma 1998'de girmiş yeni ilaçlar
- İmmün sistemde oluşan patolojileri tedavi etmede kullanılmakta

- Genetik mühendisliği tarafından insan ya da hayvan hücre kültürlerinde üretilmekte

Biyolojik Ajan- İsimlendirme

Biyolojik ajanlar, inflamasyonun özgün yollarını ve sinyallerini bloke ederler

Kullanılan kısaltmalar;

-**cept**; Reseptör füzyon proteinleri

-**mab**; Monoklonal antikorlar (mAB)

-**ximab**; Şimerik monoklonal antikorlar

-**(z)umab**; İnsan monoklonal antikorları

Biyolojik Ajanların Endikasyonları

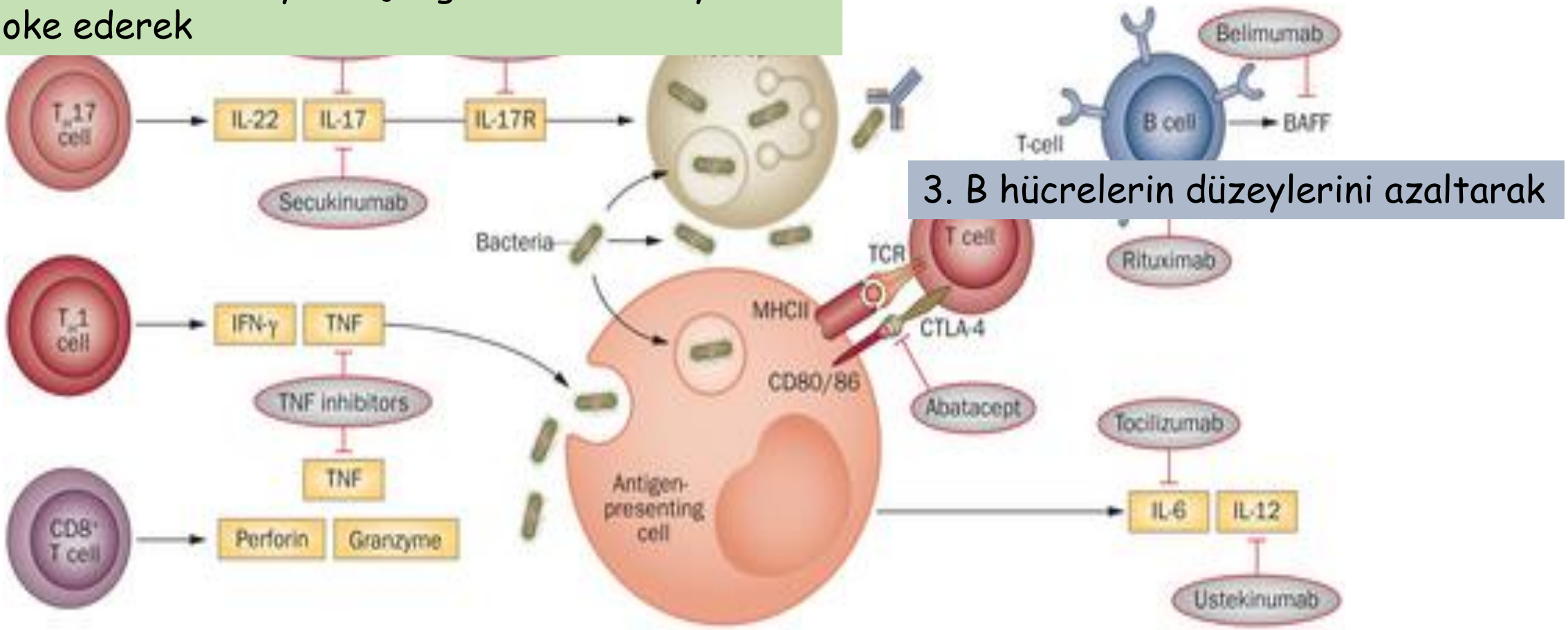
- Romatolojik hastalıklar
- Maligniteler => NHL, KML, ALL, kolorektal kanser, mide kanseri, vb.
- İnflamatuar barsak / göz hastalıkları
- Psöriazis
- Organ transplantasyonu
- Multiple skleroz
- Şiddetli astım
- .....

Biyolojik Ajanların Etki Mekanizması

1. Sitokin fonksiyonlarını bozarak

2. T hücre aktivasyonu için gerekli olan sinyalleri bloke ederek

3. B hücrelerin düzeylerini azaltarak



Biyolojik Ajanlar

- **TNF İnhibitörleri:**
  - Etanercept (soluble TNFR füzyon proteini (p75+IgG))
  - Infliksimab (kimerik anti-TNF monoklonal ab)
  - Adalimumab (rekombinant insan IgG1 monoklonal ab)
- **IL-1 Antagonistleri**
  - Rekombinant IL-1R antagonisti (Anakinra)
  - ICE inhibitoru (Pralnacasan)
- **Anti-IL-6R Monoklonal Ab (Tocilizumab)**
- **CTLA4-IgG1 (Abatacept)**
- **Adezyon Molekül Hedefli Tedaviler**
  - T hücre adezyon molekülü monoklonal antikor (Efalizumab)
  - a-4 integrin monoklonal antikor (Natalizumab)
  - CD2-binding füzyon proteini (alefacept)
- **B Hücre Baskılayıcı Tedaviler**
  - Anti-CD20 Monoklonal Antikor (Rituximab)

Soru: Biyolojik ajan kullanan hastalarda infeksiyon riski yüksek mi?

Otoimmün inflamatuar romatolojik hastalıklarda infeksiyon hastalıkları riski artar.

High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis

Karen Au,[1] George Reed,[2] Jeffrey R Curtis,[3] Joel M Kremer,[4] Jeffrey D Greenberg,[5] Vibeke Strand,[6] Daniel E Furst[1]; on behalf of the CORRONA Investigators

Ann Rheum Dis 2011;70:785–791.

Table 2 Number of infectious adv… 100 person-years) for patients on s…

Outcomes	No of event
Hospitalised infections	59
Outpatient infections	2223
URI/pneumonia	971
Sinusitis	467
UTI	189

URI, upper respiratory infection; UTI, urin…

	CDAI (N=6020)		
	Estimated IRR	95% CI	p Value
5-Unit change in CDAI			
If CDAI <10	1.56	0.94 to 2.59	0.08
If CDAI ≥10†	1.03	0.86 to 1.22	NS
DAS28 (0.6 units)	–	–	–
No prednisone use‡	1	–	–
Prednisone <7.5 mg daily	1.31	0.64 to 2.66	NS
Prednisone ≥7.5 mg daily	6.47	3.10 to 13.50	<0.001
History of infections	2.41	1.24 to 4.70	0.01
History of hospitalised infections	7.17	3.33 to 15.45	<0.001

Table 1
The prebiologic era: frequency of infections among patients with RA and healthy controls from a Minnesota cohort

Infection Type	Incidence per 100 Patient-Years RA	Incidence per 100 Patient-Years Non-RA	Relative Risk (95% Confidence Interval)
Pneumonia	4.0	2.4	1.7 (1.5–1.9)
Skin	3.0	0.9	3.3 (2.7–4.1)
Sepsis	0.78	0.51	1.5 (1.1–2.1)
Septic joint	0.40	0.02	14.9 (6.1–73.7)
Intra-abdominal	0.22	0.08	2.8 (1.4–6.2)
Osteomyelitis	0.17	0.01	10.6 (3.4–126.8)

Doran MF, et al. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum 2002;46(9):2287–93.

Winthrop KL. Infections and Biologic Therapy in Rheumatoid Arthritis Our Changing Understanding of Risk and Prevention. Rheum Dis Clin N Am 38 (2012) 727–745. **REVIEW**

RİTUXİMAB / ALEMTUZUMAB…

İnfeksiyon ne kadar sık?

- **Meta-analiz:**
- Opportunistik enfeksiyonlar
- 1996-2004
- 17 makale
- 992 hasta
  - 535 Rituximab
  - 409 Alemtuzumab
  - 48 her ikisi

	299 hasta	**% 30.1**
• Nedeni gösterilemeyen :	109 hasta	(% 36.5)
• Viral re-aktivasyon:	100 hasta	(%33.4)
• Bakteriyel enfeksiyon:	44 hasta	(%14.7)
• Fungal enfeksiyon:	26 hasta	(%8.7)
• Protozoal enfeksiyon:	11 hasta	(%3.7)
• Viral enfeksiyon:	9 hasta	(%3.0)

Cornely OA, et al. Opportunistic infections (OI) following monoclonal antibody treatment . Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings. Vol 23, No 16S (June 1 Supplement), 2005: 2562. **Meta-analiz**.

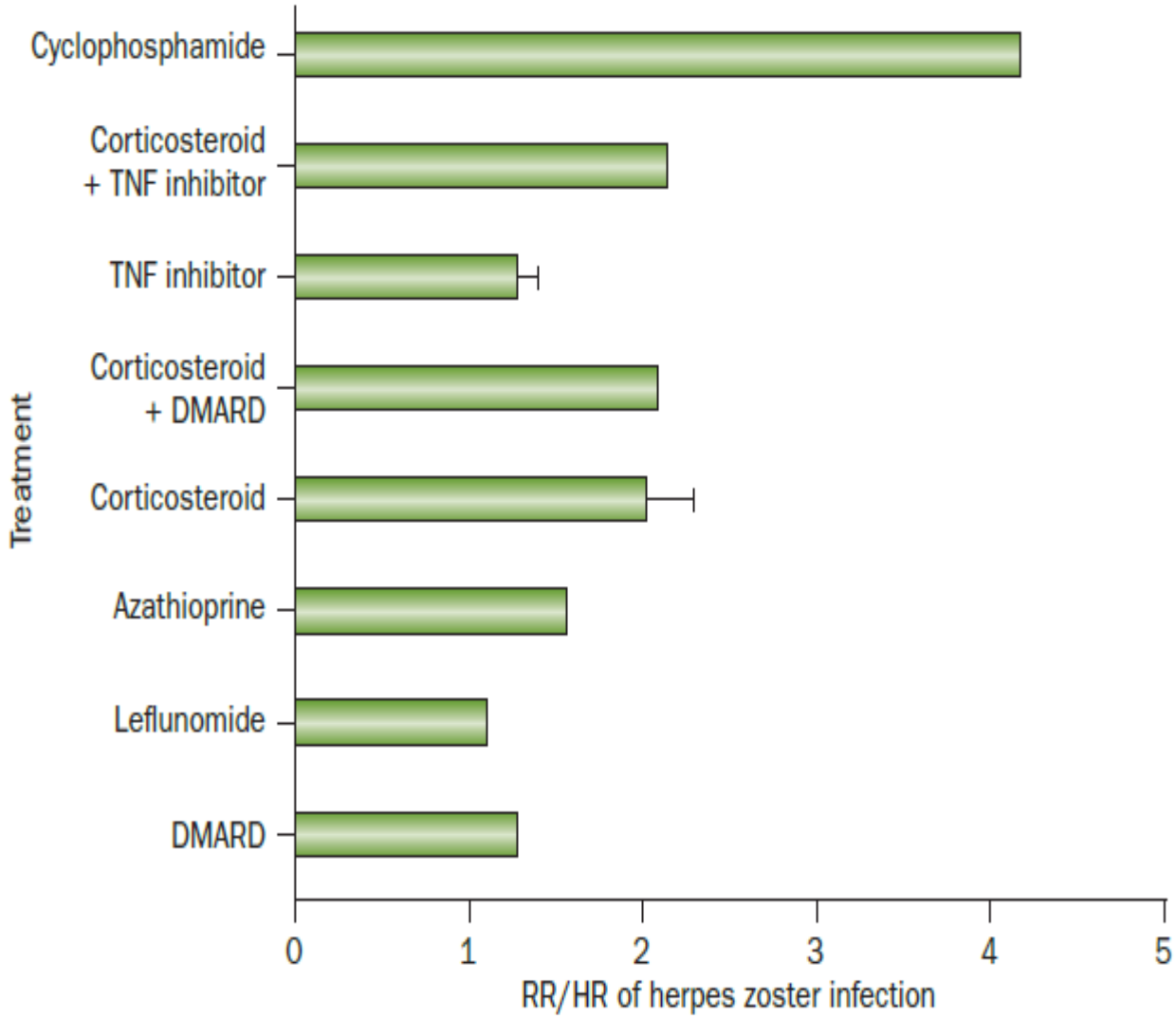
20 hasta infeksiyon nedeniyle eks

Biyolojik ajanlar ve İnfeksiyon sıklığı

Table 1 Serious infections in clinical trials of biologic therapies

Study (location)	Design	Disease	Agent
Bongartz *et al.*[3] (international)	Meta-analysis	RA	Infliximab, adalimumab
Salliot *et al.*[16] (international)	Meta-analysis	RA	Abatacept Rituximab Anakinra
Hoshi *et al.*[21] (Japan)	Clinical trial, registry control	RA	Tocilizumab
Singh *et al.*[4] (international)	Meta-analysis	All indications	All biologics Adalimumab Etanercept Certolizumab pegol Golimumab Infliximab Abatacept Anakinra Rituximab Tocilizumab

Abbreviations: RA, rheumatoid arthritis; SIR, standard incidence ratio.



Westra, J. *et al. Nat. Rev. Rheumatol.* 2015; 1: 135–145.

Woodrick RS & Ruderman EM. Safety of biologic therapy in rheumatoid arthritis. Nat Rev Rheumatol 2011;7:639–652. **Review.**

İnfeksiyonun en çok görülme zamanı;

- İlk **3-6 ay**,
- anti-TNF kullanımı sırasında ciddi infeksiyon riskinin en çok arttığı zaman dilimi (IRR 4.6)

Dixon WG, et al. Arthritis & Rheum 2006;54:2368-76
Galloway JB, et al. Rheumatology (Oxford). 2011; 50(1):124–31.

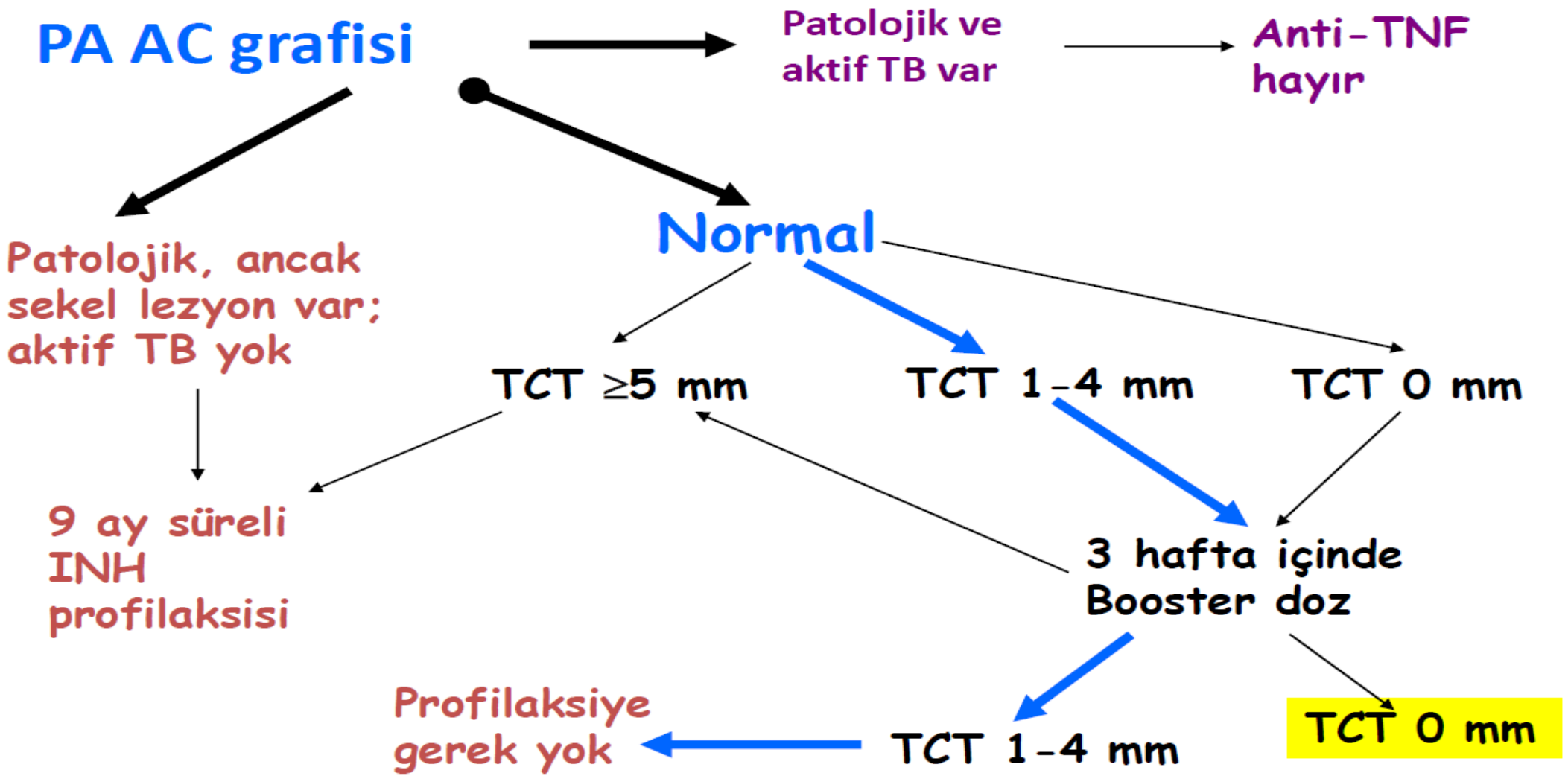
Soru: Tedavi öncesi hangi testler yapılmalı?

Tedavi başlanmadan önce;

- Aşı öyküsü alınmalı
- Aşı kaydı yoksa / öykü güvenilir değilse serolojik testler yapılmalı;
    - KKK
    - Suçiçeği
    - Viral hepatitler (HAV, HBV, HCV)
    - TB tarama

- Aşılama immünosüpresif veya biyolojik ajanlar başlanmadan önce yapılmalı

Tüberküloz Taraması



RAED Uzlaşı Raporu 2005

Tüberkülin Deri Testinin Değerlendirilmesi

BCG'lilerde	
0-5 mm	Negatif kabul edilir
6-14 mm	BCG'ye ya da *TDM'lere bağlı olabilir
15 mm ve üzeri	Pozitif kabul edilir
BCG'sizlerde	
0-5 mm	Negatif kabul edilir
6-9 mm	TDM'lere bağlı olabilir
10 mm ve üzeri	Pozitif kabul edilir
✓ *Bağışıklığı baskılanmış kişilerde 5 mm ve üzeri pozitif kabul edilir.*	

*TDM: Tüberküloz dışı mikobakteri

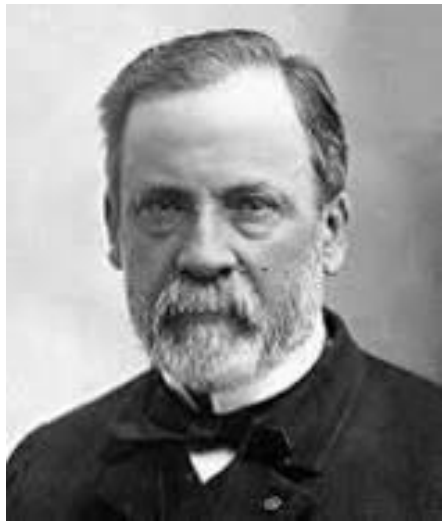
Soru: Hastaları nasıl korumak gerek?

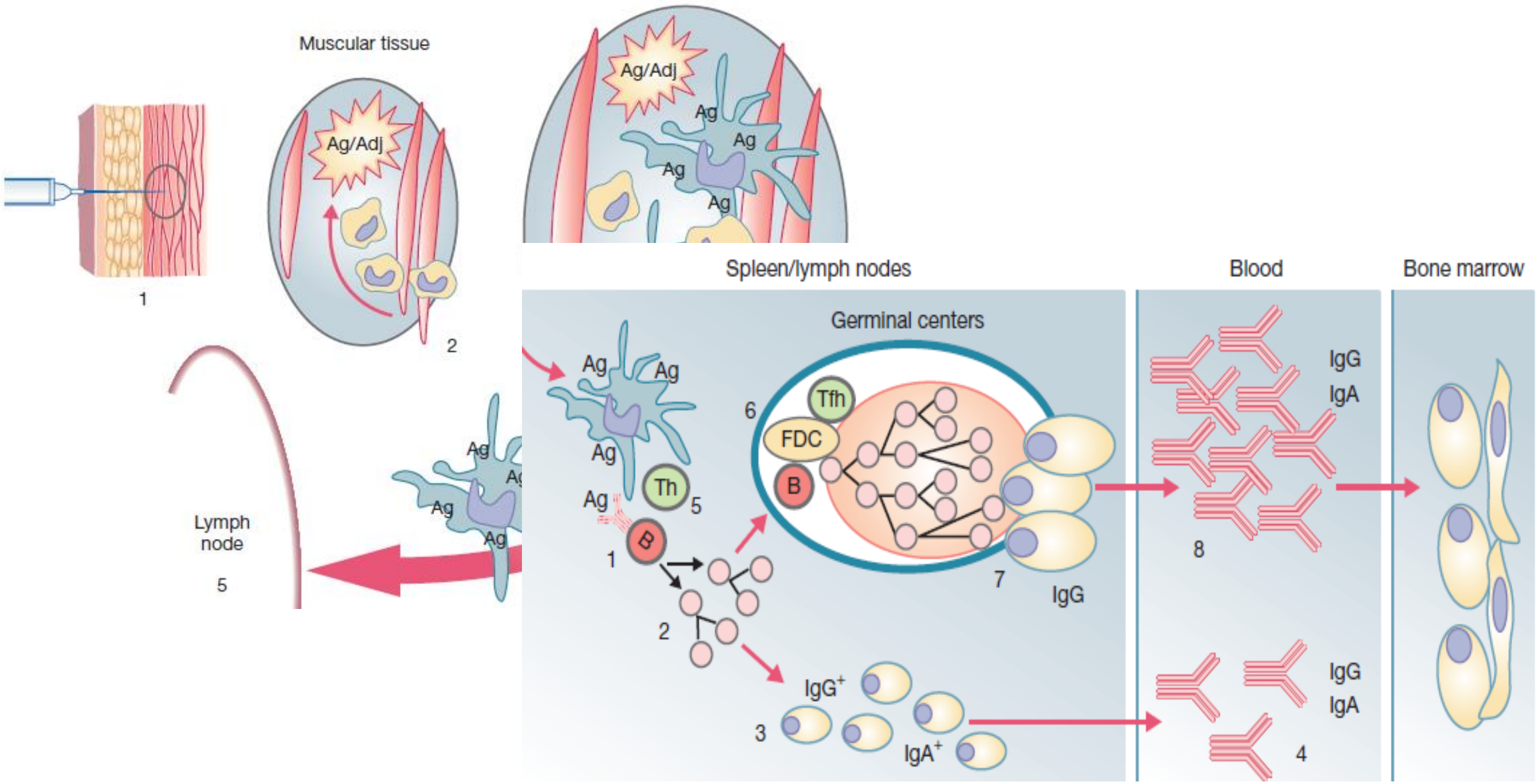
İnfeksiyon hastalıklarından korunma,
ölüm ve sekellerinin azaltılmasında en önemli
iki yöntem;
Sanitasyon ve immünizasyondur

When meditating over a disease,

I never think of finding a remedy for it, but, instead, a means of preventing it.

Louis Pasteur
(1822-1895)




Muscular tissue
Ag/Adj
Ag
Ag
Ag
Ag
1
2
Lymph node
5
Spleen/lymph nodes
Germinal centers
Blood
Bone marrow
Ag
Ag
Ag
Th
5
B
1
2
6
Tfh
FDC
B
7
IgG
IgG+
3
IgA+
8
IgG
IgA
IgG
IgA
4

AIIRD
Rheumatoid arthritis
Serum lupus erythematosus
Antiphospholipid syndrome
Adult Still disease
Systemic sclerosis
Sjögren syndrome
Mixed connective tissue disease
Relapsing polychondritis
Giant cell arteritis
Polymyalgia rheumatica
Takayasu arteritis
Polyarteritis nodosa
ANCA-associated vasculitis
Microscopic polyangiitis
Wegener granulomatosis
Churg-Strauss syndrome
Behçet disease
Goodpasture disease
Cryoglobulinaemic syndrome
Polymyositis
Dermatomyositis
Clinically amyopathic dermatomyositis
Sporadic inclusion body myositis
Antisynthetase syndrome
Eosinophilic myositis
Eosinophilic fasciitis
Spondylathropathies
Periodic fever syndromes

Immunomodulating agents
Corticosteroids
Methotrexate
Sulfasalazine
Leflunomide
Hydroxychloroquine
Azathioprine
Mycophenolic acid preparations
Ciclosporine
Tacrolimus
Cyclophosphamide
Biologicals:
TNFα blocking agents
Infliximab
Etanercept
Adalimumab
Rituximab
Tocilizumab
Abatacept
Anakinra

Vaccines
BCG
Cholera
Diphtheria
Hepatitis A
Hepatitis B
Haemophilus influenzae b
Human papillomavirus
Influenza
Japanese encephalitis
Measles*
Mumps*
Neisseria meningitidis (A/C/Y/W135, C conjugated)
Pertussis
Poliomyelitis (parenteral and oral*)
Rabies
Rubella*
Streptococcus pneumoniae (polysaccharide and conjugated)
Tetanus toxoid
Tick-borne encephalitis
Typhoid fever (parenteral and oral*)
Varicella zoster*
Yellow fever*

Ann Rheum Dis 2011;70:414–422. doi:10.1136/ard.2010.137216

Vaccines	Vaccine type	Serum IgG	Mucosal IgG	Mucosal IgA	T cells
Diphtheria toxoid	toxoid	++	(+)		
Hepatitis A	killed	++			
Hepatitis B (HbsAg)	protein	++			
Hib PS	PS	++	(+)		
Hib glycoconjugates	PS-protein	++	++		
Influenza	killed, subunit	++	(+)		
Influenza intranasal	live attenuated	++	+	+	+ ($CD8^+$)
Measles	live attenuated	++			+ ($CD8^+$)
Meningococcal PS	PS	++	(+)		
Meningococcal conjugates	PS-protein	++	++		
Mumps	live attenuated	++			
Papillomavirus	VLPs	++	++		
Pertussis, whole cell	killed	++			
Pertussis, acellular	protein	++			+?($CD4^+$)
Pneumococcal PS	PS	++	(+)		
Pneumococcal conjugates	PS-protein	++	++		
Polio Sabin	live attenuated	++	++	++	
Polio Salk	killed	++	+		
Rabies	killed	++			
Rotavirus	live attenuated			++	
Rubella	live attenuated	++			
Tetanus toxoid	toxoid	++			
Tuberculosis (BCG)	live mycob				++($CD4^+$)
Typhoid PS	PS	+	(+)		
Varicella	live attenuated	++			+?($CD4^+$)
Yellow Fever	live attenuated	++			

Figures 1 and 2 should be read with the footnotes that contain important general information and considerations for special populations.

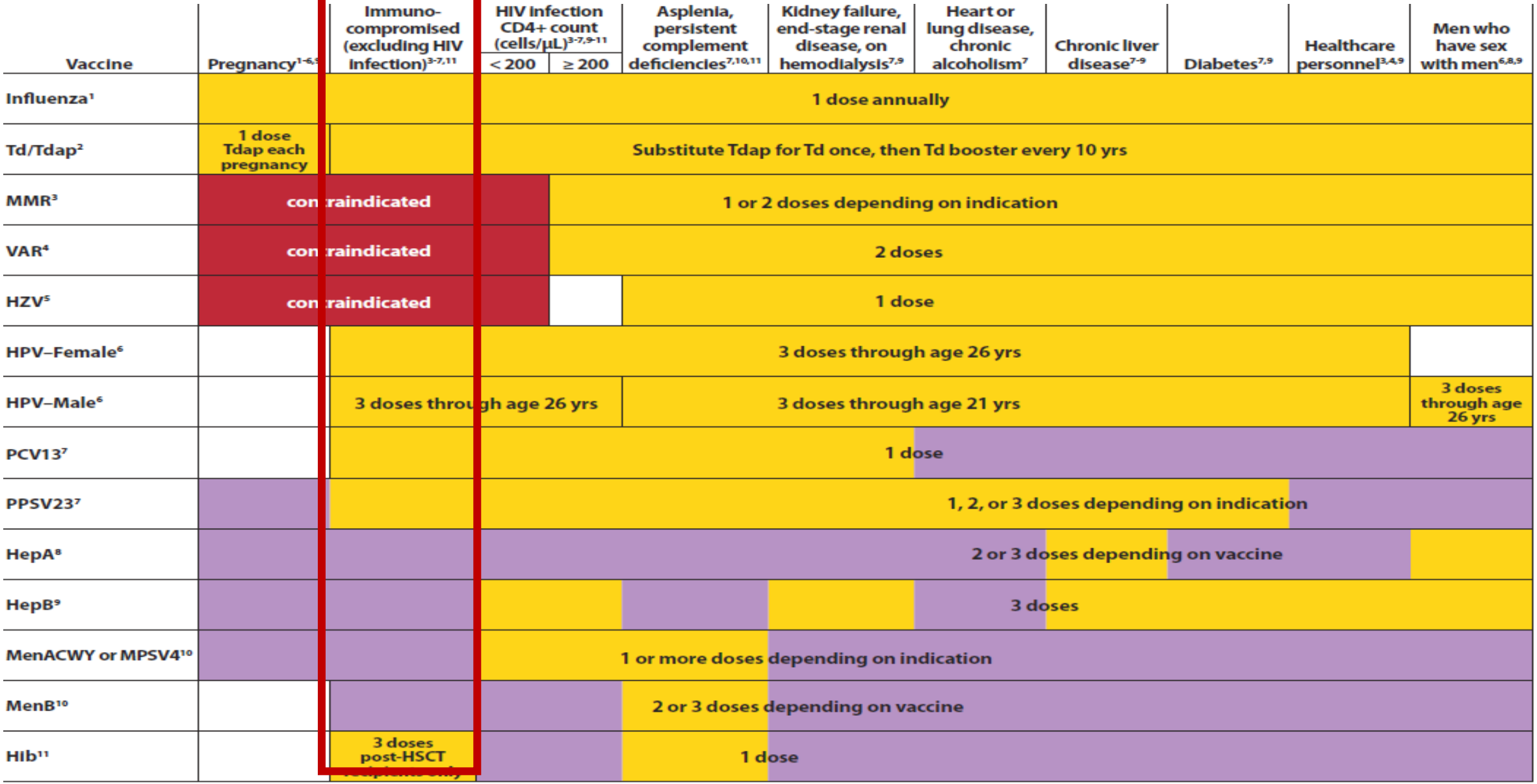
Figure 1. Recommended immunization schedule for adults aged 19 years or older by age group, United States, 2017

Vaccine	19–21 years	22–26 years	27–59 years	60–64 years	≥ 65 years
Influenza[1]	1 dose annually				
Td/Tdap[2]	Substitute Tdap for Td once, then Td booster every 10 yrs				
MMR[3]	1 or 2 doses depending on indication				
VAR[4]	2 doses				
HZV[5]				1 dose	
HPV–Female[6]	3 doses				
HPV–Male[6]	3 doses				
PCV13[7]	1 dose				
PPSV23[7]	1 or 2 doses depending on indication				1 dose
HepA[8]	2 or 3 doses depending on vaccine				
HepB[9]	3 doses				
MenACWY or MPSV4[10]	1 or more doses depending on indication				
MenB[10]	2 or 3 doses depending on vaccine				
Hib[11]	1 or 3 doses depending on indication				

Recommended for adults who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended for adults with additional medical conditions or other indications

No recommendation



Recommended Immunization Schedule for Adults, United States, 2017

Hangi Aşılar?

- İnfluenza
- Td/Tdap
- KKK
- Suçiçeği-zoster
- HPV (yaşa göre)
- Pnömokok
- Riske göre diğer aşılar

EULAR recommendations. *Ann Rheum Dis* 2011;70:414–422.

Table 6. Vaccination of Persons With Chronic Inflammatory Diseases on Immunosuppressive Medications

	Planned Immunosuppression		Low-level Immunosuppression[a]		High-level Immunosuppression[a]	
Vaccine	Recommendation	Strength, Evidence Quality	Recommendation	Strength, Evidence Quality	Recommendation	Strength, Evidence Quality
Haemophilus influenzae b conjugate	U	Strong, moderate	U	Strong, low	U	Strong, low
Hepatitis A	U	Strong, moderate	U	Strong, low	U	Strong, low
Hepatitis B	U	Strong, moderate	U	Strong, low	U	Strong, low
Diphtheria toxoid, tetanus toxoid, acellular pertussis; tetanus toxoid, reduced diphtheria toxoid; tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis	U	Strong, moderate	U	Strong, low	U	Strong, low
Human papillomavirus	U: 11–26 y	Strong, moderate	U: 11–26 y	Strong, low	U: 11–26 y	Strong, very low
Influenza-inactivated (inactivated influenza vaccine)	U	Strong, moderate	U	Strong, moderate	U	Strong, moderate
Influenza-live attenuated (live attenuated influenza vaccine)	X	Weak, very low	X	Weak, very low	X	Weak, very low
Measles, mumps, and rubella–live	U[b]	Strong, moderate	X	Weak, very low	X	Weak, very low
Measles, mumps, and rubella–varicella–live	U[b]	Strong, low	X	Weak, very low	X	Strong, very low
Meningococcal conjugate	U	Strong, moderate	U	Strong, moderate	U	Strong, low
Pneumococcal conjugate (PCV13)	R[c]	Strong, moderate	U: <6 y R: ≥6 y[c]	Strong, low strong, very low	U: <6 y R: ≥6 y[c]	Strong, low strong, very low
Pneumococcal polysaccharide (PPSV23)	R: age ≥2 y	Strong, low	R: age ≥2 y	Strong, low	R: age ≥2 y	Strong, very low
Polio-inactivated (inactivated poliovirus vaccine)	U	Strong, moderate	U	Strong, moderate	U	Strong, low
Rotavirus–live	U	Strong, moderate	X	Weak, very low	X	Weak, very low
Varicella–live	U[b]	Strong, moderate	X[d]	Weak, very low	X	Strong, moderate
Zoster–live	R: age 50–59 y[e] U: age ≥60 y	Weak, low strong, low	R: age 50–59 y[e] U: age ≥60 y	Weak, very low Strong, very low	X	Weak, very low

IDSA. Vaccination of the Immunocompromised Host CID. 2014;58(3):e44–100

Table 1. Vaccination scheme in adults with rheumatic diseases

Vaccine	18–64 years	≥65 years
Influenza	1 dose annually	
[1,2]Pneumococcal (polysaccharide/conjugate)	1–2 doses	1–2 doses
[3]Tetanus, diphtheria (Td)	A booster dose of vaccine every 10 years	
Hepatitis B	3 doses (0, 1, and 6 months) [May need to be applied as high-dose vaccine (0, 1, 2, and 6 Months) and double doses of vaccine in high risk patients who are going to receive biological agents or medium to high dose corticosteroids depending on the serological status)	
Hepatitis A	2 doses of vaccine (0 and 6 months)	
[4]Varicella/Herpes zoster	Contraindicated in persons with immunosuppression: can be administered in consultation with a specialist in specific cases	
[4]Measles, mumps, rubella (MMR)	Contraindicated in persons with immunosuppression: can be administered in consultation with a specialist in specific cases	
[2]Meningococcal (quadrivalent conjugate meningococcal vaccine)	2 doses of vaccine at least 2 months apart Can be repeated every 5 years if at continued risk	
[2]Haemophilus influenzae type B	1 dose	
[5]Human papillomavirus (HPV)	2 or 3 doses	

Individuals who do not have immunity and contraindications

Individuals who have risk factors and don't have contraindications

[1]It is recommended to comply with the schedule for the polysaccharide and conjugate pneumococcal vaccines (recommendations with regards to risk groups are summarized in Table 2).

[2]In cases of asplenia (including elective splenectomy and persistent complement deficiencies).

[3]Scheme in persons who have completed the primary immunization for tetanus vaccine.

Tanrıover M, et al. Eur J Rheumatol 2016; 3: 29-35

Aşılar Ne Zaman Verilmeli?

EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases

Mümkünse aşılar planlanan immünosüpresif ilaçlardan önce başlanmalı (güçlü-orta öneri).

EULAR recommendations. *Ann Rheum Dis* 2011;70:414–422.

Singh et al. American College of Rheumatology Guideline. Arthritis Care & Research, 2015

EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases

EULAR recommendations. *Ann Rheum Dis* 2011;70:414–422.

- **Canlı** aşılar immünosüpresif **tedaviden ≥4 hafta önce** başlanmalı Tedavi başlandıktan sonra **ilk iki hafta içinde verilmemeli** (güçlü-düşük öneri)

- **İnaktive** aşılar immünosüpresif **tedaviden ≥2 hafta önce** başlanmalı (güçlü-orta öneri)

❖ Acil tedavi gerekiyorsa, tedaviyi engellememeli!

Singh et al. American College of Rheumatology Guideline. Arthritis Care & Research, 2015

EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases

EULAR recommendations. *Ann Rheum Dis* 2011;70:414–422.

Table 2 Recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases with level of evidence, strength of recommendations and results of Dephi voting per recommendation

Recommendation	Category of evidence			Strength of recommendation	Mean (SD) level of agreement by Delphi voting (VAS)
	Increased incidence of VP infection	Efficacy of vaccination	Harms of vaccination		
Vaccination in patients with AIIRD should ideally be administered during stable disease	–			D	8.88 (1.26)
Live attenuated vaccines should be avoided whenever possible in immunosuppressed patients with AIIRD	IV			D	9.25 (1.13)

- ✓ KKK, varisella ve Herpes zoster aşıları istisna
- ✓ Düşük immünosüpresiflerde hasta temelli düşünülmeli.

Düşük düzey immünosüpresyon

- Günlük prednizon dozu< 20 mg olarak (veya eşdeğeri)
- Methotreksat ≤ 0,4 mg/kg haftalık;
- Azathioprin ≤ 3 mg/kg gün
- 6-merkaptopurin<1,5 mg/kg gün

Vaccination of Immunocompromised Host. CID 2014:58 .

EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases

EULAR recommendations. *Ann Rheum Dis* 2011;70:414–422.

Table 2 Recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases with level of evidence, strength of recommendations and results of Dephi voting per recommendation

Recommendation	Category of evidence: Increased incidence of VP infection	Category of evidence: Efficacy of vaccination	Category of evidence: Harms of vaccination	Strength of recommendation	Mean (SD) level of agreement by Delphi voting (VAS)
Vaccination in patients with AIIRD can be administered during the use of DMARDs and TNFα blocking agents, but should ideally be administered before starting B cell-depleting biological therapy	II			B	9.13 (1.02)

- Hastalığı modifiye eden anti-romatizmal ilaçlar (DMARDs), glukokortikoidler ve/veya TNF a blokerlerinin kullanımı esnasında aşılara yanıt olduğu gösterilmiş.
- Ancak B hücre inhibitörü ajan kullanımında **öncesinde**

Ya da **başlangıçtan 6 ay sonra**, diğer kürden 4 hafta önce uygulanmalı

Biyolojik Ajanlarla Tedavi Sonrası Aşılama

Table 3

Treatment-free intervals before and after vaccine administration in patients treated with biological agents, according to French recommendations[a] and summaries of product characteristics.

Vaccine	Biotherapy	TNFα antagonists					Abatacept	Tocilizumab	Ustekinumab	Anti-IL-1		Rituximab	Belimumab
		Etanercept	Adalimumab	Golimumab	Certolizumab	Infliximab				Anakinra	Canakinumab		
Live attenuated vaccines	Stop	2 to 12 weeks	10 to 12 weeks	8 to 12 weeks	10 to 12 weeks	6 to 12 weeks	10 to 12 weeks	10 to 12 weeks	12 to 15[a] weeks	2 days to 3 months	3 months	6 months	3 months
	Re-start	3 weeks	3 weeks	3 weeks	3 weeks	3 weeks	3 weeks	3 weeks	2 weeks[a]	3 weeks	3 weeks	1 month	1 month
Inactivated vaccines	Stop	No treatment interruption										6 months[b]	6 months[b]
	Re-start											1 month	1 month

[a] Issued by the French public health authority and the Inflammatory Rheumatism Group (CRI) of the French Society for Rheumatology (and based on drug half-life values)

[b] Immunization can be performed within 6 months after rituximab but, in this situation, the risk of a blunted vaccine response is high.

J. Morel et al. / Joint Bone Spine xxx (2015) xxx–x

EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases

EULAR recommendations. *Ann Rheum Dis* 2011;70:414–422.

Table 2 Recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases with level of evidence, strength of recommendations and results of Dephi voting per recommendation

Recommendation	Category of evidence			Strength of recommendation	Mean (SD) level of agreement by Delphi voting (VAS)
	Increased incidence of VP infection	Efficacy of vaccination	Harms of vaccination		
Influenza vaccination should be strongly considered for patients with AIIRD	III	Ib	Ib	B–C	9.00 (1.10)
23-valent polysaccharide pneumococcal vaccination should be strongly considered for patients with AIIRD	III	Ib	Ib	B–C	8.19 (1.38)
Patients with AIIRD should receive tetanus toxoid vaccination in accordance with recommendations for the general population. In case of major and/or contaminated wounds in patients who received rituximab within the last 24 weeks, passive immunisation with tetanus immunoglobulin should be administered	–	II	II	B–D	9.19 (1.11)

EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases

EULAR recommendations. *Ann Rheum Dis* 2011;70:414–422.

Table 2 Recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases with level of evidence, strength of recommendations and results of Dephi voting per recommendation

Recommendation	Category of evidence			Strength of recommendation	Mean (SD) level of agreement by Delphi voting (VAS)
	Increased incidence of VP infection	Efficacy of vaccination	Harms of vaccination		
Herpes zoster vaccination may be considered in patients with AIIRD	III	–	IV	C–D	8.00 (1.59)

- RA, SLE ve polimyozit/dermatomyozit hastalarında normal popülasyona göre zona riski yüksek seyretmekte
- VZV seropozitif kişilere zona aşısı önerilmekte (ACIP) (Valide edilmemiş)

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Recommendation	Category of evidence: Increased incidence of VP infection	Category of evidence: Efficacy of vaccination	Category of evidence: Harms of vaccination	Strength of recommendation	Mean (SD) level of agreement by Delphi voting (VAS)
HPV vaccination should be considered in selected patients with AIIRD	III	–	–	C–D	8.44 (1.41)

- ❖ HPV infeksiyonu sıklıkla SLE hastalarında görülmekte
- ❖ HPV aşısı özellikle bu gruba önerilmektedir
  - ✓ Tromboemboli (VTE) riski 0.2/100 000 → Altta yatan antifosfolipid sendr olanlar var)

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Recommendation	Category of evidence			Strength of recommendation	Mean (SD) level of agreement by Delphi voting (VAS)
	Increased incidence of VP infection	Efficacy of vaccination	Harms of vaccination		
In hyposplenic/asplenic patients with AIIRD, influenza, pneumococcal, *Haemophilus influenzae* b and meningococcal C vaccinations are recommended	IV			D	9.50 (0.82)
Patients with AIIRD who plan to travel are recommended to receive their vaccinations according to general rules, except for live attenuated vaccines which should be avoided whenever possible in immunosuppressed patients with AIIRD	–			D	9.25 (1.24)

Alten *et al. BMC Musculoskeletal Disorders* (2016) 17:231
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BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

Antibody response to pneumococcal and influenza vaccination in patients with rheumatoid arthritis receiving abatacept

Rieke Alten[1,7*], Clifton O. Bingham III[2], Stanley B. Cohen[3], Jeffrey R. Curtis[4], Sheila Kelly[5], Dennis Wong[5] and Mark C. Genovese[6]

- Abatacept alan hastaların çoğunluğunda pnömokok (%89) ve grip aşısı (%81) ile primer ya da pekiştirme dozu olarak yeterli yanıt elde edilmiş.

- Her iki aşı da güvenli bulunmuş.
- Tedaviden önce aşı yapılması tercih edilmeli

EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases

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Table 2 Recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases with level of evidence, strength of recommendations and results of Dephi voting per recommendation

Recommendation	Category of evidence			Strength of recommendation	Mean (SD) level of agreement by Delphi voting (VAS)
	Increased incidence of VP infection	Efficacy of vaccination	Harms of vaccination		
BCG vaccination is not recommended in patients with AIIRD	III	–	–	D	9.38 (1.09)
Hepatitis A and/or B vaccination is only recommended in patients with AIIRD at risk	–	II*	III*	D	9.13 (0.89)

HBV Reaktivasyonu

- **HBs Ag (+) hastalarda**
  - HBV DNA negatif → pozitifleşme
  - HBV DNA pozitif → bazale göre ≥1 log10 artış
  - ALT'de bazal değerin ≥3 katı artış veya ≥100IU/ml olması
    - HBV DNA'da artış ile birlikte
- **HBs Ag (-) Anti HBc (+) hastalarda**
  - HBsAg pozitifleşme (HBsAg seroreversiyonu)
  - HBsAg negatif ancak HBV DNA pozitifleşme

Klinik

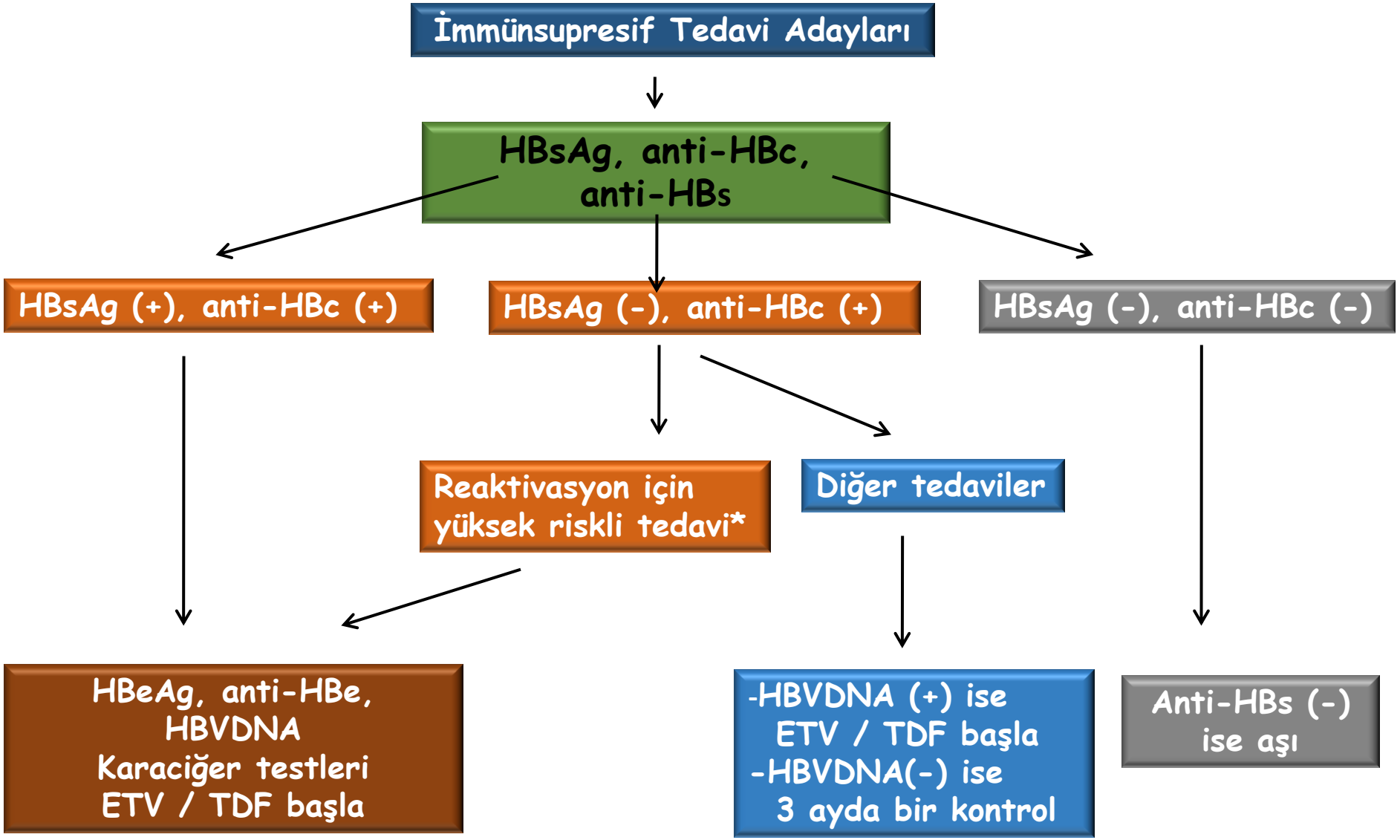
- Subklinik form ←→ şiddetli/fatal hepatit
  - Tedaviye rağmen mortalite oranı: **%4-60**

Pattula V. World J Hepatol 2015

HBV Reaktivasyon Risk Kategorileri

Risk derecesi	HBsAg + Anti-HBc+	HBsAg – Anti-HBc+	Tedavi
Yüksek risk >%10	B hücre deplesyonu yapan ajanlar (rituximab, ofatumumab) Antrasiklin deriveleri (doxorubicin, epirubicin) Orta (10–20 mg/gün) veya yüksek doz (>20 mg/gün) prednizon 4 hafta	B hücre deplesyonu yapan ajanlar (rituximab, ofatumumab)	Genetik direnç bariyeri yüksek antiviralllerle Profilaksi
Orta risk %1-10	TNF-alfa tedavisi (Sitokin veya integrin inhibitörleri (abatacept, ustekinumab, natalizumab, vedolizumab) Tirozin kinaz inhibitörleri (imatinib, nilotinib) Düşük doz steroid (<10 mg/gün prednisone), 4 haftalık tedavi	TNF-alfa tedavisi Sitokin veya integrin inhibitörleri (abatacept, ustekinumab, natalizumab, vedolizumab) Tirozin kinaz inhibitörleri (imatinib, nilotinib) Orta doz (10–20 mg/gün) veya yüksek doz (>20 mg/gün) prednizon 4 hafta antrasiklin deriveleri (doxorubicin, epirubicin)	Genetik direnç bariyeri yüksek antiviralllerle Profilaksi veya Pre-emptif ted.
Düşük risk <%1	İmmünsupresif ajanlar (azathioprine, 6-mercaptopurine, methotrexate) İntra-artiküler kortikosteroidler 1 hafta süreli herhangi bir dozda oral steroid tedavisi	İmmünsupresif ajanlar (azathioprine, 6-mercaptopurine, methotrexate) İntra-artiküler kortikosteroidler 1 hafta süreli herhangi bir dozda oral steroid tedavisi Düşük doz 4 haftalık steroid (<10 mg prednison)	Profilaksiye gerek yok

Perrillo RP, et al. Gastroenterology. 2015;148:221-244.



*rituximab, ofatumumab, anti-TNF ajanlar (etanercept, adalimumab, certolizumab, infliximab), sitokin ve integrin inhibitörleri (abatacept, ustekinumab, natalizumab, vedolizumab), tirozin kinaz inhibitörleri (imatinib, nilotinib), antrasiklin deriveleri (doksorubusin, epirubisin) ve >10 mg prednisolon ≥4 hafta kullananlar, Hemopoetik stem cell nakli olanlar

Di Bisceglie AM. Gastroenterology 2015;61:703-11

İmmunomodülatör Tedavilerde Aşı Etkinliği

Table 3 Summary of data for vaccine efficacy and safety with immunomodulatory therapies

Drug	Protein vaccines	Carbohydrate vaccines	DTH/cellular immunity	Neoantigen	Live virus
Non-biologic immunomodulators					
Corticosteroids	--/↓	--	ND	ND	Zoster OK with CCS <20 mg/day
Methotrexate	↓↓	↓	--	--	Zoster OK with MTX <0.4 mg/kg/week
Anti-malarials	--	--	ND	ND	Probably safe, possible ↓ response
Sulfasalazine	--/↓	ND	ND	ND	Probably safe, not formally studied
Leflunomide	--	ND	ND	ND	ND
Azathioprine	--	--/↓	ND	ND	Zoster OK <3 mg/kg/day
Mycophenolate	↓↓	↓↓	↓	↓	Avoid
Calcineurin Inhibitors	--/↓	ND	↓	ND	Avoid
Biologicals and targeted immunomodulators					
TNF inhibitors	--/↓	--/↓	--	ND	Avoid
Abatacept (CTLA4-Ig)	↓	↓	ND	↓	Avoid
Rituximab (anti-CD20)	--/↓	↓↓	↓	↓↓	Avoid
Tocilizumab (anti-IL6)	--	--	ND	ND	Avoid
Ustekinumab (anti-IL-12/23)	--	--	ND	ND	Avoid
IL-1 inhibitors (anakinra, Rilonacept, canakinumab)	ND	ND	ND	ND	Avoid
Belimumab (anti-BLyS)	ND	ND	ND	ND	Avoid
Tofacitinib (Jak1/3)	--/↓	↓	ND	ND	Avoid

↓ decreased, ↓↓ markedly decreased, -- no effect. BLyS, B lymphocyte stimulator; CCS, corticosteroids; DTH, delayed type hypersensitivity; MTX, methotrexate; ND, not determined; TNF, tumor necrosis factor.

McMahan and Bingham III *Arthritis Research & Therapy* 2014, **16**:506

Aşı-Otoimmünite İlişkisi?

✓ Otoimmün hastalıklarda grip aşısına hastalıkta geçici alevlenme bazı olgu raporları olsa da prospektif çalışmalarda **neden-sonuç ilişkisi gösterilememiş**

✓ SLE ve RA'li hastalarda infeksiyondan daha **fazla aktiviteye yol açmaz**.

✓ HBV aşısı SLE ve RA'li hastalarda hastalık aktivitesi üzerinde etkisi yok

✓ KKK aşısı jüvenil idiopatik artritli hastalarda klinik veya laboratuvar olarak ölçülen bir kötüleşmeye yol açmamış

✓ Multipl sklerozlu hastalarda sarı humma aşısıyla az sayıda hastada relaps rapor edilmiş.

Liao Z, et al.(2016. PLoS ONE 11(2): e0147856

Sonuç olarak

- Biyolojik ajan kullanan hastalarda aşılama çok önemli
- Hastalığa, risk durumu, daha önceki aşılanma-hastalığı geçirme ve ilaca göre aşılar belirlenmeli
- Kontrendikasyonlar iyi belirlenmeli
- Her vizit aşı-korunma açısından bir fırsattır
- Hastalar bilgilendirilmeli ve eğitimi sağlanmalı
- Erişkinde aşılamayla ilgili engeller tanımlanmalı ve stratejiler geliştirilmeli
- **Multidisipliner yaklaşım çok önemli**

Kirchner & Ruffing. Rheum Dis Clin N Am 43 (2017) 15–26

‘Haziranda ölmek zor’

Nâzım Hikmet

Orhan Kemal

Ahmet Arif

Teşekkürler...