T.C. Sağlık Bakanlığı
Türkiye Kamu Hastaneleri Kurumu
SAĞLIK BİLİMLERİ ÜNİVERSİTESİ
İSTANBUL
FATİH SULTAN MEHMET
EĞİTİM VE ARAŞTIRMA HASTANESİ

Özel gruplarda aşılama

Biyolojik ajan kullananlar

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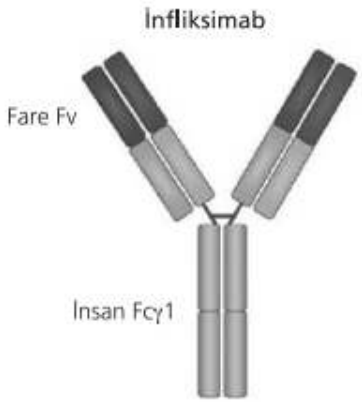
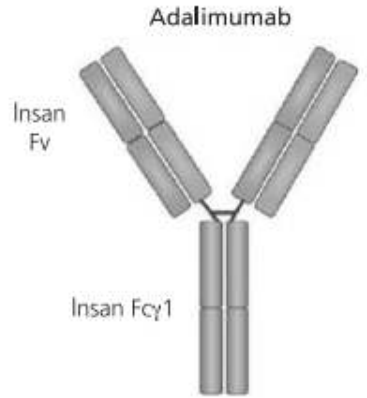
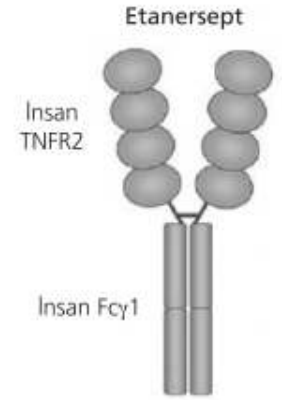
Sağlık Bilimleri Üniversitesi
Fatih Sultan Mehmet Eğitim ve Araştırma Hastanesi
Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji
28.03.2021

Biyolojik ajanlar

- Hastalık gelişim sürecinde rol alan immün veya genetik mediyatörleri özgün olarak hedef alan ilaçlar
- Üretimleri için yüksek teknoloji gerekir
- Maliyetleri oldukça fazla







Biyolojik ajanların kullanıldığı hastalıklar

- Romatizmal hastalıklar
- Maligniteler
- İnflamatuar barsak hastalıkları
- Psöriazis
- Organ nakli
- Multiple skleroz
- Şiddetli astım
- ….

Biyolojik ajanlar nelerdir?

Sitokin fonksiyonunu bozarak
T hücre aktivasyonu için gerekli sinyalleri bloke ederek
B hücre düzeyini azaltarak

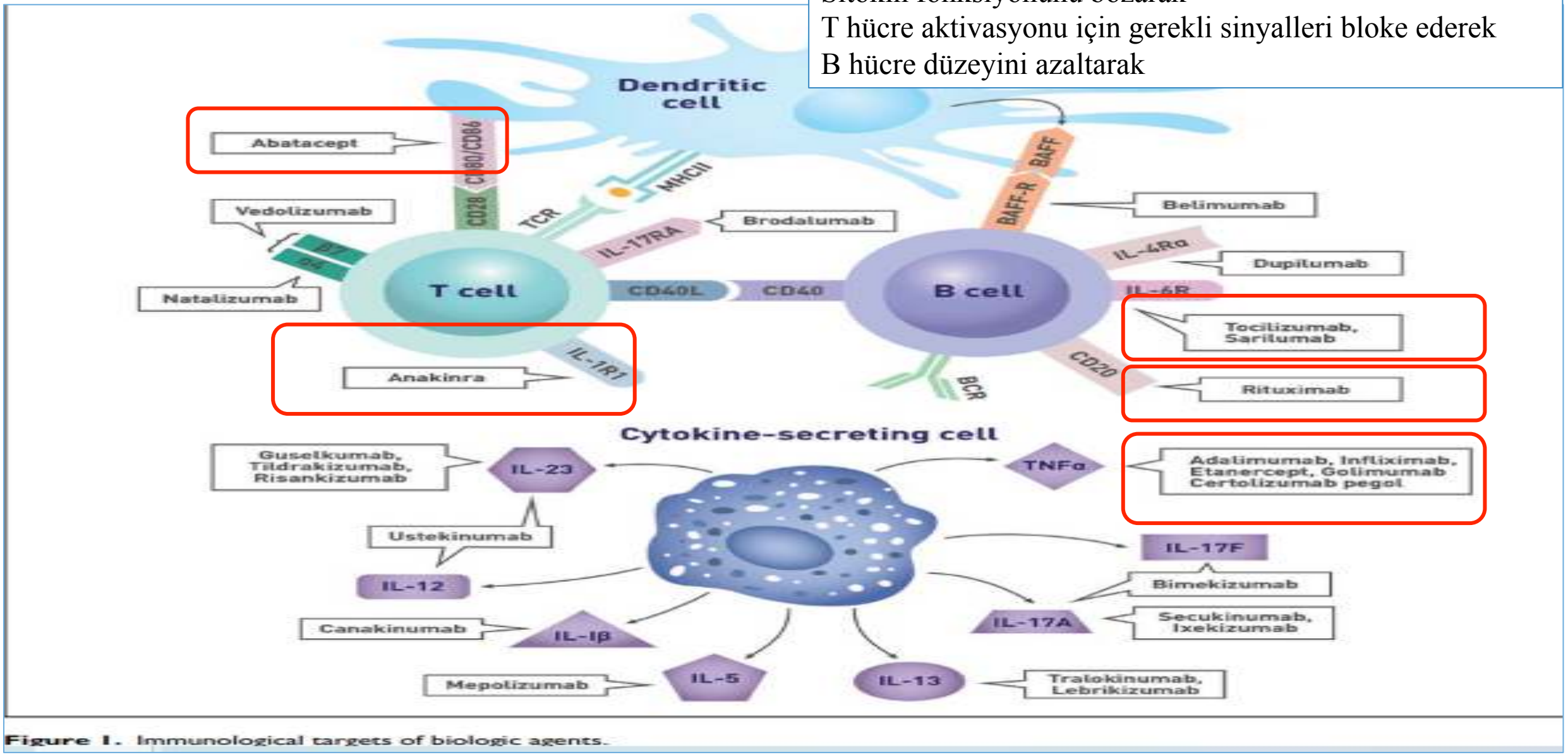


Figure 1. Immunological targets of biologic agents.

Kim A. Papp et al. Journal of Cutaneous Medicine and Surgery 2019, Vol. 23(1) 50–74

Biyolojik ajanların isimlendirilmesi

-**sept** bir ligandın reseptöre bağlanmasını engeller

-**mumab** tamamen insan monoklonal antikor

-zumab insanlaştırılmış monoklonal antikor

-ksimab kimerik monoklonal antikor

–ra reseptör antagonisti

Biyolojik ajanlar

- Biyolojik ajan kullanan hastalarda, enfeksiyon riski genel populasyona göre daha yüksek ve enfeksiyonlar daha şiddetli seyreder
- Sağlıklı bireylere göre enfeksiyon nedeniyle hastaneye yatış daha sık

Doran MF, et al. Arthritis Rheum. 2002;46:2287–93. 29
Kinder A, et al. Postgrad Med J. 2004;80:26.

❖Biyolojik ajan kullanan hastalarda gelişen enfeksiyonların bir çoğu aşı ile engellenebilir

Biyolojik ajan kullanılması planlanan hastalarda

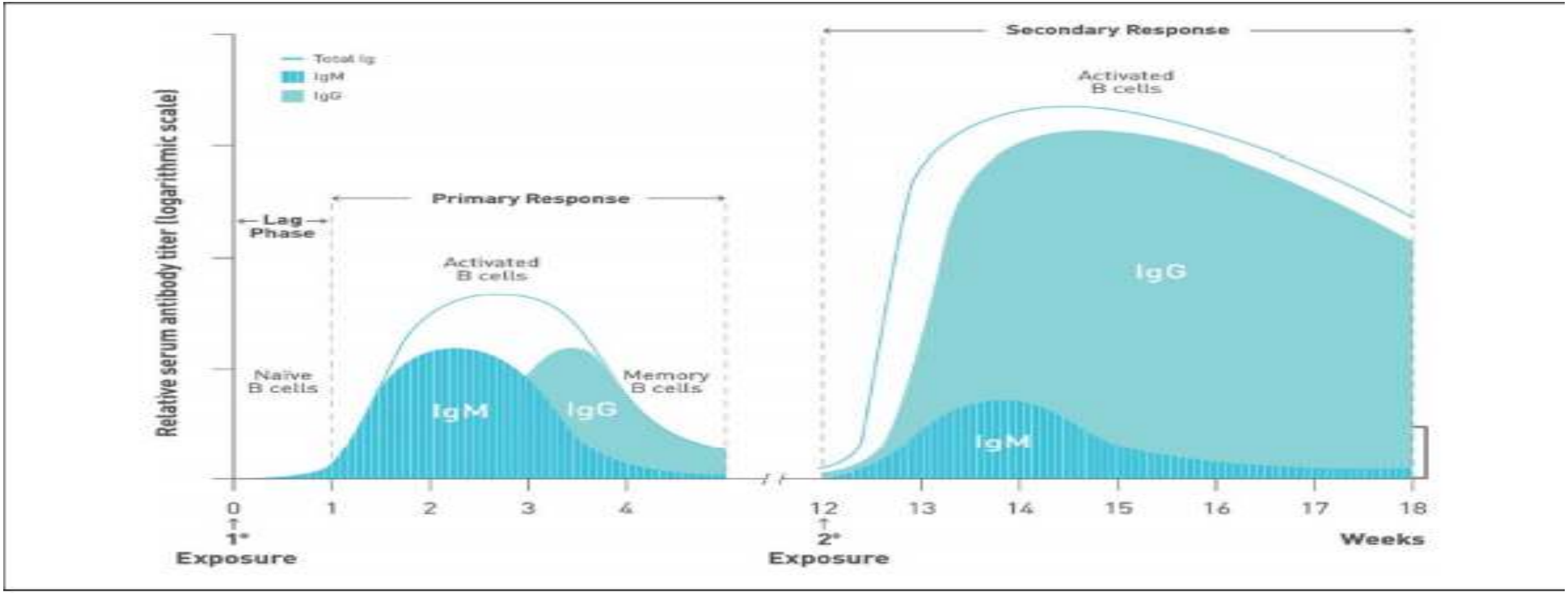
- Hasta ile ilk karşılaşmada aşılanma öyküsü alınmalı
- Aşılama için gereken serolojik testler istenmeli
- **Eksik aşılar tamamlanmalı**

Aşılar biyolojik ajandan ne kadar süre önce yapılmalı ?

İnaktif aşılar?

Canlı aşılar ?

Aşıdan sonra antikor yanıtı



İnaktif aşılar, immun yanıtın gelişmesini sağlamak için tedavi başlamadan 2 hafta önce

Kim A. Papp et al. Journal of Cutaneous Medicine and Surgery 2019, Vol. 23(1) 50–74

Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Review article | Published 28 July 2015, doi:10.4414/smw.2015.14159

Cite this as: Swiss Med Wkly. 2015;145:w14159

Vaccination recommendations for adult patients with autoimmune inflammatory rheumatic diseases

Canlı aşılar yapıldıktan sonra immunosupresif tedavi için en az 4 hafta geçmesi gerekli

Table 6. Length of Viremia Following Vaccination With Live Attenuated Vaccines.

Vaccine	Length of Viremia
Varicella (Oka strain)	The vaccine strain could not be isolated up to 14 days postvaccination in children,[225] but 1 study detected the vaccine strain by PCR up to 5 weeks after immunization in 5 of 166 (3%) asymptomatic children given the varicella vaccine.[226]
Herpes zoster (Oka strain)	Varicella zoster virus DNA can be detected by PCR analysis in 16% (11/67) of individuals 2 weeks postvaccination[227] and up to 4 weeks in 6% (2/36) of individuals >60 years old.[71]
Yellow fever	Viremia after primary immunization wanes within 7 days postimmunization[228] and is generally cleared within 2 weeks of vaccination.[229]
Measles	The vaccine strain has not been isolated from human blood after immunization of healthy children,[230] but a study on macaques has shown the persistence of the Schwarz vaccine strain 7 to 9 days postvaccination.[231]
Mumps	There is a low risk of viremia with the mumps vaccine strains; however, the incidence of aseptic meningitis occurring 2 to 3 weeks after vaccination suggests that the potential is maintained in some vaccine strains
Rubella	Viremia was documented 7 to 21 days postvaccination in some adults receiving the primary vaccination but not in children.[233]
Live polio (type 2 Sabin)	In adults, free virus is present in the serum between 2 and 5 days after vaccine administration, with antibody-bound virus being present up to 8 days after vaccination.[234] In children aged ≤17 months, free virus can be detected up to 8 days after vaccination.[235]

Canlı aşılar yapıldıktan sonraki viremi döneminde biyolojik ajanlar riskli

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Biyolojik ajanların yarılanma süreleri

Table 4. Pharmacokinetic Half-Lives of Biologic Agents.

Family	Biologic	Isotype	Target	Half-Life	Status
TNF inhibitors	Adalimumab	human IgG1	TNFα	10-20 days[184]	Approved
	Etanercept	IgG1 Fc domain + TNF receptor extracellular ligand-binding domain	TNFα, LTα (TNFβ)	4.2 days[185]	Approved
	Certolizumab pegol	Humanized Fab' conjugated to polyethylene glycol	TNFα	14 days[186]	Approved
	Golimumab	Human IgG1κ	TNFα	11-12 days[187]	Approved
	Infliximab	Chimeric IgG1κ	TNFα	7.7-14.7 days[188]	Approved
Interleukin inhibitors	Dupilumab	Human IgG4	IL-4Rα	NA[189,a]	Approved
	Mepolizumab	Humanized IgG1κ	IL-5	16-22 days[190]	Approved
	Tocilizumab	Humanized IgG1κ	IL-6R	11-13 days[191]	Approved
	Sarilumab	Human IgG1	sIL-6Rα, mIL-6Rα	Initial: 8-10 days Terminal: 2-4 days[192]	Approved
	Anakinra	IL-1 receptor antagonist	IL-1R1	4-6 hours[193]	Approved
	Canakinumab	Human IgG1κ	IL-1β	26 days[194]	Approved
	Tralokinumab	Human IgG4	IL-13	17.7 days[195]	In development
	Lebrikizumab	Humanized IgG4	IL-13	25 days[196]	In development
	Secukinumab	Human IgG1κ	IL-17A	27 days[197]	Approved
	Ixekizumab	Humanized IgG4	IL-17A	13 days[198]	Approved
	Bimekizumab	Humanized IgG1	IL-17A, IL-17F	17-22 days[199]	In development
	Brodalumab	Human IgG2κ	IL-17RA	NA[200,b]	Approved
	Ustekinumab	Human IgG1	IL-12, IL-23	15-32 days[201]	Approved
	Guselkumab	Human IgG1λ	IL-23	15-18 days[202]	Approved
	Risankizumab	Human IgG1	IL-23	20-28 days[203]	In development
	Tildrakizumab	Humanized IgG1κ	IL-23	24.5 days[204]	In development
	Nemolizumab	Humanized IgG2	IL-31RA	12.6-16.5 days[205]	In development
B-cell inhibitor	Rituximab	Chimeric IgG1κ	CD20	20.8 days[59]	Approved
	Belimumab	Human IgG1λ	BAFF (BLyS)	12.3-19.4 days[206]	Approved
Integrin blockers	Vedolizumab	Humanized IgG1	α4β7	25 days[207]	Approved
	Natalizumab	Humanized IgG4κ	α4	9.6-11.1 days[208]	Approved
Costimulatory modulator	Abatacept	CTLA-4 extracellular domain + modified IgG1 Fc domain	CD80, CD86	13.1-16.7 days[209]	Approved

- İnfluenza aşısı, rituksimab tedavisinden 6-10 ay sonra ve
- 4-8 hafta sonra sonra yapılanlar değerlendirilmiş

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İlaçların canlı aşıdan önce kesilmesi ve canlı aşı yapıldıktan sonra ilaçların başlanması için gereken süreler

	Aşıdan önce kesilmesi gereken zaman	Aşı yapıldıktan sonra başlanması için geçmesi gereken zaman
Glukokortikoid tedavi ≥20 mg/gün, ≥14 gün	1 ay	2-4 hafta
Glukokortikoid bolus tedavi	3 ay	2-4 hafta
Metotreksat ≥0.4 mg/kg/hafta	3 ay	2-4 hafta
Leflunomid	6-12 ay	2-4 hafta
Etanersept	2-12 hafta	3 hafta
Adalimumab	10-12 hafta	3 hafta
Certolizumab	10-12 hafta	3 hafta
Golimumab	8-12 hafta	3 hafta
İnfliksimab	6-12 hafta	3 hafta
Abatasept	10-12 hafta	3 hafta
Tokilizumab	10-12 hafta	3 hafta
Ustekinumab	12-15 hafta	2 hafta
Anakinra	2 gün-3 ay	3 hafta
Kanakinumab	3 ay	3 hafta
Rituksimab	6 ay	1 ay
Belimumab	3 ay	1 ay

EKMUD, Erişkin Bağışıklama Rehberi, 2019

- İnaktif aşılar eğer tedavi başlanmışsa hastalığın aktivitesinin ve immunosupresif tedavi etkinliğinin en düşük olduğu dönemde yapılmalı

Tanrıover MD, et al. Eur J Rhematol 2016;3(1):29-35.

Tablo 12. Romatolojik hastalığı olan erişkinlerde aşılama şeması

Aşı	18-64 yaş	65 ≥ yaş
İnfluenza	Yılda 1 doz aşı	
Pnömokok [1,2]	1-2 doz aşı	1-2 doz aşı
Tetanoz, difteri (Td) [3]	Her 10 yılda bir rapel doz aşı	
Hepatit B	3 doz aşı (0,1,6. aylar) (biyolojik ajan veya orta-yüksek doz kortikosteroid alan yüksek riskli hastalarda seroloji durumuna göre yüksek doz aşı 0,1,2 ve 6. aylarda çift doz- uygulanabilir)	
Hepatit A	2 doz aşı (0,6. aylar)	
Suçiçeği/Herpes zoster [4]	*İmmünsupresyonu olan hastalarda ve gebelerde kontrendike- özel durumlarda uzman görüşü alınarak aşı uygulanabilir.	
Kızamık, kızamıkçık, kabakulak (KKK) [4]	*İmmünsupresyonu olan hastalarda ve gebelerde kontrendike- özel durumlarda uzman görüşü alınarak aşı uygulanabilir	
Meningokok (kuadrivalan konjuge meningokok aşısı) [2]	*En az 2 ay arayla 2 doz aşı. Risk devam ediyorsa 5 yılda bir tekrarlanabilir.	
***Haemophilus influenzae* tip B** [2]	*1 doz	
Human papillomavirüs (HPV) [5]	2 veya 3 doz	

EKMUD, Erişkin Bağışıklama Rehberi, 2019

Pnömokok enfeksiyonları

Table 1 Potential respiratory pathogens according to immune defect

Immune defect	Potential respiratory pathogens
Neutropenia/impaired neutrophil chemotaxis	Gram positive bacteria (e.g., *Staphylococcus aureus*, *Streptococcus pneumoniae*, Nocardia species)
	Gram negative bacteria (e.g., *Klebsiella pneumoniae*)
	Fungi (e.g., Aspergillus species, Candida species)
T-cell mediated immunity	Herpesviruses (e.g., herpes simplex virus, Cytomegalovirus)
	Respiratory viruses (e.g., influenza)
	Fungi (e.g., *Pneumocystis jirovecii*, *Histoplasma capsulatum*, *Cryptococcus neoformans*)
	Mycobacteria
	Nocardia species
	Legionella pneumophila
B-cell mediated immunity	Encapsulated bacteria (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*)

Özellikle TNF-alfa inhibitörleri, rituksimab, ekulizumab kullanan hastalarda *S. pneumonia*'ya bağlı enfeksiyon riskinde artış

Ricardo J. José, Maria Mouyis. Ann Res Hosp 2017;1:40

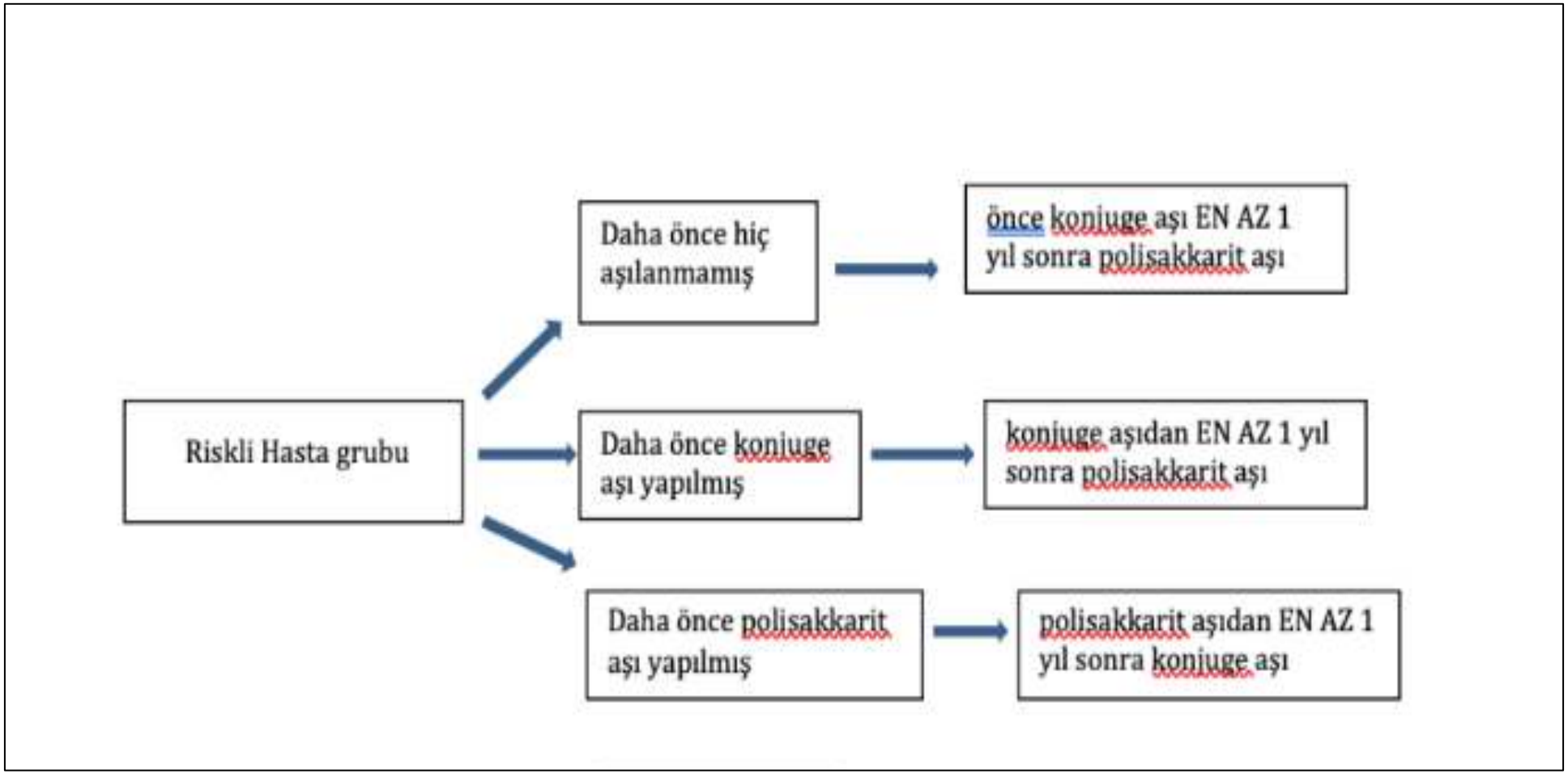
Pnömokok aşısı

TABLE 1. Recommendations for 13-valent pneumococcal conjugate vaccine (PCV13) and 23-valent pneumococcal polysaccharide vaccine (PPSV23) among adults aged ≥19 years

Medical indication group	Specific underlying medical condition	PCV13 for persons aged ≥19 years	PPSV23* for persons aged 19–64 years	PCV13 for persons aged ≥65 years	PPSV23 for persons aged ≥65 years
None	None of the below	No recommendation	No recommendation	Based on shared clinical decision-making†	1 dose; if PCV13 has been given, then give PPSV23 ≥1 year after PCV13
Immunocompetent persons	Alcoholism Chronic heart disease§ Chronic liver disease Chronic lung disease¶ Cigarette smoking Diabetes mellitus	No recommendation	1 dose	Based on shared clinical decision-making†	1 dose; if PCV13 has been given, then give PPSV23 ≥1 year after PCV13 and ≥5 years after any PPSV23 at age <65 years
	Cochlear implant CSF leak	1 dose	1 dose ≥8 weeks after PCV13	1 dose if no previous PCV13 vaccination	1 dose ≥8 weeks after PCV13 and ≥5 years after any PPSV23 at <65 years
Immunocompromised persons	Congenital or acquired asplenia Sickle cell disease/other hemoglobinopathies Chronic renal failure Congenital or acquired immunodeficiencies** Generalized malignancy HIV infection Hodgkin disease Iatrogenic immunosuppression†† Leukemia Lymphoma Multiple myeloma Nephrotic syndrome Solid organ transplant	1 dose	2 doses, 1st dose ≥8 weeks after PCV13 and 2nd dose ≥5 years after first PPSV23 dose	1 dose if no previous PCV13 vaccination	1 dose ≥8 weeks after PCV13 and ≥5 years after any PPSV23 at <65 years

- **1 doz PCV13 8 hafta sonra PPSV23, PPSV23'den en az 5 yıl sonra PPSV23**
- **65 yaş altında PPSV23 yapılan hastalarda, en az 5 yıl sonra PPSV23**
- **65 yaş üzerinde sadece 1 doz PPSV23**

https://www.cdc.gov/mmwr/volumes/68/wr/pdfs/mm6846a5-H.pdf



Pnömokok aşılama algoritması

EKMUD, Erişkin Bağışıklama Rehberi, 2019

Effect of immunosuppressive agents on vaccine immunogenicity

	Methotrexate	TNF-alpha inhibitors	Anti-CD20 antibodies (eg, rituximab)	CTLA-4 inhibitors (eg, abatacept)	Janus kinase inhibitors (eg, tofacitinib)	Anti-IL-6 antibodies (eg, tocilizumab)
Pneumococcal vaccine	Decrease	Minimal effect	Substantial decrease	Decrease	Decrease	Minimal effect
Seasonal influenza vaccine	Probable decrease	Minimal effect	Substantial decrease	Decrease	Minimal effect	Minimal effect
Hepatitis B virus vaccine	Unknown	Decrease	Unknown	Unknown	Unknown	Unknown

TABLE 1 Clinical characteristics of four patients with features of BD who developed severe inflammation after receiving 23-valent pneumococcal vaccination

Age, years/ gender	Origin	Clinical presentation of BD	Disease duration, years	HLA allele	Pathergy testing	BD treatment at vaccination	Symptoms after vaccination
32/male	Swiss	Recurrent aphthous oral ulcers, genital ulcers, pseudofolliculitis, erythema nodosum, arthralgia, thrombophlebitis, cerebral venous thrombosis, retinochoroiditis	11	B51+	ND	Abatacept, prednisolone (20 mg)	Day 1: ipsilateral axillar pain, redness, calor and tenderness at the injection site Day 2: fever (40.0°C), chills, nausea and vomiting, CRP 385 mg/l Day 3: pseudofolliculitis at injection site (supplementary figure)
41/male	Turkish	Recurrent aphthous oral ulcers, genital ulcers, arthritis, erythema nodosum, pseudofolliculitis	6	ND	Negative	Etanercept	Day 1: local pain, calor, redness and swelling, fever (38.9°C), CRP 223 mg/l, headache, shivering, dyspnoea
41/female	Turkish	Recurrent aphthous oral ulcers, oligoarthritis	6	B51+	Negative	Ibuprofen	Day 1: local pain, calor and swelling at injection site after 1 h
46/male	Turkish	Recurrent aphthous oral ulcers, pseudofolliculitis, thrombophlebitis, uveitis	15	B51+	Negative	AZA	Day 1: local pain, calor, swelling, fever (40°C), asthenia, CRP 158 mg/l

❖ Polisakkarit pnömokok aşısı Behçet hastalarında inflamasyonu tetikleyebilir

Hügle T et al. Rheumatology (Oxford) 2012 Apr;51(4):761-2.

Table 2. Safety and Efficacy of Vaccination in Patients on Biologic Agents.

Vaccine	Biologic Agent	Patient Population	Efficacy	Safety
Pneumococcal (polysaccharide or conjugate)	Abatacept	RA	Results are variable but may reduce humoral response to the polysaccharide and conjugate vaccines[137,148,149]	Well tolerated[137,148,149]
	Adalimumab	RA	No significant effect on the immunogenicity of the polysaccharide vaccine[138]	Well tolerated[138]
	Certolizumab pegol	RA	No significant effect on the pneumococcal polysaccharide vaccine[45]	Well tolerated[45]
	Etanercept	RA	May reduce humoral response to the conjugate vaccine[150]	Well tolerated[150]
	Infliximab	RA	No significant effect on immunogenicity of the polysaccharide vaccine[151]	NA
		IBD	Reduced humoral response to the polysaccharide vaccine[27]	Well tolerated[27]
	Golimumab	RA	Reduced fold-increase in vaccine-specific IgG titres in response to the polysaccharide vaccine but maintained opsonophagocytic function[152]	Well tolerated[152]
	Rituximab	RA	Diminished humoral response to the polysaccharide and conjugate vaccines[37,148,153]	Well tolerated[148,153]
	Tocilizumab	RA	No significant effect on the immunogenicity of the polysaccharide or conjugate vaccines[51,144,148,154]	Well tolerated[51,144,148,154]
	TNFi (pooled)	RA, SpA	No significant effect on the immunogenicity of the polysaccharide and conjugate vaccines[22,37,47]	Well tolerated, but some patients treated with methotrexate or TNFi reported a transient worsening of joint pain 1 week after vaccination[23]
		IBD	Diminished humoral response to the polysaccharide and conjugate vaccines[18,25,27,30]	Well tolerated[25,27]
	Ustekinumab	PsO	No significant effect on the immunogenicity of the polysaccharide vaccine[155]	Higher incidence of mild injection site reactions in ustekinumab-treated patients but otherwise well tolerated[155]

- Pnömokok aşısı güvenilir, iyi tolere edilir
- Bazı çalışmalarda bildirilen aktivasyonlar ise geçici ve kendiliğinden düzelmiş

Kim A. Papp et al. Journal of Cutaneous Medicine and Surgery 2019, Vol. 23(1) 50–74

İnfluenza enfeksiyonları

Table 1. Influenza associated with anti-tumor necrosis factor therapy reported to the US Food and Drug Administration 2004—2008.

		IBD	Psoriasis/Psoriatic arthropathy	Rheumatoid arthritis	Spondyloarthropathy	Other indication
		$n=60$	$n=162$	$n=407$	$n=31$	$n=54$
Etanercept	Monotherapy		116	108	17	15
	+IM*	—	9	61	6	7
($n=345$)	+CS	—	—	2	—	—
	+IM + CS	—	—	4	—	—
Adalimumab	Monotherapy	30	28	79	5	21
	+IM*	5	1	46	1	5
($n=305$)	+CS	6	2	34	—	—
	+IM + CS	1	—	41	—	—
Infliximab	Monotherapy	10	4	6	1	3
	+IM*	1	1	5	1	1
($n=60$)	+CS	3	—	7	—	—
	+IM + CS	4	—	11	—	2
Combined anti–TNF	Monotherapy	—	—	1	—	—
	+IM*	—	1	1	—	—
($n=4$)	+CS	—	—	1	—	—
	+IM + CS	—	—	—	—	—

TNF, tumor necrosis factor; IBD, inflammatory bowel disease; IM, immunomodulators; CS, corticosteroids. Immunomodulators include methotrexate, azathioprine, 6-mercaptopurine, leflunomide.
*Immunomodulator was methotrexate in 80% of cases.

Akciğerdeki viral replikasyon TNF-alfa ile inhibe edilir.

Matt Shale et al. Therap Adv Gastroenterol. 2010 May;3(3):173-7.

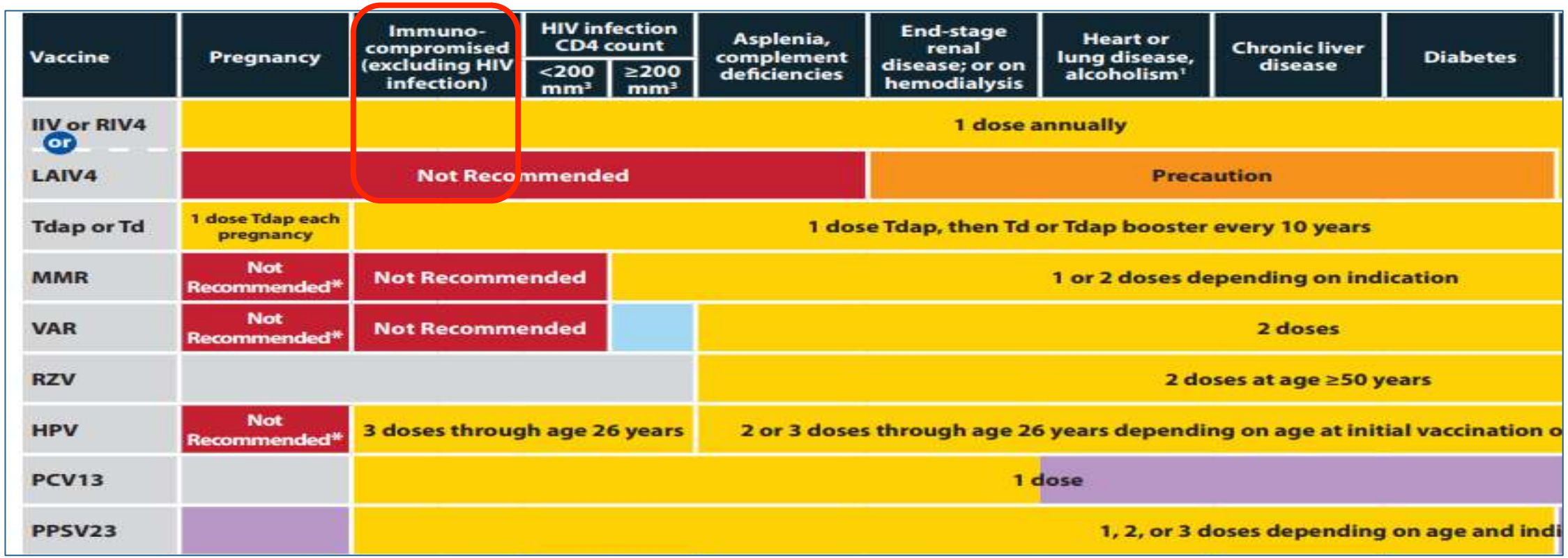
İnfluenza aşıları

TABLE 1. Influenza vaccines — United States, 2020–21 influenza season*

Trade name (Manufacturer)	Presentation	Age indication	HA (IIVs and RIV4) or virus count (LAIV4) for each vaccine virus (per dose)	Route	Mercury (from thimerosal) µg/0.5 mL
IIV4					
Standard dose, egg based†					
Afluria Quadrivalent (Seqirus)	0.25-mL PFS§	6 through 35 mos	7.5 µg/0.25 mL	IM¶	—
	0.5-mL PFS	≥3 yrs	15 µg/0.5 mL		—
	5.0-mL MDV§	≥6 mos (needle/syringe) 18 through 64 yrs (jet injector)			24.5
Fluarix Quadrivalent (GlaxoSmithKline)	0.5-mL PFS	≥6 mos	15 µg/0.5 mL	IM¶	—
FluLaval Quadrivalent (GlaxoSmithKline)	0.5-mL PFS	≥6 mos	15 µg/0.5 mL	IM¶	—
Fluzone Quadrivalent (Sanofi Pasteur)	0.5-mL PFS**	≥6 mos	15 µg/0.5 mL	IM¶	—
	0.5-mL SDV	≥6 mos			—
	5.0-mL MDV	≥6 mos			25
Standard dose, cell culture based (ccIIV4)					
Flucelvax Quadrivalent (Seqirus)	0.5-mL PFS	≥4 yrs	15 µg/0.5 mL	IM¶	—
	5.0-mL MDV	≥4 yrs			25
High dose, egg based† (HD-IIV4)					
Fluzone High-Dose Quadrivalent (Sanofi Pasteur)	0.7-mL PFS	≥65 yrs	60 µg/0.7 mL	IM¶	—
Standard dose, egg based† with MF59 adjuvant (aIIV4)					
Fluad Quadrivalent (Seqirus)	0.5-mL PFS	≥65 yrs	15 µg/0.5 mL	IM¶	—
IIV3					
Standard dose, egg based† with MF59 adjuvant (aIIV3)					
Fluad (Seqirus)	0.5-mL PFS	≥65 yrs	15 µg/0.5 mL	IM¶	—
RIV4					
Recombinant HA					
Flublok Quadrivalent (Sanofi Pasteur)	0.5-mL PFS	≥18 yrs	45 µg/0.5 mL	IM¶	—
LAIV4					
Egg based†					
FluMist Quadrivalent (AstraZeneca)	0.2-mL prefilled single-use intranasal sprayer	2 through 49 yrs	$10^{6.5-7.5}$ fluorescent focus units/0.2 mL	NAS	—

https://www.cdc.gov/mmwr/volumes/69/rr/pdfs/rr6908a1-H.pdf

İnfluenza aşısı



Vaccine	Pregnancy	Immuno-compromised (excluding HIV infection)	HIV infection CD4 count		Asplenia, complement deficiencies	End-stage renal disease; or on hemodialysis	Heart or lung disease, alcoholism[1]	Chronic liver disease	Diabetes
			<200 mm³	≥200 mm³					
IIV or RIV4	1 dose annually								
or									
LAIV4	Not Recommended					Precaution			
Tdap or Td	1 dose Tdap each pregnancy	1 dose Tdap, then Td or Tdap booster every 10 years							
MMR	Not Recommended*	Not Recommended	1 or 2 doses depending on indication						
VAR	Not Recommended*	Not Recommended			2 doses				
RZV					2 doses at age ≥50 years				
HPV	Not Recommended*	3 doses through age 26 years			2 or 3 doses through age 26 years depending on age at initial vaccination o				
PCV13		1 dose							
PPSV23		1, 2, or 3 doses depending on age and indi							

Table 2. Safety and Efficacy of Vaccination in Patients on Biologic Agents.

Vaccine	Biologic Agent	Patient Population	Efficacy	Safety
Influenza	Abatacept	RA	Results are variable but may reduce humoral response to the vaccine[136,137]	Well tolerated[136,137]
	Adalimumab	RA	No significant effect[138]	Well tolerated[138]
	Belimumab	SLE	Lower fold-increase in titres for some influenza strains compared with controls[139]	NA
	Certolizumab pegol	RA	No significant effect[45]	Well tolerated[45]
	Infliximab	RA	No significant effect[140]	Well tolerated and did not exacerbate disease activity[140]
		IBD	Diminished humoral response[141,142]	Well tolerated, without incidence of serious adverse events[141,142]
	Rituximab	RA	Cellular responses maintained but diminished humoral response to the vaccine[33-36]	Well tolerated[33-34]
	Secukinumab	Healthy individuals	No significant effect among individuals who received a single secukinumab dose[143]	Well tolerated[143]
	Tocilizumab	RA	No significant effect[43,144]	Well tolerated and did not result in exacerbatio of disease activity[42,144]

- ❖ Hastalık aktivitesini artırmaz, ciddi yan etki belirlenmemiş
- ❖ Aşının etkinliği azalabilir

Kim A. Papp et al. Journal of Cutaneous Medicine and Surgery 2019, Vol. 23(1) 50–74

2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host

Lorry G. Rubin,[1] Myron J. Levin,[2] Per Ljungman,[3,4] E. Graham Davies,[5] Robin Avery,[6] Marcie Tomblyn,[7] Athos Bousvaros,[8] Shireesha Dhanireddy,[9] Lillian Sung,[10] Harry Keyserling,[11] and Insoo Kang[12]

- İmmunosuprese hastanın yakın çevresindekiler, **canlı influenza** aşısı yaptırmamalı
- Aşı yapılmış ise aşıdan sonraki 7 gün hasta ile temas etmemeli

Clinical Infectious Diseases

IDSA GUIDELINE

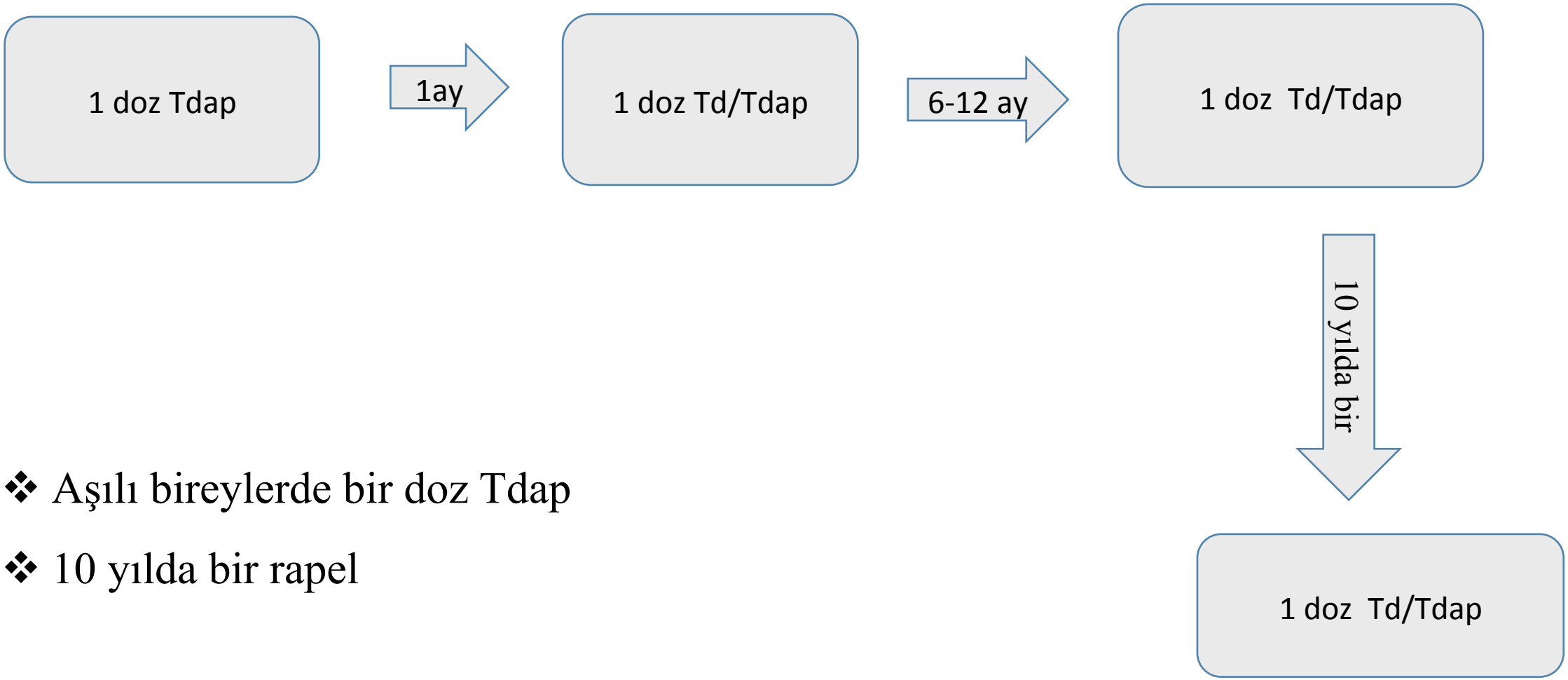
Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza[a]

Biyolojik ajan kullanan kişi influenzalı hasta ile yakın temas etmişse

48 saat içinde antiviral profilaksi başlanmalı

(Oseltamivir 75 mg/gün)

Tetanoz-Difteri (Td) aşısı



- Aşılı bireylerde bir doz Tdap
- 10 yılda bir rapel

Biyolojik ajan kullanan hastalarda tetanoz aşısının güvenirliği ve etkinliği

Table 2. Safety and Efficacy of Vaccination in Patients on Biologic Agents.

Vaccine	Biologic Agent	Patient Population	Efficacy	Safety
Tetanus	Abatacept	Type I diabetes	Achieved protective titres but diminished the magnitude of recall humoral response compared to controls[156]	NA
	Rituximab	RA	Recall response not significantly affected[153]	Well tolerated[153]
	Tocilizumab	RA	No significant effect on recall humoral response to tetanus toxoid[154]	Well tolerated[154]
	Ustekinumab	PsO	No significant difference[155]	Higher incidence of mild injection site reactions but otherwise well tolerated[155]
	TNFi (pooled)	IBD	TNFi monotherapy had no significant effect on the immunogenicity of booster vaccination[157]	Well tolerated, without incidence of disease flares[157]

Kim A. Papp et al. Journal of Cutaneous Medicine and Surgery 2019, Vol. 23(1) 50–74

Hepatit A virüs enfeksiyonu

Hepatitis A-Associated Macrophage Activation Syndrome in Children with Systemic Juvenile Idiopathic Arthritis: Report of 2 Cases

RICARDO A.G. RUSSO, SERGIO D. ROSENZWEIG, and MARÍA M. KATSICAS

ABSTRACT. We describe two 3-year-old patients with systemic juvenile idiopathic arthritis (SJIA) who developed hepatitis A-associated macrophage activation syndrome (MAS). One patient showed MAS as the presenting manifestation of SJIA, while MAS complicated SJIA during the second year of the disease course in the other child. Both girls presented with fever, jaundice, hepatosplenomegaly, neurological involvement, mucosal hemorrhage, and purpura. Cytopenias, hypofibrinogenemia, and hemophagocytosis confirmed the diagnosis. After aggressive treatment with high-dose corticosteroids and immunosuppressants one patient entered remission while the other one died. Hepatitis A virus may induce severe MAS in SJIA. (First Release Nov 15 2007; J Rheumatol 2008;35:166–8)

The Journal of Rheumatology 2008; 35:1

Hepatit A aşısı

Table 2. Safety and Efficacy of Vaccination in Patients on Biologic Agents.

Vaccine	Biologic Agent	Patient Population	Efficacy	Safety
Hepatitis A	TNFi (pooled)	RA	Diminished humoral response compared to healthy individuals, but 86% of patients achieved seroprotection with 2 vaccine doses[132]	Well tolerated and did not result in exacerbation of disease activity[132]

- 2 doz aşı ile aşı yanıtı biyolojik ajan kullananlarda sağlıklı bireylere göre daha düşük
- İyi tolere edilir, hastalık aktivitesini artırmaz

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Hepatit B virüsünün alevlenme riski

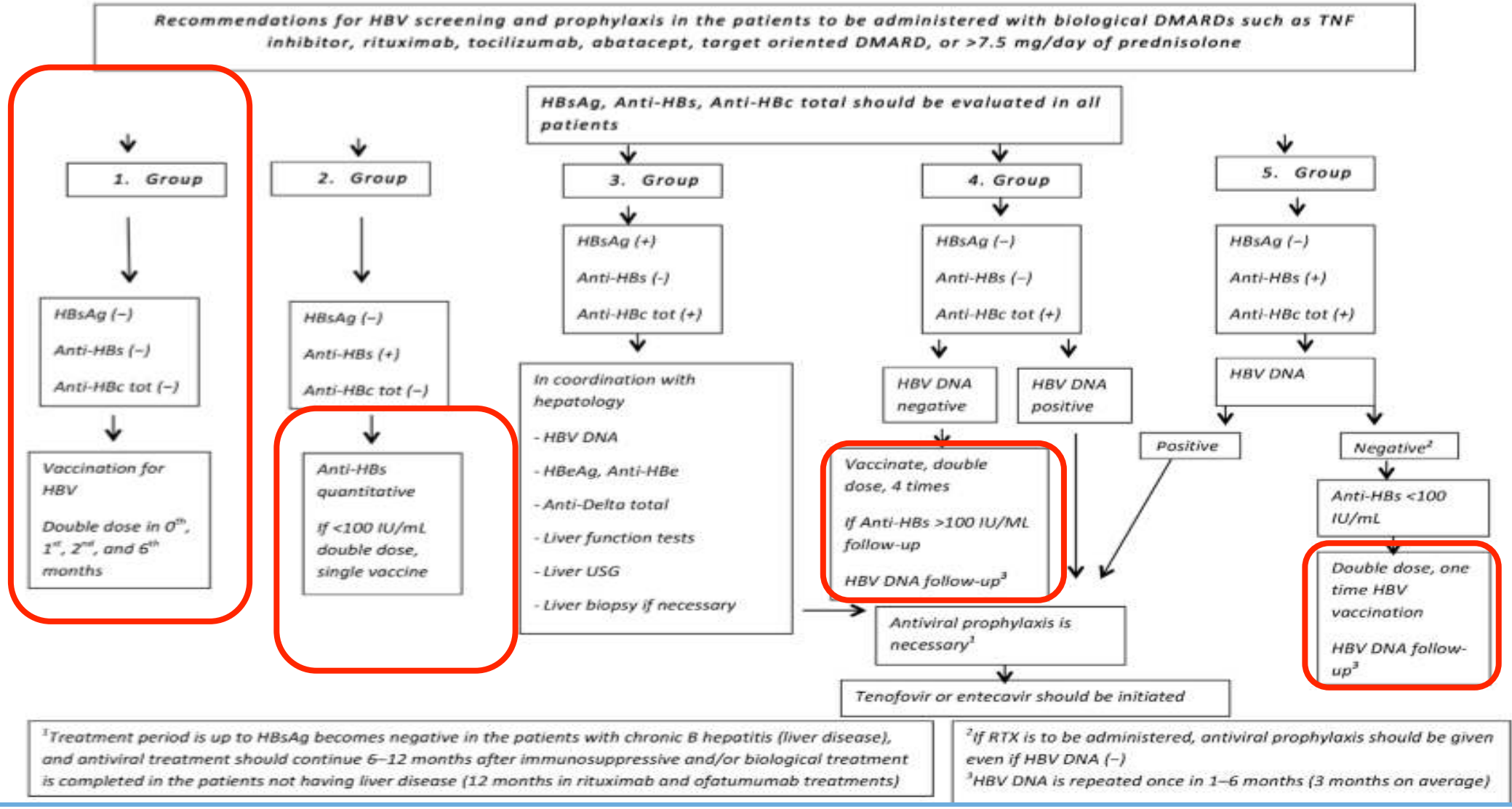
Risk group and HBV serology	Immunosuppressive or chemotherapy
High-risk group (> 10%)	
HBsAg positive OR HBsAg negative and anti-HBc positive (high risk regardless of anti-HBs titre levels)	B-cell-depleting agents such as rituximab and ofatumumab
HBsAg positive	Anthracycline derivatives such as doxorubicin and epirubicin Corticosteroid therapy for ≥4 weeks (prednisone equivalent > 10–20 mg/day)
Moderate-risk group (1%–10%)	
HBsAg positive OR HBsAg negative and anti-HBc positive (may be lower risk and monitoring may be sufficient if high anti-HBs titres > 100 IU/L)	TNF-α inhibitors: etanercept, adalimumab, certolizumab, certolizumab, infliximab Other cytokine inhibitors and integrin inhibitors: abatacept, ustekinumab, natalizumab, vedolizumab Tyrosine kinase inhibitors: imatinib, nilotinib, ibrutinib
HBsAg positive	Corticosteroid therapy for ≥ 4 wk (prednisone equivalent < 10 mg/day)
HBsAg negative and anti-HBc positive (may be lower risk and monitoring may be sufficient if high anti-HBs titres > 100 IU/L)	Corticosteroid therapy for ≥4 weeks (prednisone equivalent > 10–20 mg/day) Anthracycline derivatives: doxorubicin and epirubicin
Low-risk group (< 1%)	
HBsAg positive OR HBsAg negative and anti-HBc positive (low risk especially if high anti-HBs titres > 100 IU/L)	Traditional immunosuppressive agents: azathioprine, 6-mercaptopurine, methotrexate Intra-articular corticosteroids Corticosteroid therapy for ≤1 week
HBsAg negative/anti-HBc positive (low risk especially if high anti-HBs titres > 100 IU/L)	Corticosteroid therapy for ≥ 4 wk (prednisone equivalent < 10 mg/day)

İmmunosupresif tedavi altında hepatit B alevlenebilir

Clinical Practice Guidelines Committee. Canadian Liver Journal 1.4, 2018

Hepatit B aşısı

	Age group and associated conditions	Recommended schedule ¶
Single-antigen vaccines		
Recombivax HB		
Pediatric/adolescent formulation	18 through 19 years	0, 1, and 6 months Δ
Adult formulation	≥20 years	
Dialysis formulation	≥20 years and receiving dialysis ◊	0, 1, and 6 months
Engerix-B	18 through 19 years	0, 1, and 6 months Δ
	≥20 years	
	≥20 years and receiving hemodialysis ◊	0, 1, 2, and 6 months
Heplisav-B ¥	≥18 years	0 and 1 months
Combination vaccine		
Twinrix (combined HepB-HepA vaccine)	≥18 years	Standard: 0, 1, and 6 months Accelerated: 0, 7, and 21 to 30 days, and 12 months


Recommendations for HBV screening and prophylaxis in the patients to be administered with biological DMARDs such as TNF inhibitor, rituximab, tocilizumab, abatacept, target oriented DMARD, or >7.5 mg/day of prednisolone
HBsAg, Anti-HBs, Anti-HBc total should be evaluated in all patients
1. Group
HBsAg (–)
Anti-HBs (–)
Anti-HBc tot (–)
Vaccination for HBV
Double dose in 0th, 1st, 2nd, and 6th months
2. Group
HBsAg (–)
Anti-HBs (+)
Anti-HBc tot (–)
Anti-HBs quantitative
If <100 IU/mL double dose, single vaccine
3. Group
HBsAg (+)
Anti-HBs (-)
Anti-HBc tot (+)
In coordination with hepatology
- HBV DNA
- HBeAg, Anti-HBe
- Anti-Delta total
- Liver function tests
- Liver USG
- Liver biopsy if necessary
4. Group
HBsAg (–)
Anti-HBs (–)
Anti-HBc tot (+)
HBV DNA negative
HBV DNA positive
Vaccinate, double dose, 4 times
If Anti-HBs >100 IU/ML follow-up
HBV DNA follow-up3
5. Group
HBsAg (–)
Anti-HBs (+)
Anti-HBc tot (+)
HBV DNA
Positive
Negative2
Anti-HBs <100 IU/mL
Double dose, one time HBV vaccination
HBV DNA follow-up3
Antiviral prophylaxis is necessary1
Tenofovir or entecavir should be initiated
1Treatment period is up to HBsAg becomes negative in the patients with chronic B hepatitis (liver disease), and antiviral treatment should continue 6–12 months after immunosuppressive and/or biological treatment is completed in the patients not having liver disease (12 months in rituximab and ofatumumab treatments)
2If RTX is to be administered, antiviral prophylaxis should be given even if HBV DNA (–)
3HBV DNA is repeated once in 1–6 months (3 months on average)

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Review

CMH
http://dx.doi.org/10.3350/cmh.2016.0024
Clinical and Molecular Hepatology 2016;22:219-237

Prevention of Hepatitis B reactivation in the setting of immunosuppression

Venessa Pattullo

34.4%; *P*=0.01).[10] In a study of 29 patients with lymphoma, a threshold anti-HBs titre >100 IU/mL was associated with 0% HBV reactivation, and lower anti-HBs titre was independently associated with HBV reactivation.[11] Cho et al similarly observed 0% HBV reactivation in patients with pre-chemotherapy anti-HBs titres >100 IU/mL, but incidence of HBV reactivation of 8.3% at 6-months and 17.3% at 24 months post-chemotherapy in those with anti-HBs titres below this threshold.[12] In patients receiving hematopoetic stem cell transplantation, the *donor* anti-HBs titre was associated with a decreased risk of HBV reactivation.[13] These findings are yet to be validated. Until then, the presence or titre of anti-HBs cannot be used to assess risk of HBV reactivation, nor guide decisions on the use of antiviral prophylaxis for HBV reactivation.

- Anti-HBc pozitif hastalarda anti-HBs titresi >100 IU/ml olduğunda reaktivasyon gelişme olasılığının daha düşük olduğunu gösteren çalışmalar mevcut
- Ancak, anti-HBc pozitiflerde anti-HBs varlığının veya titresinin HBV reaktivasyonu riskini değerlendirmede kullanılamayacağı

Pattullo V. Clin Mol Hepatol. 2016 Jun;22(2):219-37.

Efficacy and Safety of Hepatitis B Vaccination in Rheumatoid Arthritis Patients Receiving Disease-Modifying Antirheumatic Drugs and/or Biologics Therapy

Samanan Intongkam, MD, Parinya Samakarnthai, MD, Rattapol Pakchotanon, MD, Pongthorn Narongroeknawin, MD, Paijit Assavatanabodee, MD, and Sumapa Chaiamnuay, MD

- 0-1-6. aylarda hepatit B aşılaması
- Hepatit B'ye karşı antikor yanıtı daha düşük
- Hepatit B aşısı RA hastalığını alevlendirmez

Journal of Clinical Rheumatology • Volume 00, Number 00, Month 2018

AP&T Alimentary Pharmacology and Therapeutics

Comparison of the effectiveness of two protocols for vaccination (standard and double dosage) against hepatitis B virus in patients with inflammatory bowel disease

J. P. Gisbert*, L. Menchén†, V. García-Sánchez‡, I. Marín†, J. R. Villagrasa§ & M. Chaparro*

- 148 hastanın katıldığı çalışma, %70 immunosupresif tedavi almış (Bunların yaklaşık %50'si de TNF inhibitörü kullanmış)
- 0-1 ve 6. aylarda aşılama
- Çift doz aşılama ile yanıt %75, tek doz aşılama ile %41

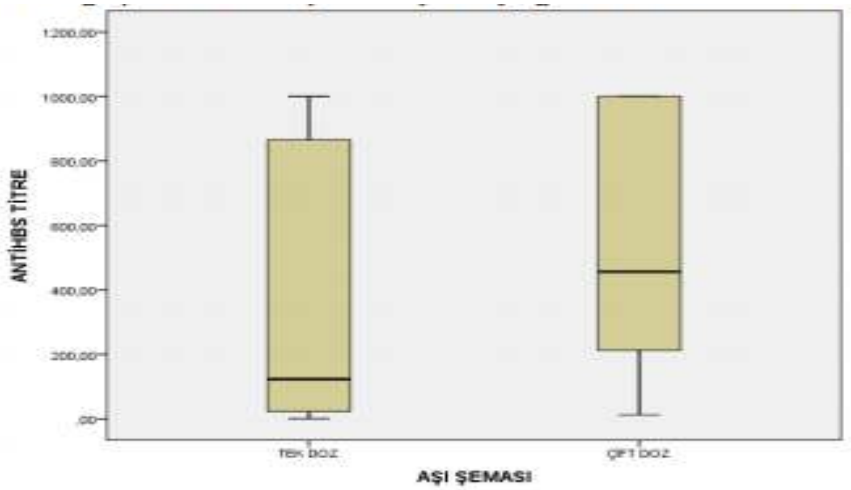
HEPATİT B AŞILAMA SONUÇLARI
İMMÜNSÜPRESİF HASTALARDA TEK DOZ MU? ÇİFT DOZ MU?

Hepatitis B Vaccination Results

Which dose is Sufficient for Immunosuppressive Patients? Single or Double?

Servet ÖZTÜRK, Merve KAÇAR EKER, Semra KAVAS, Onur ÇOLAK, Derya ÖZTÜRK ENGİN, Canan AĞALAR

İlk Aşı Şeması	n	%
Tek Doz 0-1-6	239	79,4
Tek Doz 0-1-2-12	3	1,0
Çift Doz 0-1-6	25	8,3
Çift Doz 0-1-2-6	28	9,3
Çift Doz 0-1-2-12	4	1,3
Tek Doz 0-1	2	0,7



- **Toplam 301 olgu**
- **Çift doz aşı ile anti HBS titresi daha yüksek**

Namık Kemal Tıp Dergisi 2020; 8(3): 499 - 506

Hepatit B aşısı

Table 2. Safety and Efficacy of Vaccination in Patients on Biologic Agents.

Vaccine	Biologic Agent	Patient Population	Efficacy	Safety
Inactivated and subunit vaccines				
Cholera (oral)	Vedolizumab	Healthy individuals	No significant difference in seroconversion rates but diminished the magnitude of antibody titre increase[131]	Well tolerated[131]
Hepatitis A	TNFi (pooled)	RA	Diminished humoral response compared to healthy individuals, but 86% of patients achieved seroprotection with 2 vaccine doses[132]	Well tolerated and did not result in exacerbation of disease activity[132]
		IBD	Diminished humoral response to the vaccine[28]	NA
Hepatitis B	Infliximab	IBD	Reduced humoral response to the vaccine[133]	NA
	TNFi (pooled)	SpA	Diminished humoral response to the vaccine[134]	NA
		IBD	Humoral response unaffected by TNFi treatment; however, patients with IBD generally had lower responses than healthy controls regardless of treatment[135]	NA
	Vedolizumab	Healthy individuals	No significant difference[131]	Well tolerated[131]

- Aşı yanıtı azalabilir
- İyi tolere edilir

Kim A. Papp et al. Journal of Cutaneous Medicine and Surgery 2019, Vol. 23(1) 50–74

Meningokok aşıları

Vaccines	Abbreviations	Trade names
Haemophilus influenzae type b vaccine	Hib	ActHIB® Hiberix® PedvaxHIB®
Hepatitis A vaccine	He	
Hepatitis A and hepatitis B vaccine	He	
Hepatitis B vaccine	He	Heplisav-B®
Human papillomavirus vaccine	HPV	Gardasil 9®
Influenza vaccine (inactivated)	IIV	Many brands
Influenza vaccine (live, attenuated)	LAIV4	FluMist® Quadrivalent
Influenza vaccine (recombinant)	RIV4	Flublok® Quadrivalent
Measles, mumps, and rubella vaccine	MMR	M-M-R II®
Meningococcal serogroups A, C, W, Y vaccine	MenACWY-D MenACWY-CRM MenACWY-TT	Menactra® Menveo® MenQuadfi®
Meningococcal serogroup B vaccine	MenB-4C MenB-FHbp	Bexsero® Trumenba®
Pneumococcal 15-valent conjugate vaccine	PCV15	Prevnar 15®
Pneumococcal 23-valent polysaccharide vaccine	PPSV23	Pneumovax 23®
Tetanus and diphtheria toxoids	Td	Tenivac® Tdvax™
Tetanus and diphtheria toxoids and acellular pertussis vaccine	Tdap	Adacel® Boostrix®
Varicella vaccine	VAR	Varivax®
Zoster vaccine, recombinant	RZV	Shingrix

Menectra:Polisakkarit difteri toksoid konjuge aşı
Menveo: Oligosakkarit difteri CRM197 konjuge aşı
MenQuadfi: Oligosakkarit tetanoz toksoid konjuge aşı

https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf

Meningokok aşısı

- Kompleman eksikliği
- Ekulizumab ve Ravulizumab kullanımı

Men ACWY-D (Menectra/Menveo/MenQuadfi): 8 hafta ara ile 2 doz

5 yılda bir rapel

MenB-4C (Bexero):1 ay arayla 2 doz

MenB-FHbp (Trumenba): 0.1-2 ve 6. ayda 3 doz

İlk seriden 1 yıl sonra ve her 2-3 yılda bir rapel

https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf

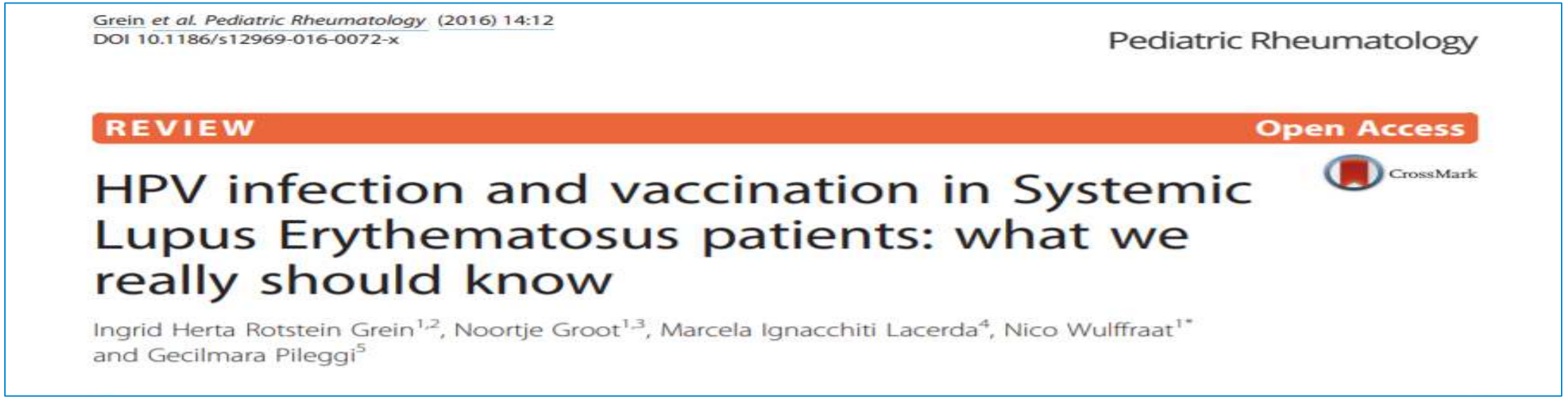
Meningokok aşısı

Meningococcal	Usual	Severe allergic reaction after a previous vaccine or a vaccine component (e.g., anaphylaxis).	• Methotrexate, azothioprine (no change or decreased response), TNF inhibitors (no change or decreased response), abatacept, rituximab, and tofacitinib may decrease vaccine response. Vaccination should be commenced before these drugs are initiated.

- ❖ TNF inhibitörleri (etkilemez veya azaltır),
- ❖ Abatasept, rituksimab ve tofasitinib ile aşının etkinliği azalır

Tanrıover MD, et al. Eur J Rhematol 2016;3(1):29-35.

HPV enfeksiyonları



Grein et al. Pediatric Rheumatology (2016) 14:12
DOI 10.1186/s12969-016-0072-x

Pediatric Rheumatology

REVIEW

Open Access

HPV infection and vaccination in Systemic Lupus Erythematosus patients: what we really should know

Ingrid Herta Rotstein Grein[1,2], Noortje Groot[1,3], Marcela Ignacchiti Lacerda[4], Nico Wulffraat[1*] and Gecilmara Pileggi[5]

- Sağlıklı bireylerle kıyaslandığında SLE hastalarında HPV enfeksiyonları daha sık görülür

HPV aşılaması

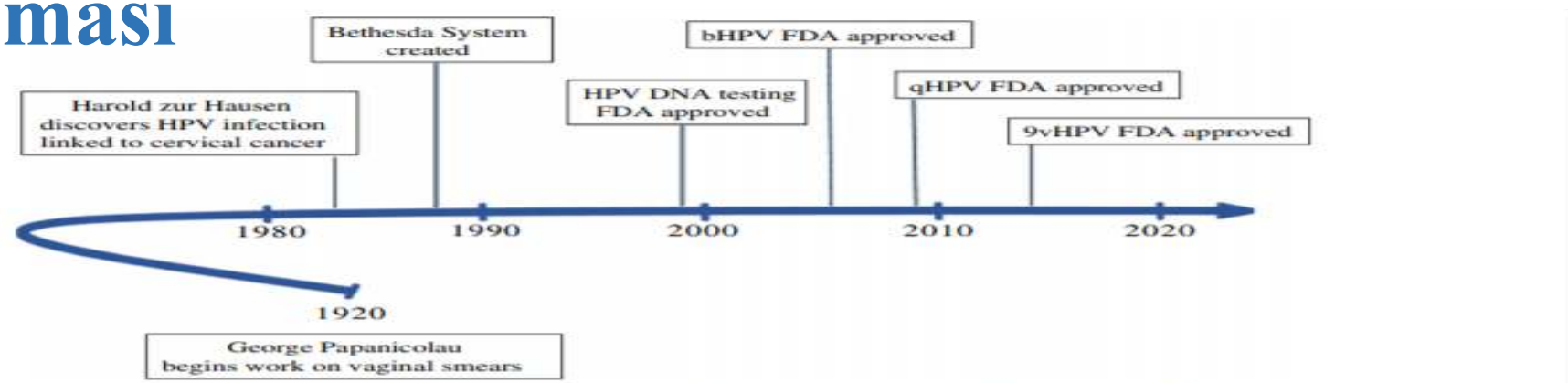


Fig. 2 Important events regarding cervical cancer and HPV. Abbreviations: bHPV, bivalent vaccine; qHPV, quadrivalent vaccine; 9vHPV, 9-valent vaccine; HPV, human papillomavirus; FDA, Food and Drug Administration. Adapted from Lees et al. [16]

Table 3 HPV vaccines efficacy and cervical cancer coverage

Vaccine	HPV genotypes	Vaccine efficacy	Cervical cancer coverage
bHPV	6 and 18	>98 % for HPV disease related to genotypes 6 and 18	70 %
qHPV	6, 11, 16 and 18	>99 % for HPV disease related to genotypes 6, 11, 16 and 18 (women) 90 % for external genital disease (men)	70 %
9vHPV	6, 11, 16 and 18 31, 33, 45, 52 and 58	>99 % for HPV disease related to genotypes 6, 11, 16 and 18 96,7 % for HPV disease related to genotypes 31, 33, 45, 52 and 58	90 %

Abbreviations: *bHPV* bivalent vaccine, *qHPV* quadrivalent vaccine, *9vHPV* 9-valent vaccine, *HPV* human papillomavirus
Adapted from Committee Opinion number 641 [57]

Grein et al. Pediatric Rheumatology (2016) 14:12

HPV aşılaması

- 26 yaş altı erişkinlere
- 0,1-2, 6. aylarda

- 27-45 yaşları için klinik karara göre

H. influenzae tip b aşısı

Guidance for Haemophilus influenzae type b (Hib) vaccination in high-risk groups

High-risk group*	Hib vaccine guidance
Patients aged <12 months	Follow routine Hib vaccination recommendations
Patients aged 12 to 59 months	If unimmunized or received 0 or 1 dose before age 12 months: 2 doses, 8 weeks apart
	If received ≥2 doses before age 12 months: 1 dose, 8 weeks after last dose
	If completed a primary series and received a booster dose at age ≥12 months: No additional doses
Patients aged <60 months undergoing chemotherapy or radiation therapy ¶	If routine Hib doses administered ≥14 days before starting therapy: Revaccination not required
	If dose administered within 14 days of starting therapy or given during therapy: Repeat doses starting at least 3 months following therapy completion
Patients aged ≥15 months undergoing elective splenectomy	If unimmunized Δ: 1 dose prior to procedure ◊
Asplenic patients aged >59 months and adults	If unimmunized Δ: 1 dose
HIV-infected children aged ≥60 months	
HIV-infected adults	
Recipients of hematopoietic stem cell transplant, all ages	Regardless of Hib vaccination history: 3 doses (at least 4 weeks apart) beginning 6 to 12 months after transplant

- ❖ Hematopoetik kök hücre alıcılarında 3 doz
- ❖ Diğer riskli durumların varlığında tek doz

Biyolojik ajan kullananlarda canlı aşılar

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

Drug	Protein vaccines	Carbohydrate vaccines	DTH/cellular immunity	Neoantigen	Live virus
			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.

Biyolojik ajan kullananlarda canlı aşı önerilmez

McMahan ZH, et al. Arthritis Res Ther 2014;16:506.

Herpes Zoster

- Biyolojik ajan kullanan hastalarda herpes zoster riski artar

Open Forum Infect Dis.2020 Jan; 7(1): ofaa005.

Rekombinant Herpes Zoster Aşısı

ACIP

- 50 yaş ve üzeri 2 doz

  (2-6 ay ara ile /en az 1 ay ara)

- Daha önce geçirilmiş zoster öyküsü olsa da canlı zoster aşısı yapılmış olsa da

  (Canlı zoster aşısından en az 2 ay sonra)

Canlı Herpes Zoster Aşısı

- CDC ------ 60 yaş üzeri
- FDA-------50 yaş üzeri
- **Biyolojik ajan başlanmadan önce canlı herpes zoster aşısı yapılmalı**
- Daha önce herpes zoster geçirip geçirmediğine bakılmaksızın tek doz

Sıngh JA et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care & Research

	Killed vaccines			Recombinant vaccine	Live attenuated vaccine
	Pneumococcal[1]	Influenza (intramuscular)	Hepatitis B[2]	Human Papilloma	Herpes Zoster[3]
Before initiating therapy					
DMARD monotherapy	✓	✓	✓	✓	✓
Combination DMARDs	✓	✓	✓	✓	✓
TNFi biologics	✓	✓	✓	✓	✓ *(PICO J.1)*[5]
Non-TNF biologics	✓	✓	✓	✓	✓*(PICO J.1)*[5]
While already taking therapy					
DMARD monotherapy	✓	✓	✓	✓	✓
Combination DMARDs	✓	✓	✓	✓	✓
TNFi biologics	✓	✓	✓ **(PICO J.4, J.5)**[6]	✓	*Not recommended (PICO J.2, J.3)*[7]
Non-TNF biologics[4]	✓	✓	✓ **(PICO J.4, J.5)**[6]	✓	*Not recommended (PICO J.2, J.3)*[7]

DMARD monoterapy (Metotreksat. hidroksiklorokin, leflunamid veya sulfasalazin)
Combination DMARDs (İkili kombinasyonlar : Metotreaksat+sulfasalazin; metotreksat+hidroksiklorokin; sulfalazin + hidroksiklorokin veya leflunamid kombinasyonu ; Üçlü kombinasyonlar: Metotrekasat+sulfasalazin+hidroksiklorokin
TNFi biologics: Adalimumab, sertolizumab pegol, etanersept, golimumab, or infliximab
Non-TNF biologics: Abatasept, rituximab, or tocilizumab (anakinra hariç)

- Biyolojk ajan başlamadan 2 hafta önce herpes zoster aşısı yapılmalı

Arthritis Care & Research Vol. 68, No. 1, January 2016, pp 1–2

Düşük doz immunosupresif tedavi alan hastalarda canlı zoster aşısı

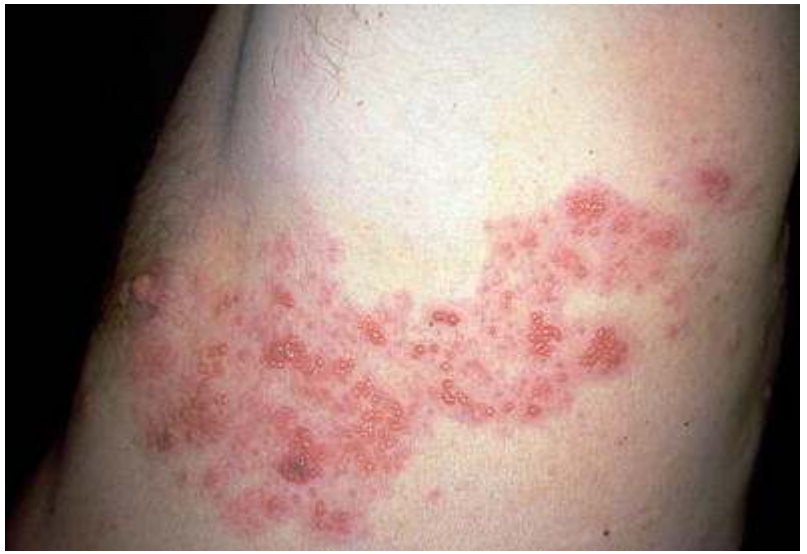
- Adrenal yetmezlikte glikokortikoid replasman tedavisi
- İntraartikuler, bursal ve tendona kortikosteroid uygulanması
- Düşük veya orta doz kortikosteroid kullanımı (<20 mg/gün prednizolon veya benzer doz)
- Metotreksat (0.4 mg/kg/hafta), azatioprin (<3.0 mg/kg/gün), 6-merkaptopurin (<1.5 mg/ kg/gün)

Tanrıover MD et al. Eur J Rhematol 2016;3(1):29-35.

Varicella aşısı

- Varicella geçirme öyküsü olmayan veya laboratuvar kanıtı olmayan hastalara en az 4-8 hafta ara ile 2 doz
- İmmunsüprese hastalarda kontrendike

Malaiya R et al. Rhematology (Oxford)2015 Apr;54(4):567-9.
https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html



İmmunosupresif hastalar, **varicella ve zoster aşısı** sonrası deri lezyonları gelişen yakınlarıyla deri lezyonları iyleşene kadar temastan kaçınmalı

Rubin LG, et al. Clin Infect Dis. 2014;58(3):e44-100.

- Suçiçeği ve/veya kızamığa karşı koruyuculuğu olmayan immunosuprese bireyin, infekte bireyle temas durumunda immunoglobulin/antiviral tedavi düşünülmeli

Bühler S, et al. Swiss Med Wkly 2015;145:w14159

Kızamık-Kızamıkçık-Kabakulak Aşısı

- Hastalığı geçirdiğinin veya immunite geliştiğinin laboratuvar kanıtı olmayanlarda tek doz aşı

- Şiddetli immunosüpresyonu olanlarda kızamık-kızamıkçık-kabakulak aşısı kontrendike
- Kızamıklı hasta ile temas eden immunosuprese kişiye 6 gün içerisinde immunglobulin verilmeli

https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf
https://www.uptodate.com/contents/measles-mumps-and-rubella-immunization-in-adults

Table 2 Recommended Adult Immunization Schedule by Medical Condition and Other Indications, United States, 2021

Vaccine	Pregnancy	Immuno-compromised (excluding HIV infection)	HIV infection CD4 count <200 mm³	HIV infection CD4 count ≥200 mm³	Asplenia, complement deficiencies	End-stage renal disease; or on hemodialysis	Heart or lung disease, alcoholism[1]	Chronic liver disease	Diabetes	Health care personnel[2]	Men who have sex with men
IIV or RIV4	1 dose annually										
or										or	
LAIV4	Not Recommended						Precaution			1 dose annually	
Tdap or Td	1 dose Tdap each pregnancy	1 dose Tdap, then Td or Tdap booster every 10 years									
MMR	Not Recommended*	Not Recommended	1 or 2 doses depending on indication								
VAR	Not Recommended*	Not Recommended			2 doses						
RZV					2 doses at age ≥50 years						
HPV	Not Recommended*	3 doses through age 26 years			2 or 3 doses through age 26 years depending on age at initial vaccination or condition						
PCV13		1 dose									
PPSV23		1, 2, or 3 doses depending on age and indication									
HepA					2 or 3 doses depending on vaccine						
HepB					2, 3, or 4 doses depending on vaccine or condition				<60 years ≥60 years		
MenACWY	1 or 2 doses depending on indication, see notes for booster recommendations										
MenB	Precaution	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations									
Hib		3 doses HSCT[3] recipients only			1 dose						

Recommended vaccination | Recommended vaccination | Precaution—vaccination | Recommended vaccination | Not recommended/ | No recommendation/

https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf

Tablo 4. İmmün Sistemi Baskılanmış Kişilerde Kuduz Profilaksisi

	Kategori	Önerilen Yaklaşım
İmmün sistemi baskılanmış hastalar (splenektomi dahil), kemoterapi gibi immün sistemi baskılayan ilaç alan hastalar CD4+ hücre sayısı <200/ mm3 olan HIV+ kişiler	Kategori I	Herhangi bir işlem yapılmasına gerek yok
	Kategori II-III-IV	Yara bakımı (Antibiyotik) ➢ Tetanoz profilaksisi için değerlendirilir İmmünglobülin[1] Aşılama (0., 3., 7. günlerde birer doz ve 14-28. günler arasında bir doz daha olmak üzere toplam 4 doz)*

[1]İmmünglobülin ilk doz aşı uygulamasından sonra en geç 7 gün içinde yapılmalıdır.

*İmmunsupresyon durumuna göre ek doz aşı ihtiyacı için vaka bazlı değerlendirilir.

Sağlık Bakanlığı, Kuduz Profilaksi Rehberi, 2019

SONUÇ

- Biyolojik ajanlar konağın immunitesini bozarak, enfeksiyon riskini artırır
- Bu enfeksiyonların çoğu aşı ile önlenebilir
- Biyolojik ajan başlamadan önce aşılanma tamamlanmalı
- Uygun şekilde yapılan aşılama ile bu hastalıklara bağlı morbidite ve mortalite azalır