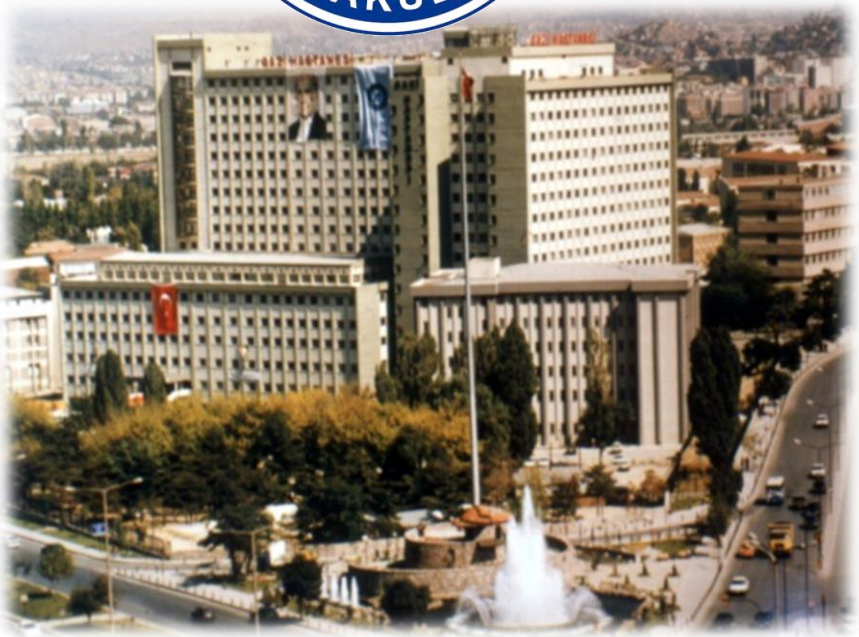
BAĞIŞIKLIK SİSTEMİ BASKILANMIŞ HASTADA AŞILAMA

27.12. 2017, ANKARA

Prof. Dr. Esin Şenol



ERİŞKİN AŞILAMA PROGRAMLARI

- YAŞ
- YAŞAM TARZI
- MESLEK
- DAHA ÖNCEKİ AŞILANMA /İMMUNİTE DURUMU
- ÖZEL RİSK DURUMU
- SEYAHAT
- TEMAS SONRASI

AŞI İLE ÖNLENEBİLİR HASTALIKLARIN YÜKÜ

Pnömoniden 3–4 milyon ölüm

Avrupa ‘da Erişkinlerde Enfeksiyon

Ölümlerin En Sık Nedeni

PNÖMOKOKAL HASTALIKLARIN neden olduğu yaklaşık 700,000 ölüm aşılama ile önlenebilir

İNFLUENZA her yıl 500 milyon kişiyi enfekte ediyor.

3-5 milyon şiddetli olgu, 250-500.000 ölüm

İnfluenza’nın neden olduğu hastalıklar ve komplikasyonlar %60'a kadar ve yaşlı hastalarda ölümler %80 kadar azaltılabilir

Lynch JP, Zhanel GG.Semin Resp Crit Care Med 2009:30:189-209
Brundage JF. Lancet Infect Dis 2006:6:303-12
Ludwig E. Eur Respir Rev. 212:21:123:57-65

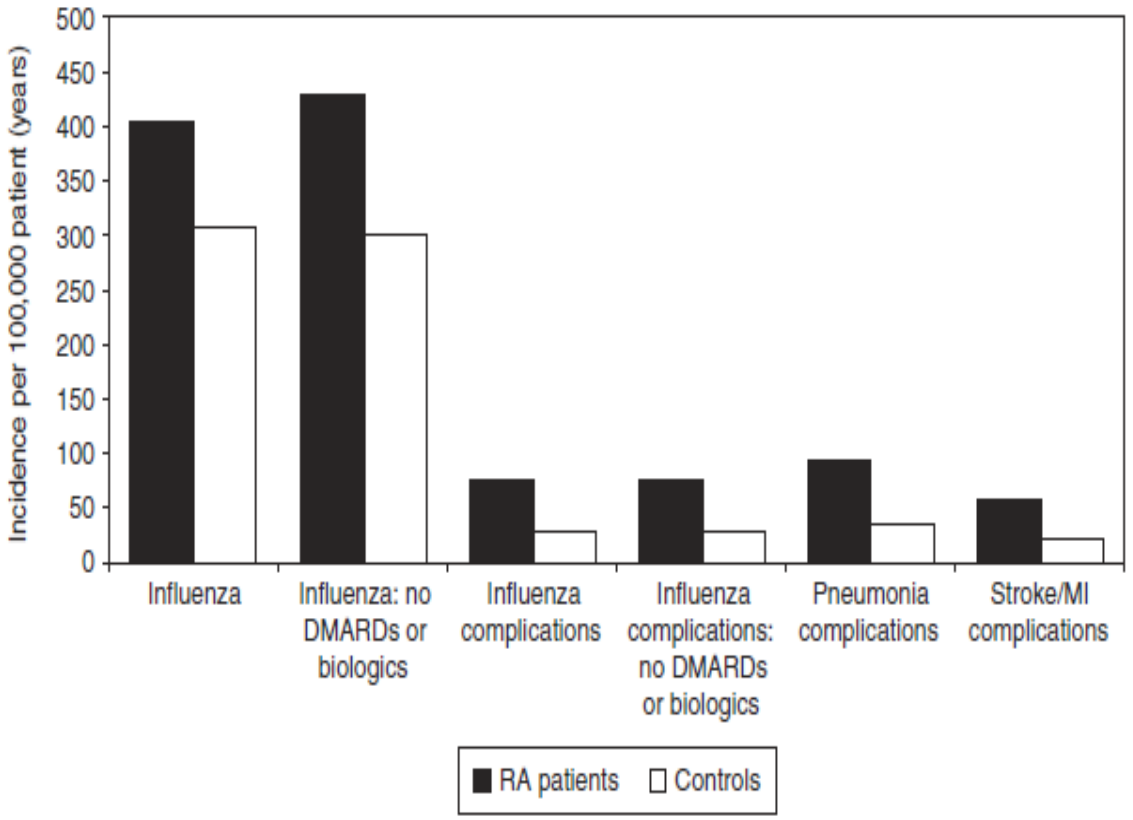


Figure 1 Incidence of influenza and complications in RA patients and controls recruited from the MarketScan database.

İPH VE PNÖMOKOKAL PNÖMONİ RİSKİ

Yaş[1]	Konak faktörler		Çevresel faktörler[3,4]	Davranış faktörleri[2,3]
	Riskli grup[2,3,5,6]	Yüksek riskli grup[2,3,5,6]		
• ≤ 2 yaş • ≥ 65 yaş	• Kronik kalp hastalığı • Kronik akciğer hastalığı* • Diyabet • Fonksiyonel veya anatomik aspleni • Kronik karaciğer hastalığı • Serebrospinal sıvı kaçakları	• HIV enfeksiyonu • Kronik böbrek yetmezliği, nefrotik sendrom • Kanser (solid ve hematolojik) • Solid organ transplantasyonu • Otoimmün hastalıklar • İmmünsüpresif tedavi ve kortikosteroidler • Primer immün yetmezlikler	• Geçirilmiş viral solunum yolu enfeksiyonu (örn. influenza) • Bir kurumda konaklama (örn. bakım evi)	• Sigara • Alkol kullanımı

*Kronik obstrüktif akciğer hastalığı, amfizem ve astım dahil olmak üzere.

HIV, insan immün yetmezlik virüsü; İPH, invaziv pnömokok hastalığı.

1. Centers for Disease Control and Prevention. Available from: http://www.cdc.gov/abcs/reports-findings/survreports/spneu12.pdf. Accessed March 2015. 2. Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 2010;59:1102–6. 3. Musher DM. In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 7th edn, 2010:2623–42. 4. Centers for Disease Control and Prevention. Available from: http://www.cdc.gov/h1n1flu/vaccination/provider/provider_pneumococcal.htm. Accessed March 2015. 5. van Hoek AJ, et al. J Infect 2012;65:17–24. 6. Klemets P, et al. BMC Infect Dis 2008;8:96.

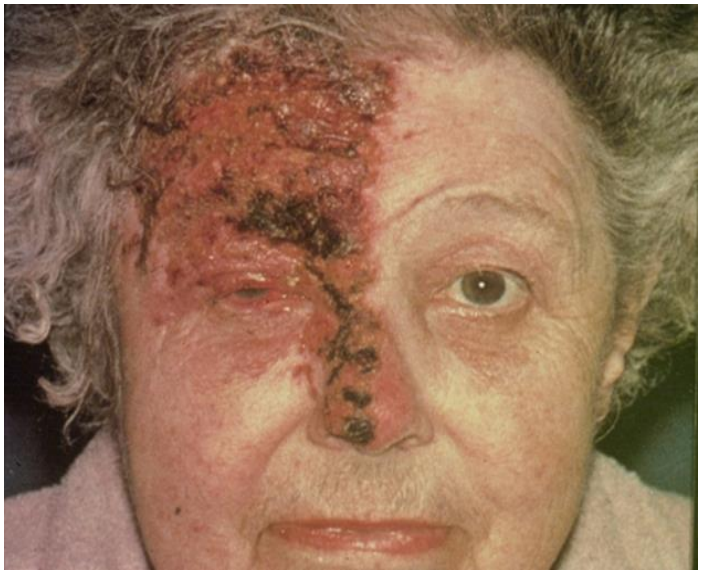
KLİMİK-EBÇG 2016

	YAŞ GRUBU					
	19-21 YAŞ	22-26 YAŞ	27-49 YAŞ	50-59 YAŞ	60-64 YAŞ	≥ 65 YAŞ
İnfluenza	Her yıl 1 doz					
Tetanos, difteri, boğmaca (Td/Tdap)	1 doz Tdap ile rapel; takiben her 10 yılda bir Td					
Suçiçeği	2 doz					
Human papillomavirus (HPV) kadınlarda	3 doz					
Human papillomavirus (HPV) erkeklerde	3 doz	3 doz				
Zoster					1 doz	
Kızamık, kızamıkçık, Kabakulak (KKK)	1 veya 2 doz					
Konjuge pnömokok aşısı-13 valan (PCV13)	Yaşam boyu					1 doz
Polisakkarid pnömokok aşısı (PPV23)	1 veya 2 doz					1 doz
Meningokok	1 veya daha fazla doz					
Hepatit A	2 doz					
Hepatit B	3 doz					
Hemophilus influenza tip b (Hib)	1 veya 3 doz					

Tüm erişkinlere | Riskli gruplara | Öneri yok

ÖZEL KONAK KİM ?

- **Hematopoetik Kök Hücre Nakil (HKHN) alıcıları**
- **Kanser hastaları ve immunsupresif tedavi** alan hastalar (TNF-inhibitörleri , Steroid gibi)
- **HIV infeksiyonlu** hastalar
- **Kronik hastalıklar**
  - ✓ Diyabetik hastalar
  - ✓ Kronik karaciğer
  - ✓ Kronik akciğer hastalığı
  - ✓ Kalp hastalığı
  - ✓ Kronik böbrek yetmezliği olan hastalar
- **Asplenik hastalar**
- **Gebeler**
- **Sağlık personeli**



IDSA GUIDELINES

Clinical Infectious Diseases 2014;58(3):e44–100

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]

- KİM SORUMLU?
- NE ZAMAN?

- **İMMUNSUPRESYONDAN ÖNCE**
- **İNAKTİF AŞILAR ≥2, CANLI AŞILAR≥4 HAFTA**

- AİLE/YAKINLARININ AŞILANMASI
- SEYAHAT

Dermatoloji ve Romatoloji İmmunsupresif (Biyolojik Tedaviler) Kullanılan Hastalar

Immunomodulating agents

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

RA
IBD
PSÖRİAZİS

DÜŞÜK DÜZEY İMMUNSUPRESYON:
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

ROMATİZMAL HASTALIKLARDA KULLANILAN AJANLAR

- cDMARDs: Konvansiyonel Hastalık Modifiye Edici AntiRomatizmal İlaçlar: methotreksat, leflunomid, azathioprin, siklosporin, siklofosfamid, mikofenolat
- bDMARDs:
  - TNF-inhib: etanercept, adalimumab, infliximab
  - T-hc-ko-stimulasyon (abatacept), interleukin-1 (anakinra, canakinumab), interleukin-6 (tocilizumab) or B-hc deplesyon (rituximab).

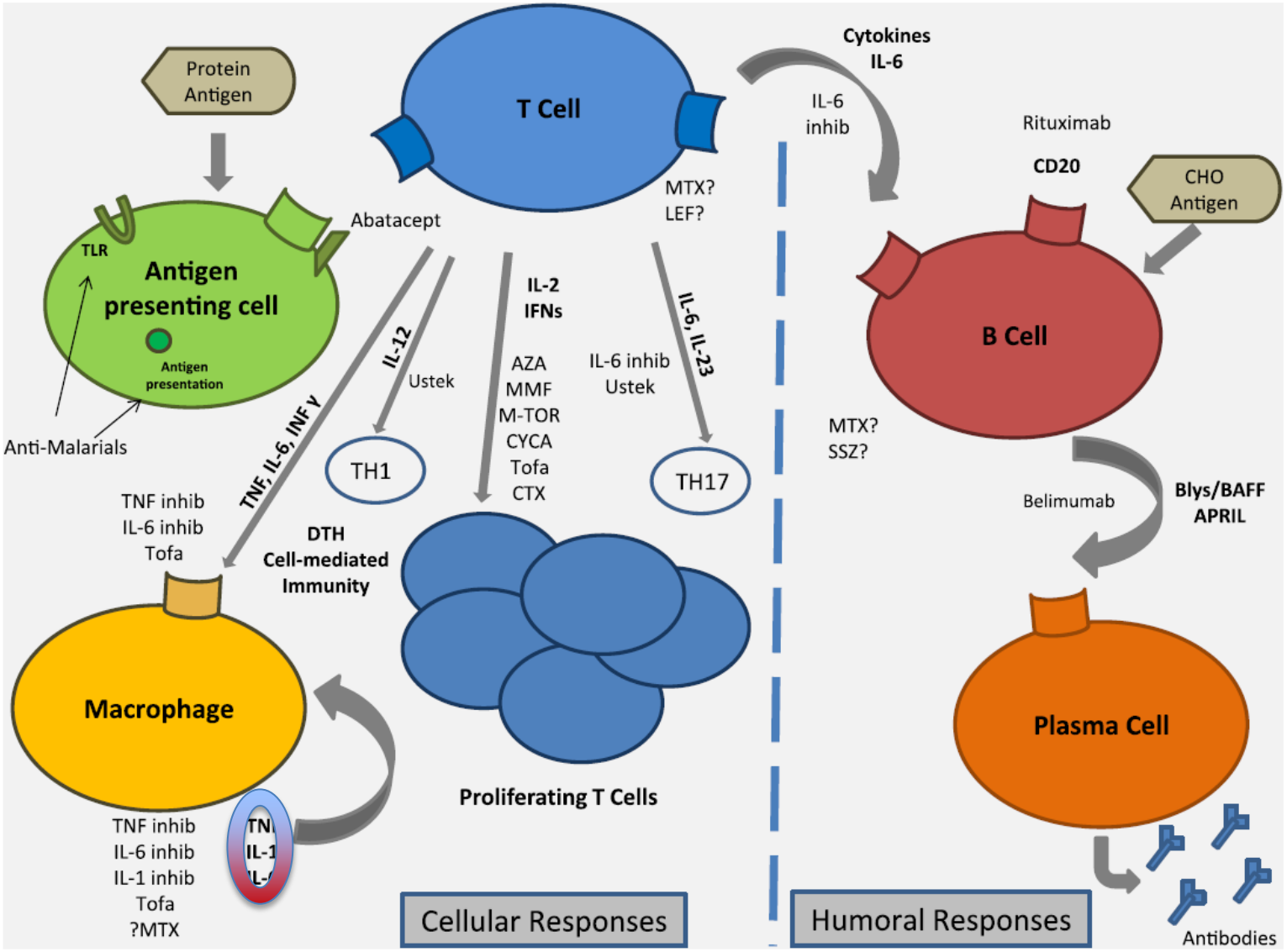


Figure 1 Immunomodulatory therapies. AZA, azathioprine; BAFF, B-cell activating factor; Blys, B lymphocyte stimulator; CHO, carbohydrate; CTX, cyclophosphamide; CYCA, cyclosporine A; DTH, delayed type hypersensitivity; INF, interferon; inhib, inhibitor; LEF, leflunomide; MMF, mycophenolate mofetil; M-TOR, mammalian target of rapamycin; MTX, methotrexate; SSZ, sulfasalazine; TLR, toll-like receptor; Tofa, tofacitinib; Ustek, ustekinumab.

TEDAVİ 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**

ACR RA Treatment Recommendations

	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]

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

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

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

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–xxx

OTOİMMUN HASTALIKLAR-AŞILAMA

- ✓ BU GRUP –AŞI İLE ÖNLENİLEBİLİR HASTALIK RİSKİ ARTMIŞ
- ✓ AŞI ETKİNLİĞİ?
- ✓ EMNİYETİ?
- ✓ HASTALIK ALEVLENMESİ?

IDSA-2013

risks of adverse effects from vaccination.

Concerns have been expressed that antigenic stimulation of vaccination could trigger a flare or onset of chronic inflammatory disease. The Institute of Medicine recently assessed the relationships between vaccines (MMR, acellular pertussis-containing, DT, tetanus toxoid, influenza, HepB, HepA, and HPV vaccines) and adverse effects [5]. Evidence was inadequate to establish or refute a causal relationship between each vaccine and onset or exacerbation of multiple sclerosis, systemic lupus erythematosus (SLE), vasculitis, rheumatoid arthritis (RA), or juvenile idiopathic arthritis. Overall, the preponderance of

OTOİMMUNİTE: Genetik +çevresel faktörler=OTOANTİKORLAR/OTOREAKTİF T-HÜCRELER-IMID DÖNÜŞMEZ

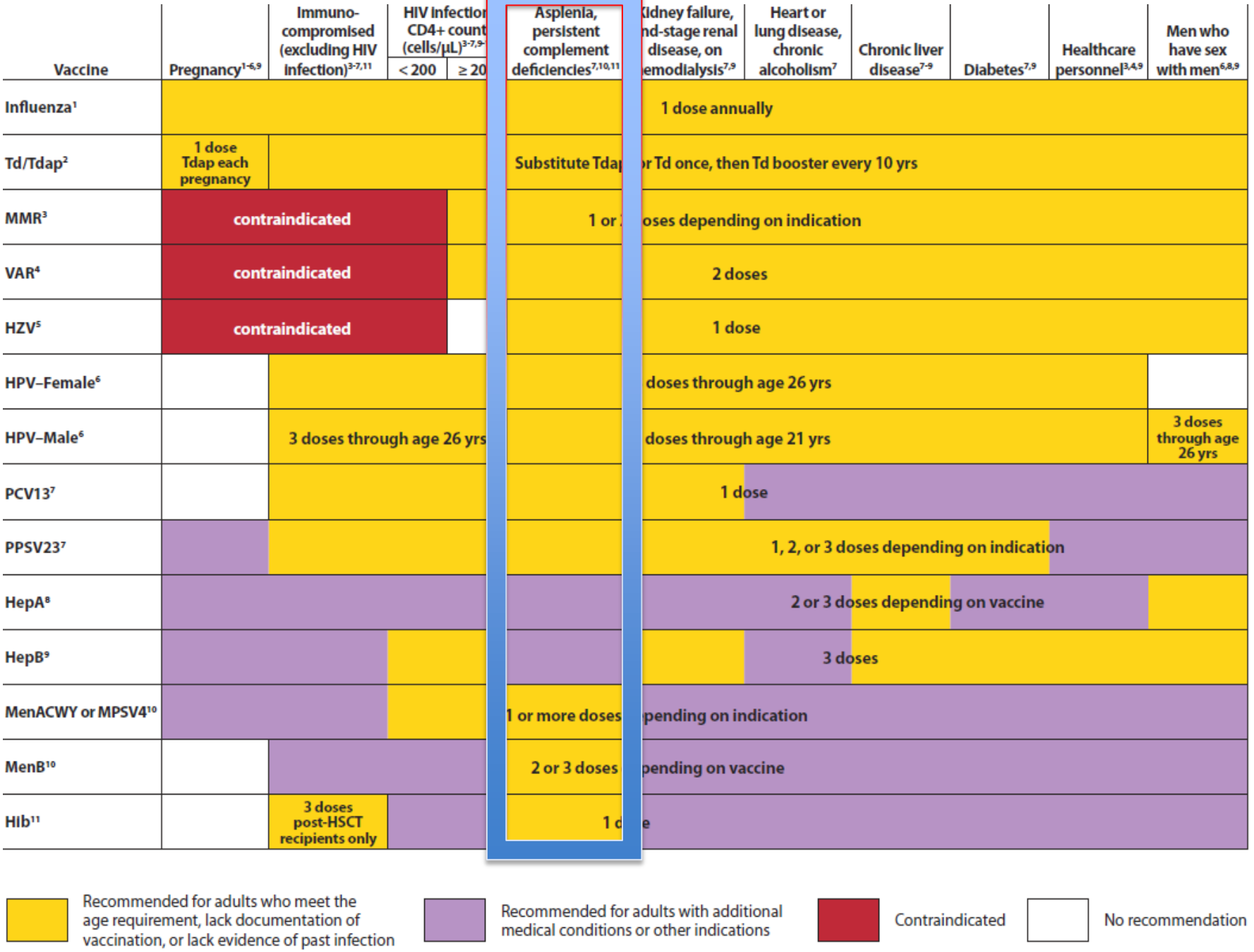
KANSER HASTALARI-AŞILAMA

- **Tercihan kemoterapi öncesi; aşı etkinliğini sağlamak amacıyla**
  - **Kemoterapi öncesi :**
    - **İnaktive aşılar- 2 hafta önce,**
    - **Canlı aşılar -4 hafta önce**
- **Yoğun kemoterapi süresi boyunca aşı etkinliği azaldığı için tercih edilmemelidir.**
- **Kemoterapi sonrası aşılama zamanı:**
  - **Kanser tedavi tamamlanmasından 3 ay sonra, Anti-B hücre antikor (ritüksimab veya alemtuzumab) tedavilerinden ise 6 ay sonra aşı uygulamalarına başlanması önerilir.**

SPLENEKTOMİ/ASPLENİ

- Tercihan splenektomiden preop 14 gün önce; yapılamadıysa Postop 14 gün sonra

- Splenektomi sonrası immunosupresif tedavi ya da kemoterapi alacak ise en az 3 ay sonraya ertelenir.



Recommended Immunization Schedule for Adults, United

GEBE AŞI YAPILABİLİR Mİ ?

EVET

GEBELİK-AŞILAMA

- Tüm gebelerde **Td, inaktive influenza** aşıları önerilir.
- Gebelikte en uygun dönem bebeği korumak açısından **27-36 hafta**lar arasıdır (ACIP 2014 önerileri)
- **GEBE: NORMALDE <25 YAŞ, %10.4 ->35 %22 DÜŞÜK, İNFLUENZA DÜŞÜK İLİŞKİLİ**
- **CANLI AŞILAR YAPILMAZ**
- Gebelik döneminde risk yüksek ise hepatit A ve B aşıları, pnömokok, meningokok, kuduz aşısı yapılabilir

AŞI İLİŞKİLİ YAN ETKİLER

- **%10-60: AŞI YAPILAN BÖLGE,**
- **ATEŞ,MYALJİ, BAŞ AĞRISI<48 SA.**
- **%1.4 CİDDİ ---YAŞAMSAL, ÖLÜM, HOSPİTALİZASYON, HOSPİTALİZASYON UZAMASI**
- **ANAFİLAKSİ:** ~~0.0001%
- **OKULER RESPİRATUVAR SENDROM: 2000-2001 KANADA: 2-24 sa. Sonra…**
  - Gözlerde kızarma,Öksürük,Göğüste basınç,Solunum sıkıntısı,Boğaz ağrısı,Yüzde şişme
- **GBS:10-20/milyon /yıl..**
- **Aşı-1 fazla /1milyon aşı**
- **1976-- 1 fazla /100.000**

MMWR.2016:65:5

AŞILAMA-YAN ETKİLER

Aşılama sonrası, yaşamsal önem taşıyan anafilaksi türü acil reaksiyon nadir olup, milyonda bir olarak bildirilmektedir. Aşılamayı izleyen dakikalar içinde ortaya çıkması beklenir. Anafilaksi bulgularına karşı önlemler (ek, anafilaksi durumunda müdahale) kolay ulaşılabilir ve uygulanabilir durumda olmalıdır.

Adölesan ve erişkinlerde anafilaksiden daha sık karşılaşılan bir reaksiyon ise vazovagal refleksdir. Aşılamayı izleyen 5-15 dakika içinde gelişmektedir. İğne fobisi olanlarda daha sık karşılaşılmaktadır. Senkopa bağlı düşmenin yarattığı istenilmeyen kazalar olabilir. Aşılama sonrası, baş dönmesi, göz kararması gibi bulguları olan hastaların hemen uygun pozisyona getirilerek dinlendirilmeleri önemlidir.

İLK 5-15 DK.AŞILAMA YERİ TERKEDİLMEMELİ

The Vaccine Handbook:Immunization Action Coalition

Addressing Concerns About Vaccines

Vaccines have saved more lives than virtually any other public health intervention, and they are safer now than ever before. Yet, providers face a daily challenge convincing parents and patients that vaccines are safe, effective, and necessary. Good things have come from public concern about vaccines—the replacement, for example, of DTwP with the less reactogenic DTaP. However, while the sensational claims made by antivaccination activists, celebrities, wealthy financiers, and rogue "researchers" have not held up to scientific scrutiny, they have nevertheless received airtime and established an Internet presence. As a result, well-meaning parents are either refusing to have their children vaccinated or asking for alternative schedules, and adults who should be vaccinated are opting out. This has translated directly into personal and public harm.

Communicating Risks and Benefits

- Safety

Safe does not mean *harmless*—this would imply that any negative consequence of vaccines would make them *unsafe*. All vaccines have side effects. Pain, redness, swelling, and tenderness are relatively common; febrile seizures can occur but are unusual; much more serious side effects, like anaphylaxis, are very rare. The point is that few things in life are harmless, and that in all things we make decisions about *risks versus benefits*.

Each year in the United States, 350 people are killed in bath- or shower-related accidents and 200 people choke to death on food. Just being outdoors can be dangerous, as 40 people are killed each year by lightning. Thus, by the harmless criterion, even routine daily activities could be considered unsafe. Yet we engage in baths, eating and outdoor activities because the benefits outweigh the risks. This is not to say we don't make attempts to mitigate those risks.

Safe also means *being preserved from a real danger*. In this sense, vaccines are *safe* because the danger they prevent (*the diseases*) far outweighs the danger (*the side effects*) they represent.

Vaccine Immunology). Aluminum salts have been used as adjuvants for over 80 years, and hundreds of millions of people have received vaccines containing them. Whereas local reactions such as erythema, nodules, hypersensitivity, and granuloma formation have been reported, serious or persistent adverse events have not. In a meta-analysis published in 2004, vaccines containing aluminum hydroxide were seen to cause nearly twice as much erythema and induration in young children as those without adjuvant, but there was no increase in collapse, convulsions, or persistent screaming or crying.[42] In older children, aluminum-containing vaccines caused more localized, persistent pain, but not erythema, induration, or fever. In a sense, *the pain is part of the gain*—the inflammation (and hence pain) caused by the adjuvant also drives the immune response.

Large quantities of aluminum can cause neurologic disease. However, the burden of aluminum exposure through vaccines is far less than the guidelines for safe exposure established by the Agency for Toxic Substances Disease Registry. In fact, a study done in preterm infants showed no significant changes in urinary or serum aluminum levels after they received a total of 1200 mcg of aluminum in the form of Pediarix, PedvaxHIB, and Prevnar 13.[43] Infants are exposed to much more aluminum through their diets than through vaccines: whereas the total aluminum exposure from vaccines in the first 6 months of life is <5 mg, breast-fed infants ingest 7 mg and formula-fed infants as much as 38 to 117 mg over the same period of time, depending on the type of formula.[44]

AS04, the adjuvant used in HPV2 (a vaccine no longer distributed in the United States but used elsewhere in the world), contains a derivative of lipopolysaccharide, a component of bacterial cell walls. Patients may cite this when they say that vaccines "contain toxins." However, they need to understand that exposures to toxins like lipopolysaccharide occur continuously given our symbiotic relationship with bacteria. The truth is that anything (even water!) can be dangerous if taken in large amounts. The amount of lipopolysaccharide in AS04-adjuvanted vaccines is just enough to stimulate a robust antibody response but not nearly enough to cause major problems. This is borne out by many studies demonstrating excellent tolerability and no association with serious adverse events. Even more insidious events have been carefully studied; for example, in an integrated analysis of randomized controlled trials involving nearly 70,000 vaccinees, autoimmune events occurred in the same proportion (about 0.5%) of AS04-exposed and nonexposed individuals.[45]

Commentary

Successful Control of Vaccine-Preventable Diseases Requires More than Vaccines

Walter A. Orenstein, MD, Lance E. Rodewald, MD

Edward Jenner, 1796

AŞILARIN BİLİMSEL BİR BULUŞ OLARAK İSTENİLEN ETKİYİ YAPMASI ANCAK UYGULANMALARI İLE MÜMKÜN OLACAKTIR

DİNLEDİĞİNİZ İÇİN TEŞEKKÜRLER…

SORULARINIZ?

Prof. Dr. Esin Şenol