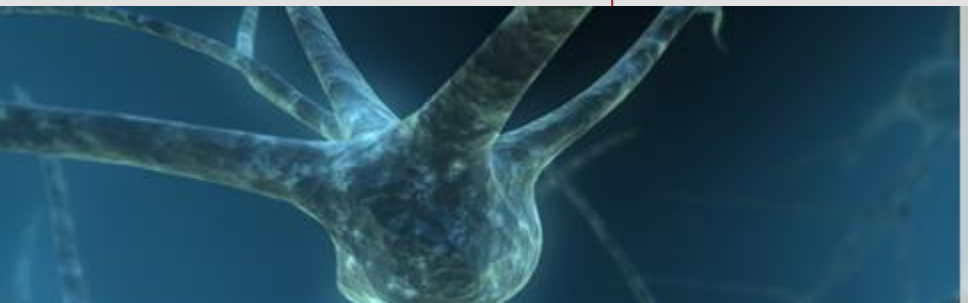
Hücresel İmmün Yetmezlik Düşündüren İnfeksiyonlarda Klinik Semptom ve Bulgular Nelerdir? Tanısal Yaklaşım Nasıl Olmalı? -Antifungal ile Başarılı Tedavi Edilen Olgu-

Prof. Dr. Necla TÜLEK
Ankara Eğitim ve Araştırma Hastanesi
16 MART 2017



İİÇG

OLGU

- 58 Y, E,

- İki haftalık ateş, bulantı-kusma,
- Peltek konuşma, yürüme bozukluğu
- Bilinçte bulanıklık

- Romatoid artrit ve Myastenia gravis tanıları var.
- Azathioprin 50 mg/gün ve prednizon 40 mg/gün

Fizik Muayene

- A: 38,2 C°
- Konfüzyon
- Her iki dizden ayak sırtına ve tabana doğru yaygın 2-3 mm. basmakla solmayan makulopapüler döküntüler.
- Her iki dirsekte benzer döküntüler

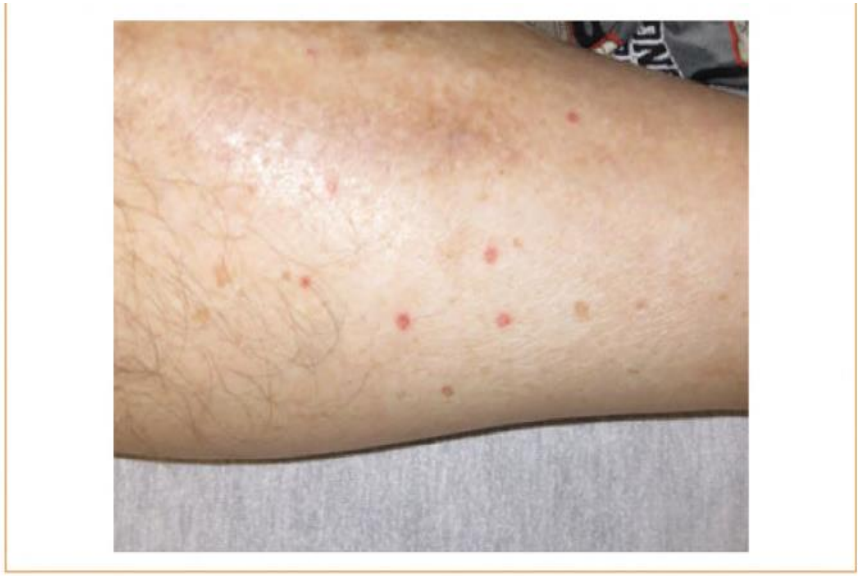


Figure 1c.1. The rash on the lower extremities consisted of 2–3mm maculopapular, non-blanching lesions from his bilateral knees to the dorsum of his feet (sparing the

- İlk laboratuvar testleri
- Kan sodyum: 130 mg/m
- Serebral tomografi

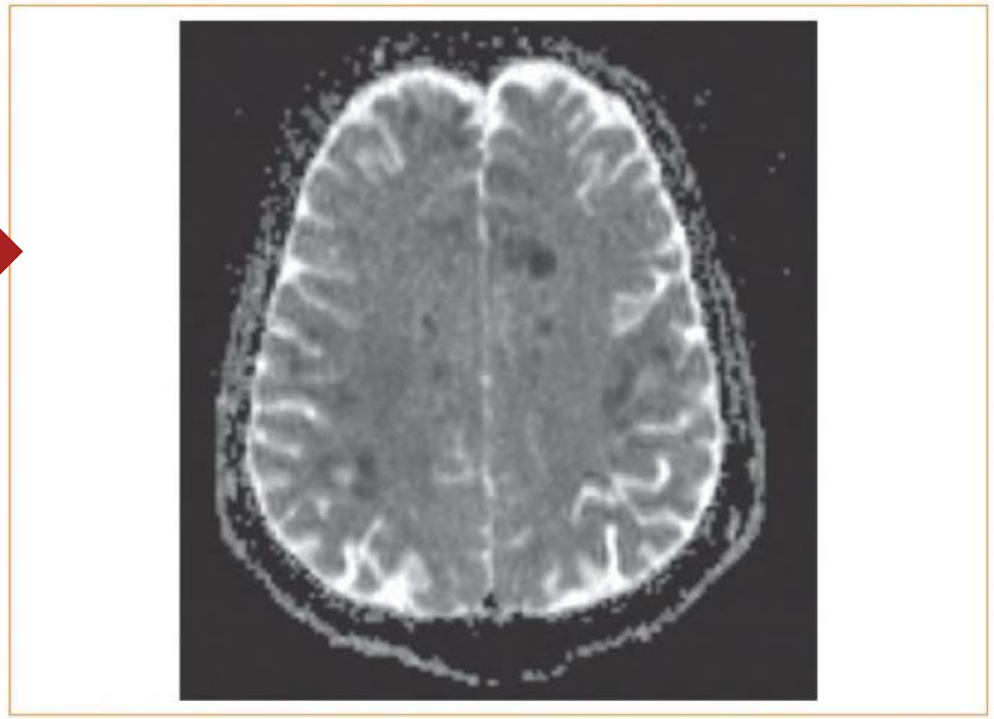
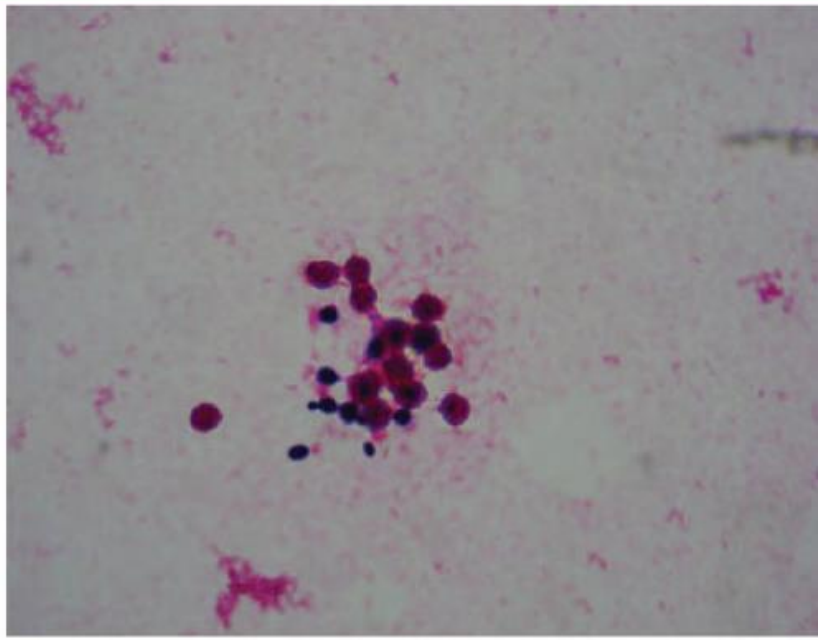


Figure 1c.3. CT scan brain, axial view showing numerous acute cerebral infarcts.

Lomber Ponksiyon

- Açılış basıncı: 380 mmHg
- Hücre sayısı: 37 lökosit (%40 nötrofil), 78 eritrosit
- BOS proteini: 500 mg/dl
- BOS glukoz: 18 mg/dl (EKŞ:90 mg/dl)
- BOS Gram boyama:



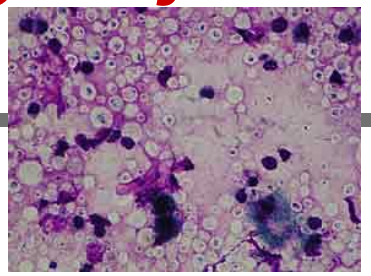
Diğer Laboratuvar Bulguları

- BOS Kriptokok Ag : >1/2048
- MRG: Leptomeningeyal kontrastlanma, yaygın infarkt
- Kan ve BOS kültürü: *Cryptococcus neoformans*

Tedavi ?

- Lipozomal amfoterisin B; 5 mg/kg
- Tekrarlayan LP: Kültür pozitifliği
- + Flukonazol 800 mg/gün, IV

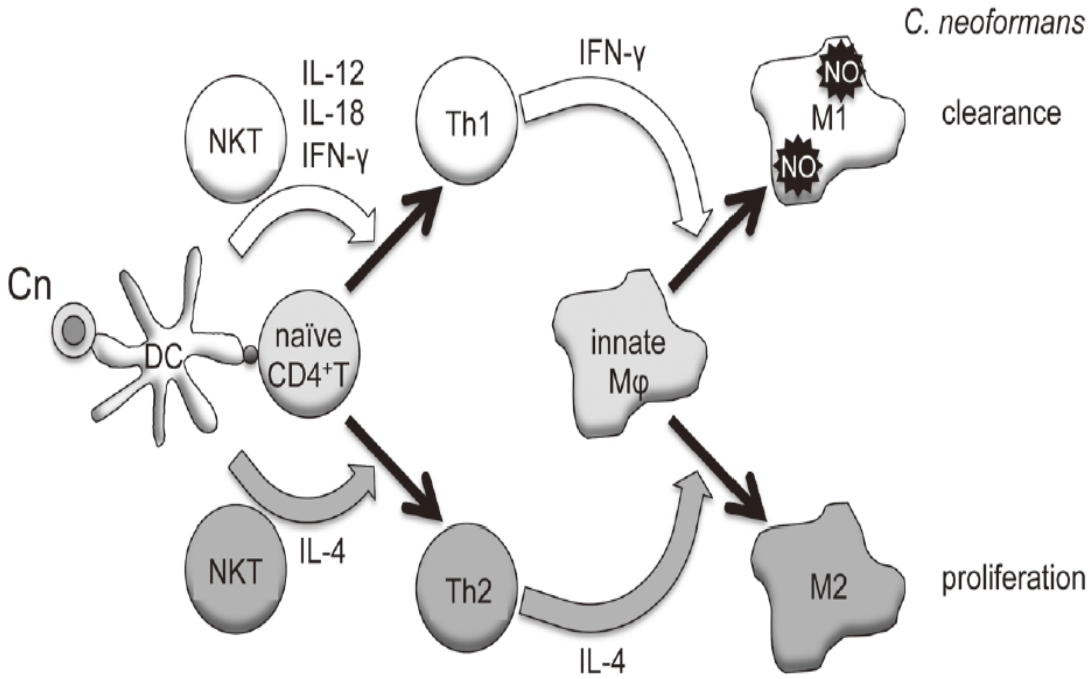
Cryptococcus neoformans Epidemiyolojisi



- ***Cryptococcus neoformans var neoformans***
- *Cryptococcus neoformans var gattii* (immunkompetanlarda *)*

- HIV öncesi 100000'de 0,2-0,8 menenjit etkeni
- HIV+'lerde meningoensefalitlerde %45 etken; mortalite %20
  - HIV+ 'lerde ~1 000 000 kriptokok infeksiyonu
- İmmunosupresif tedavi, kortikosteroid
- Transplantasyon (%2,8)
- Ağır cerrahi girişimler
- HIV negatiflerde mortalite ve kronik sekel daha fazla
- Hücresel immün yetmezliği olanlarda ağır infeksiyonlar

C. *neoformans* İnfeksiyonlarında T hücre Aktivasyonu ve Makrofaj Yanıtı



Kriptokok İnfeksiyonları

- MSS
- Akiğer
- Deri
- Kas-iskelet
- Genital tutulum
- Diğer organlar

MSS Kriptokok İnfeksiyonları

- Akut
- Subakut
- Kronik
- Meningoensefalit

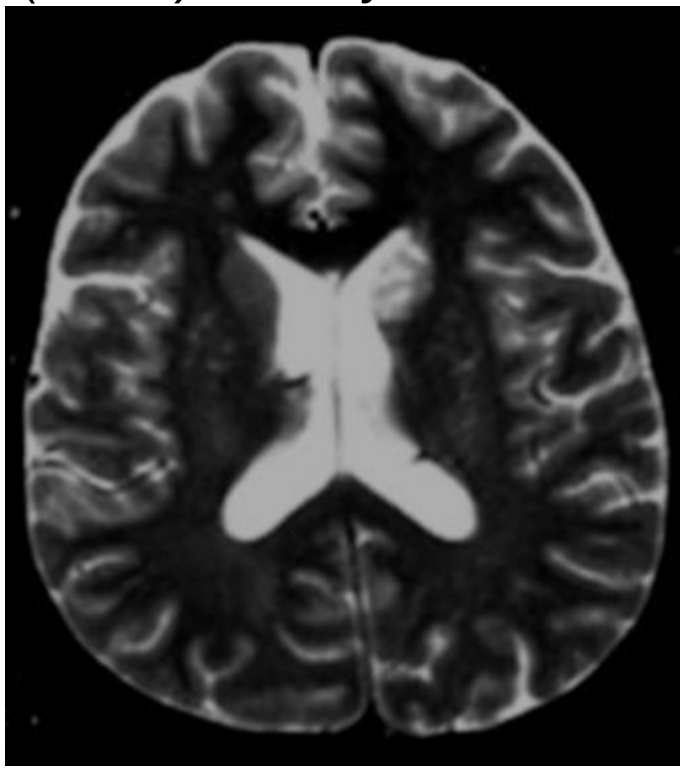
İmmunokompetanlarda
- Genellikle kronik
- Ekstranöral semptomlar yok
- Daha çok parankimal
- Hücre sayısı fazla, protein yüksek, antijen titresi düşük

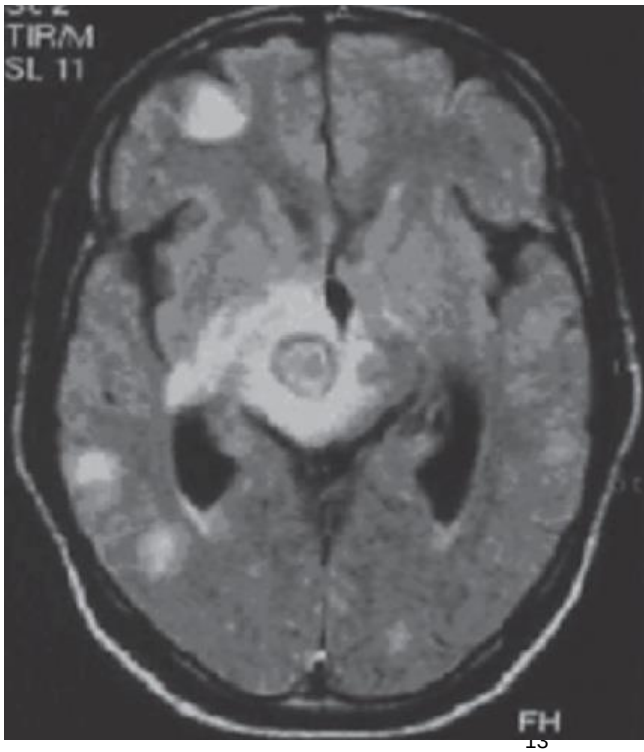
İmmunokompromize hastalardan; ateş, başağrısı ve MSS infeksiyonu kuşkusu olanlar kriptokok infeksiyonu yönünden araştırılmalı

Kriptokok İnfeksiyonları

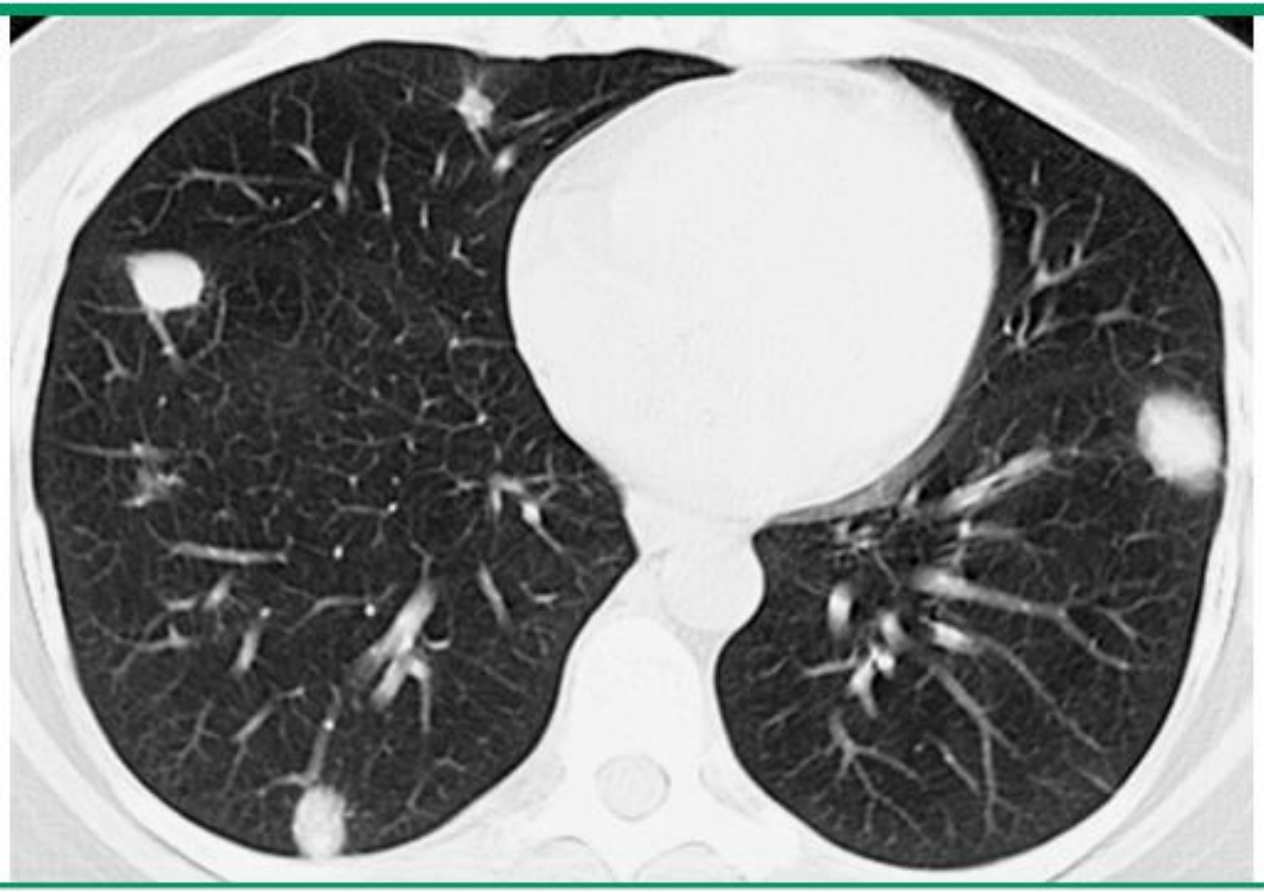
BOS

- Basınç yüksek
- Hücre sayısı düşük (HIV+'lerde daha düşük),
- Mononükler hücre (0-200) hakimiyeti
- Glukoz düşük
- Protein yüksek





Transverse computed tomography scan in 46-year-old woman shows several nodules in the lung bases (7 mm-thick section)



Most of the nodules have smooth margins.

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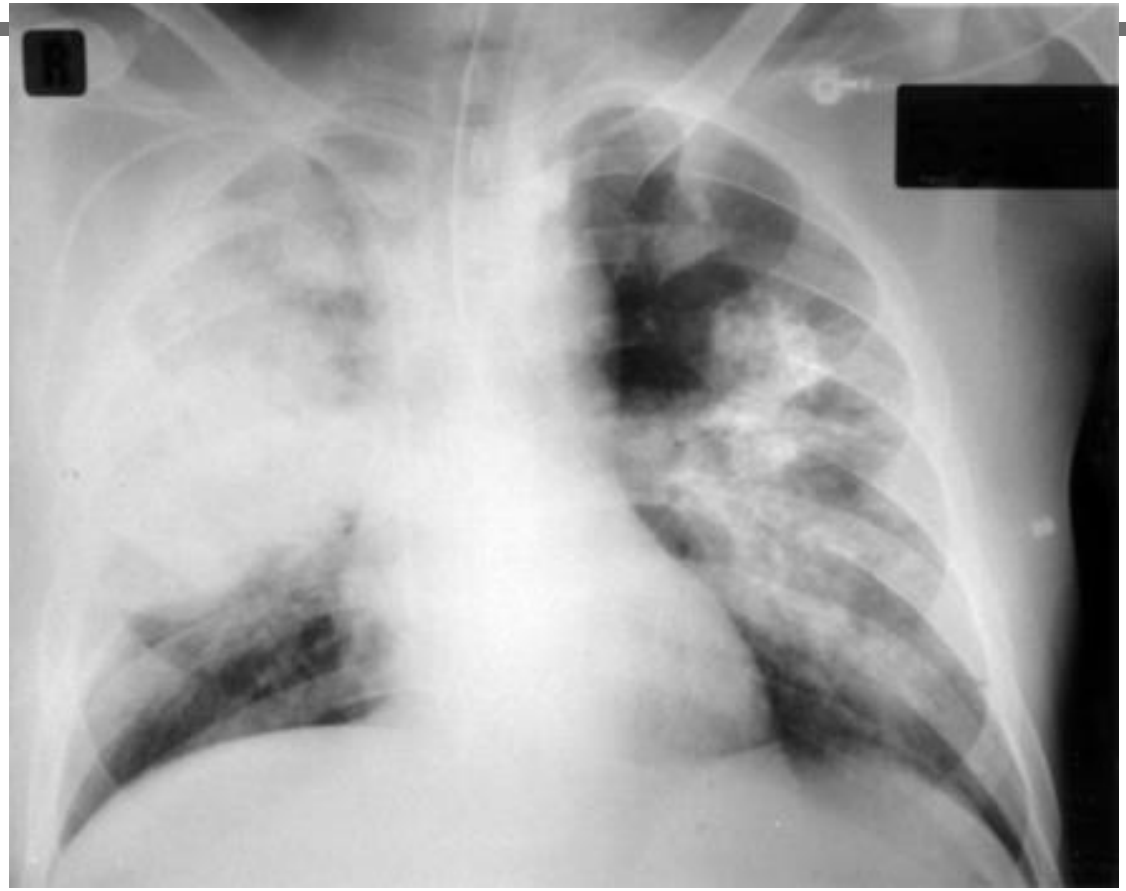
Kriptokok Pnömonisi

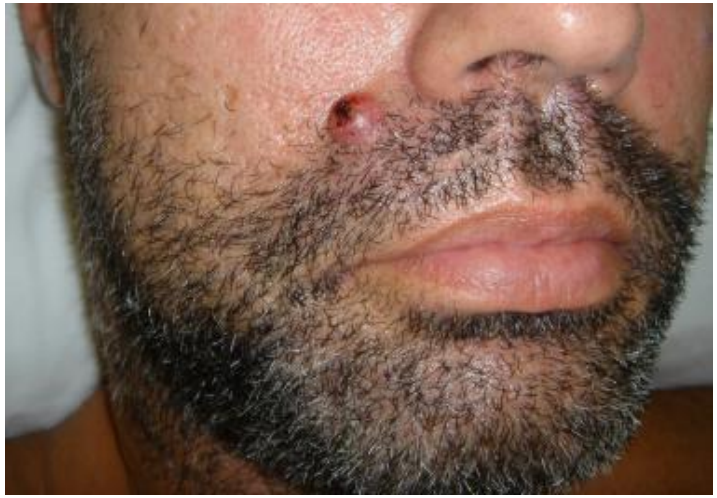


Asemptomatik antijenemi (%4-12)
veya kültür pozitifliğinde LP !

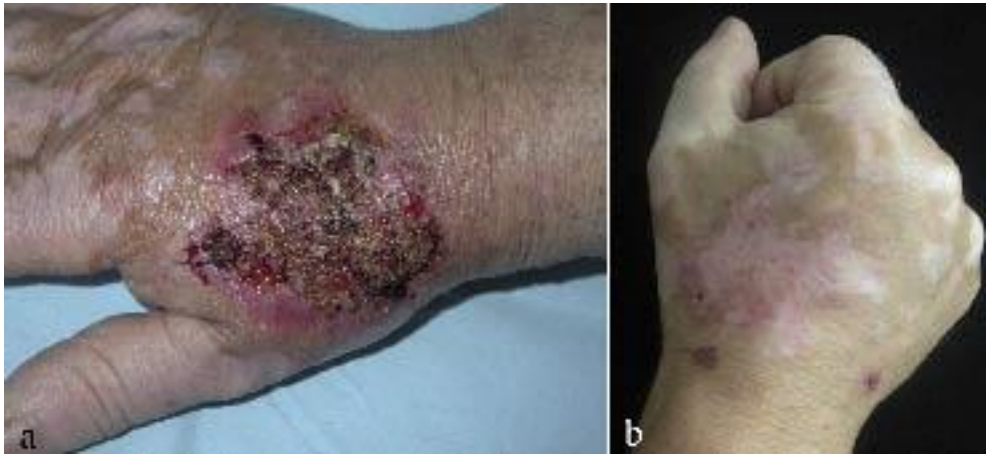
Çoğunlukla ekstrapulmoner infeksiyonlarla birlikte

http://thorax.bmj.com/content/53/7/554.full

Deri Kriptokokkozu



İmmunkompetan



İmmunokompromize

Kriptokok İnfeksiyonlarına Yatkınlık Sağlayan Koşullar

- HIV infeksiyonu
- Transplantasyon (kök hücre ve solid organ)
- Siroz
- Renal yetmezlik
- Kronik akciğer hastalığı
- Diabetes mellitus
- Cushing sendromu
- Glukokortikoid veya TNF-α antagonistleri
- Sarkoidoz
- Hiper IgM sendromu
- SLE

300 Kriptokok infeksiyonlu HIV-negatif hasta

- %50 MSS tutulumu

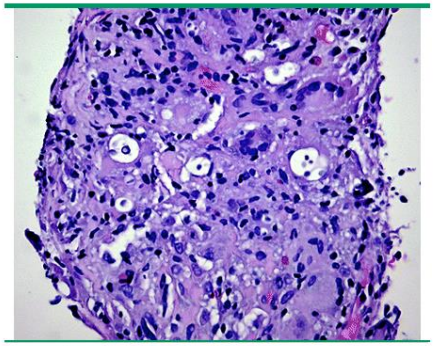
- %25 steroid tedavisi
- %24 kronik karaciğer, böbrek ya da akciğer hastalığı
- %16 malignansi
- %15 solid organ alıcısı

Pappas, P. G. *et al. Clin Infec. Dis 2001;* **33**, 690–699

Tanı

- Kültür (BOS'ta %90 pozitif)
- Histopatolojik inceleme
- Antijen testi (serum, BOS)
  - BOS'ta %93-100 duyarlılık, %93-98 özgüllük
- BOS'ta çini mürekkebi boyama
- Görüntüleme
- Lateral flow testi

Pleural biopsy with *Cryptococcus*



Hematoxylin and eosin stain of a pleural biopsy specimen from a patient with cryptococcal pneumonia.

Reproduced with permission from: Cartwright E, Rouphael N, Jain S, Iksoy N. Pleural Effusion in a Patient with AIDS. Clin Infect Dis 2008; 46:1887. Copyright ©2008 University of Chicago Press. UpToDate®

Cryptococcus neoformans on Sabouraud's agar

Culture of *Cryptococcus neoformans* on Sabouraud's agar.

Courtesy of Harriet Provine.

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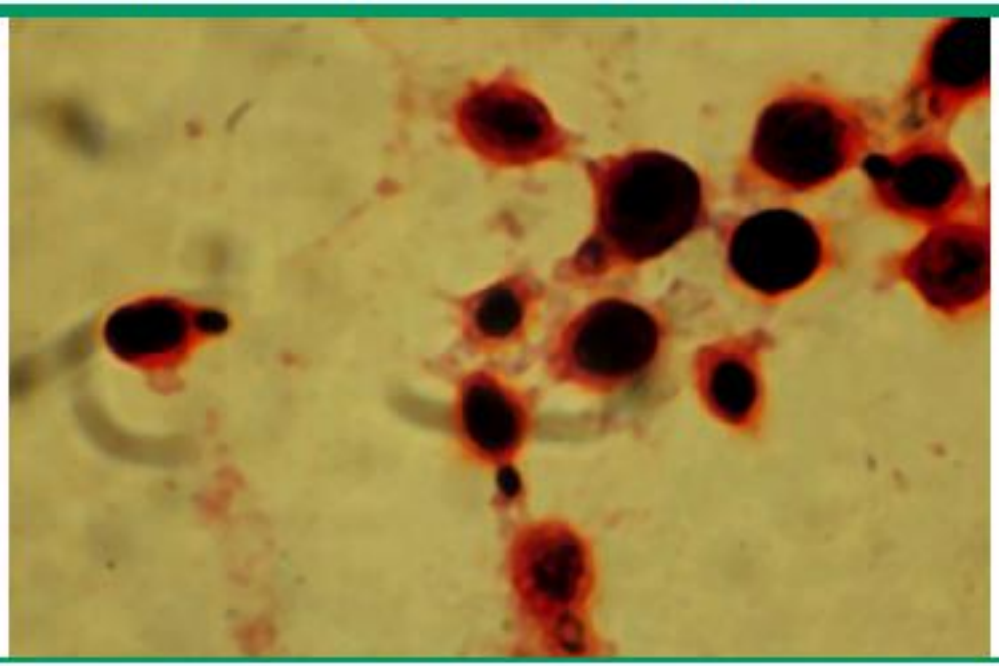
Cryptococcus neoformans in cerebrospinal fluid



Gram stain of cerebrospinal fluid (x1000) shows likely yeast forms, a few with cell walls and budding. These forms can be confused with host cells on the Gram stain and are more easily identified by India ink. The most definitive procedures are testing for cryptococcal antigen and culture. Cryptococcus neoformans grew from this specimen.

Courtesy of Harriet Provine.

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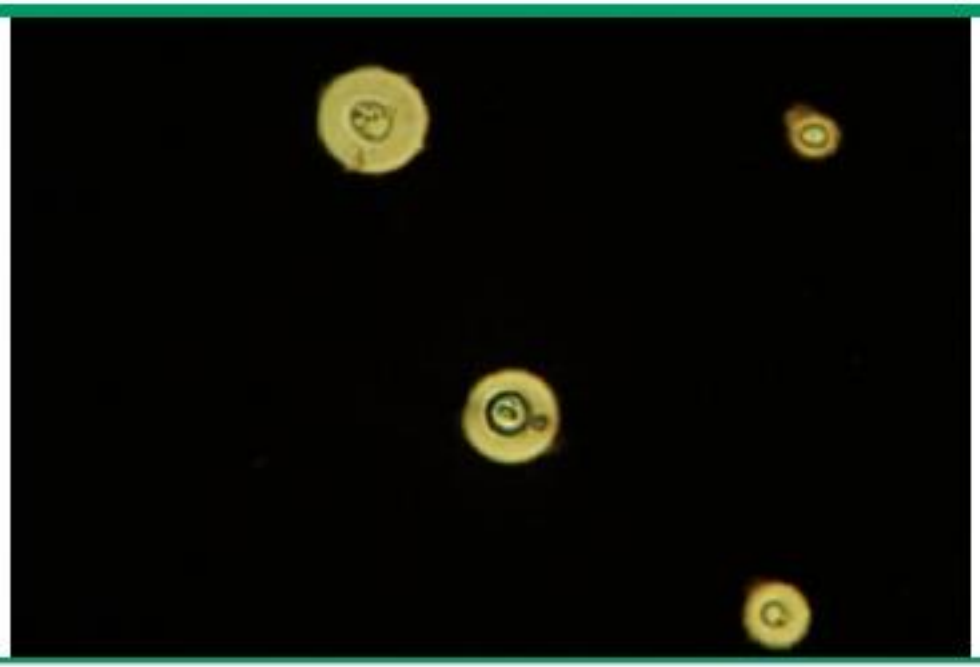
Cryptococcus neoformans in an India ink preparation



India ink preparation of cerebrospinal fluid (x400) shows a prominent clear zone around individual yeasts, consistent with the capsule of *Cryptococcus neoformans*. The yeast in the center of the slide is budding.

Courtesy of Harriet Provine.

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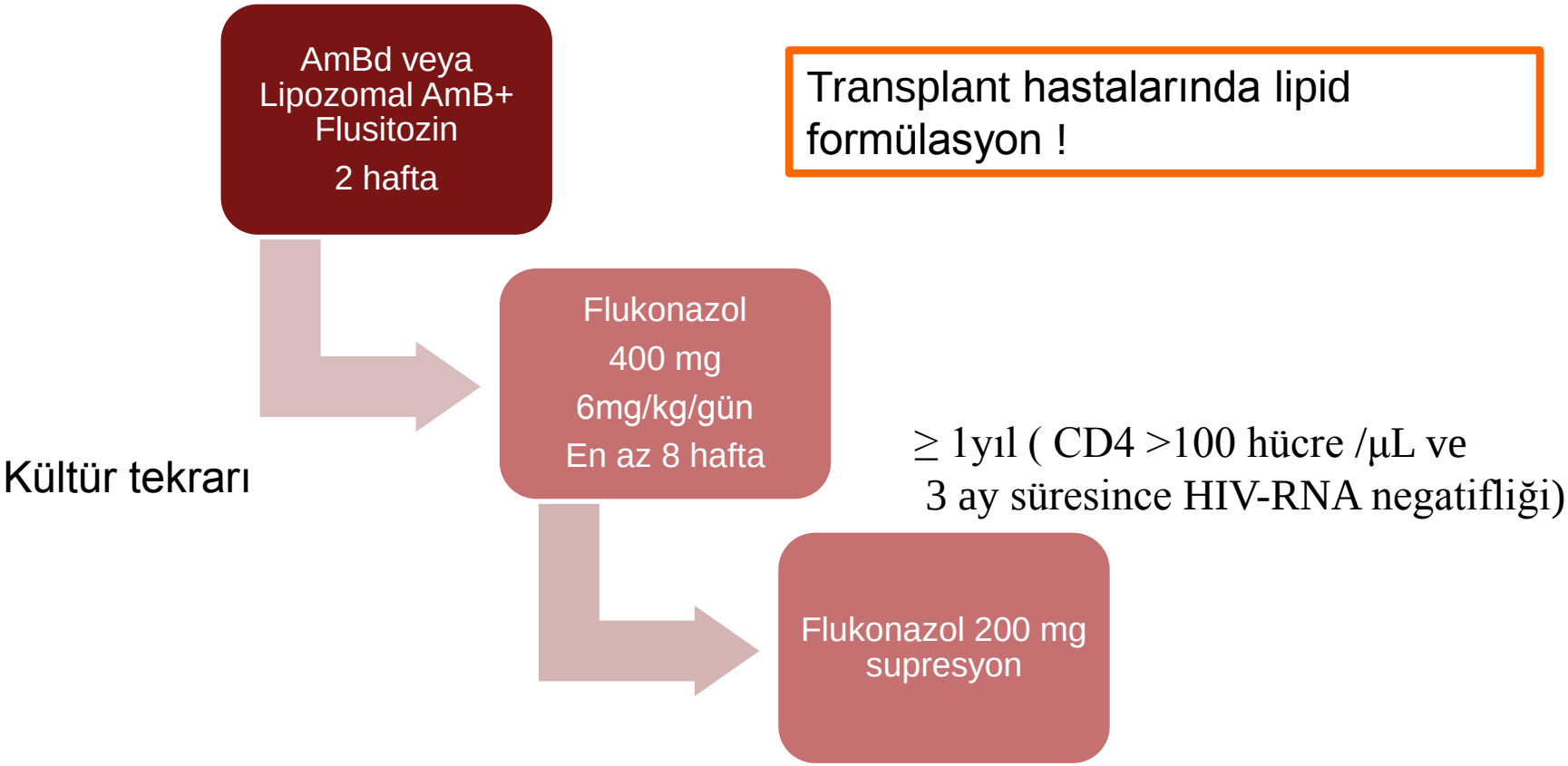
Kriptokok Meningoensefalit Tedavisi

- Antifungal tedavi
- BOS basıncı monitörizasyonu
- İmmunosupresif tedavinin azaltılması

Kriptokok Meningoensefalit Primer Tedavi (HIV+)

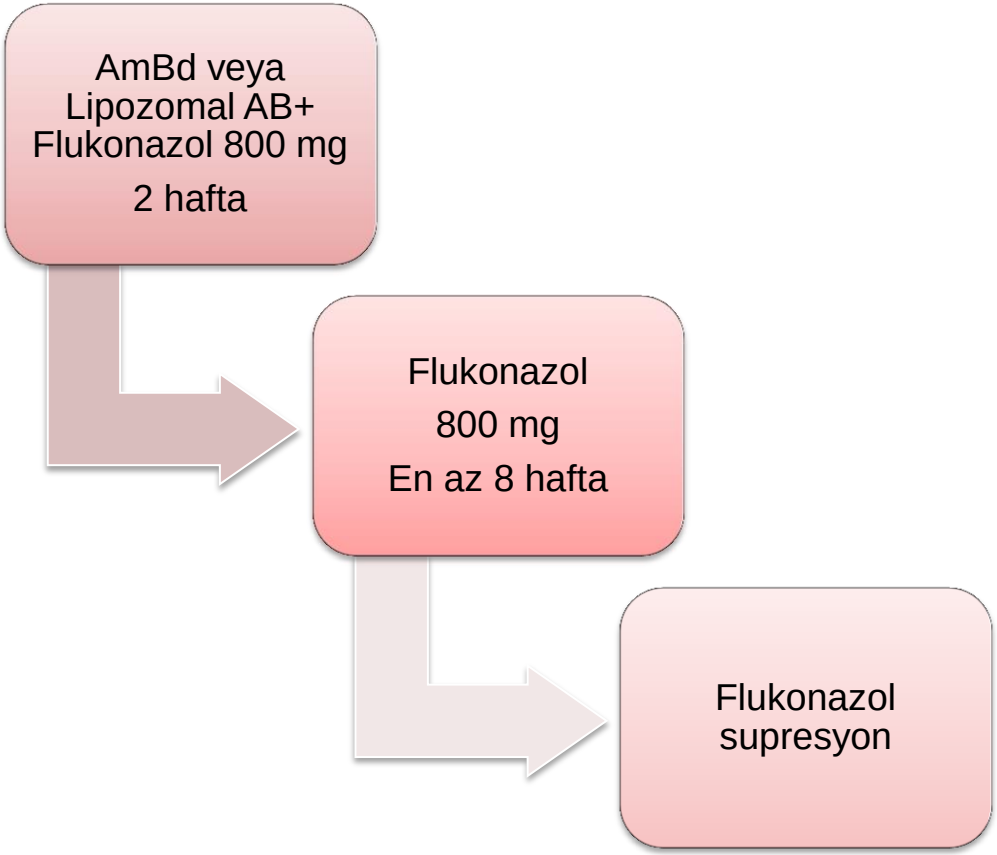
- Lipozomal amfoterisin B : 3-5 mg/Kg/gün, AmB-LC: 5 mg/kg
- Amfoterisin B deoksikolat 0,7-1 mg/kg +
- Flusitozin: 100 mg/kg/gün (4 dozda)



Guidelines for Management of Cryptococcosis • **CID 2010:50 (1 February)** • 317

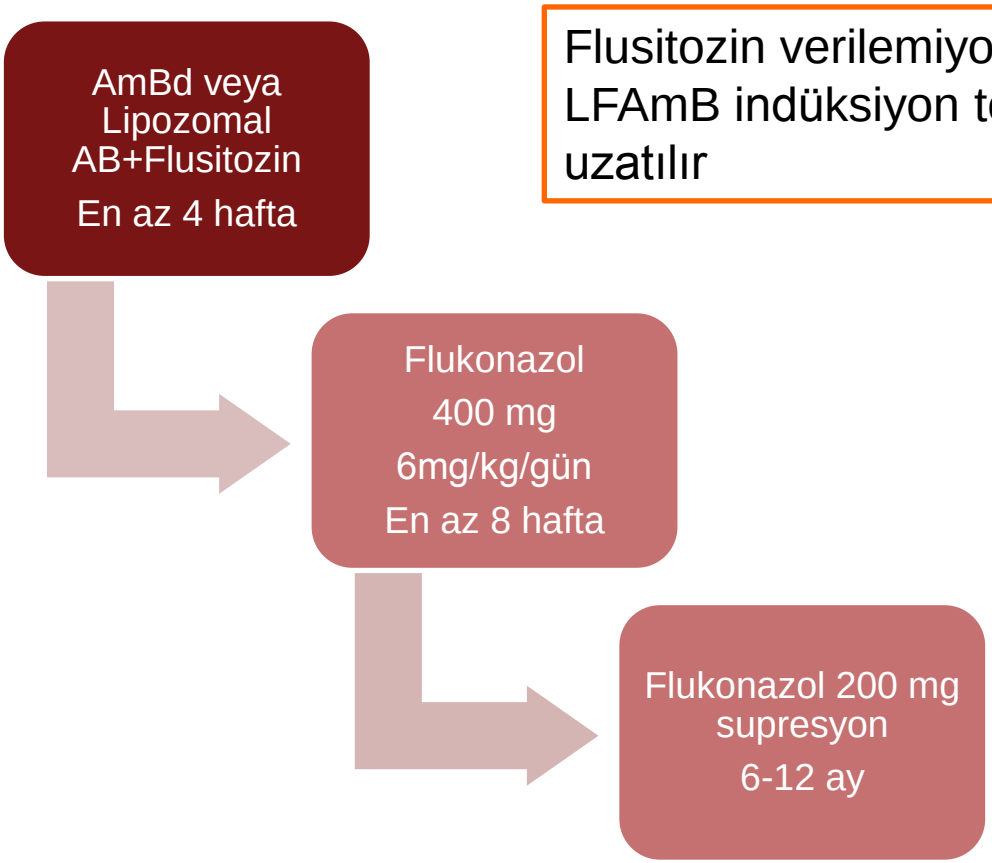
Kriptokok Meningoensefaliti Diğer Seçenekler (HIV+)

Amfoterisin B ; 4-6 hafta
(böbrek yetmezliği, tedavi yanıtsızlığı veya ağır hastalıkta lipozomal tercih



Perfect CR, et al. Guidelines for Management of Cryptococcosis • **CID 2010:50 (1 February)** • 317

Kriptokok Meningoensefaliti non-HIV+, non transplant



Flusitozin verilemiyorsa AmBd veya LFAmB indüksiyon tedavisi en az iki hafta uzatılır

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Kötü Prognoz

- HIV dışı immunokompromize
- BOS’ta çini mürekkebi pozitifliği
- BOS hücre sayısı <20/mikroL
- BOS ya da serum antijen titresi başlangıçta >1:32
- Yüksek açılış basıncı

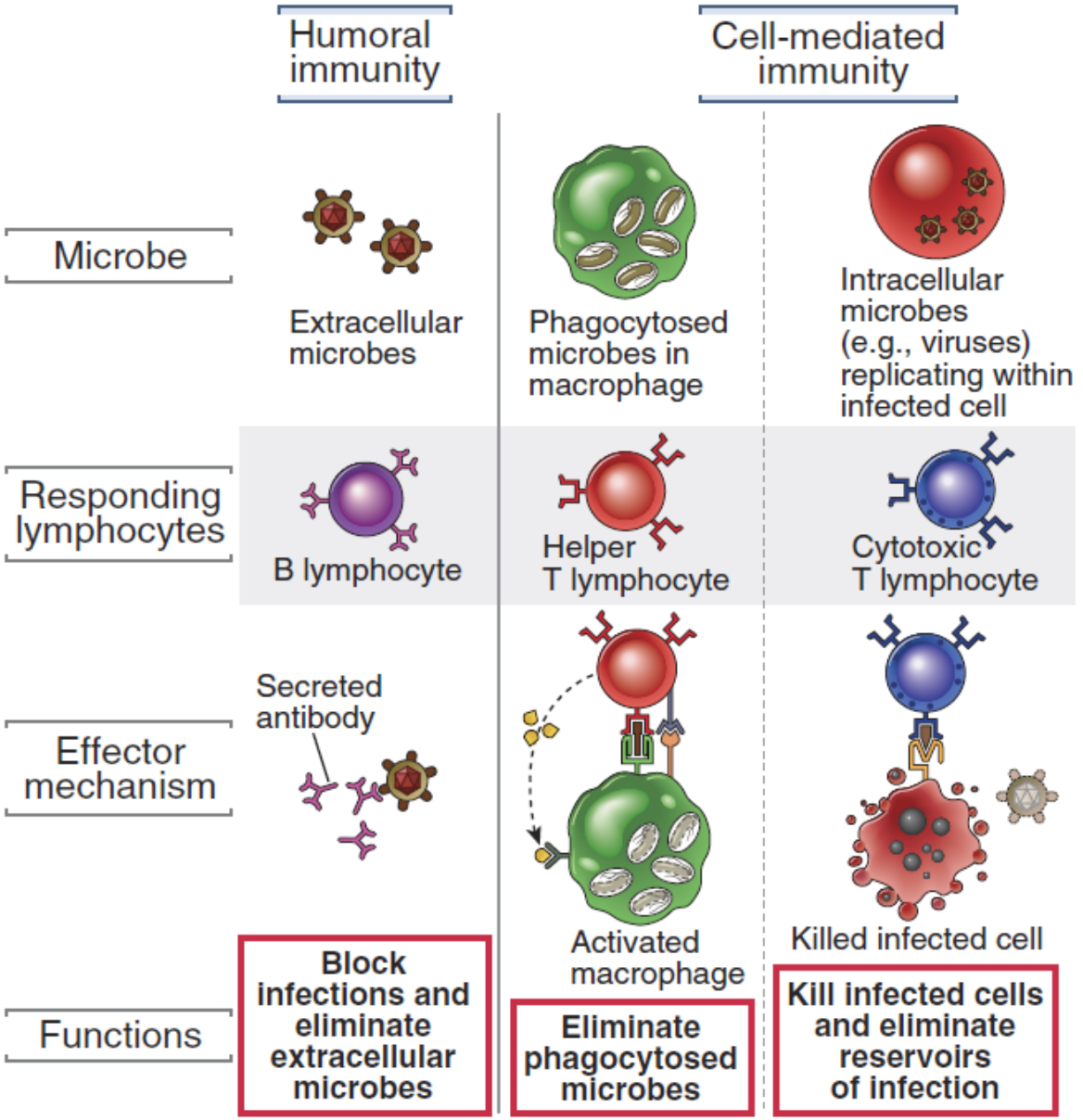
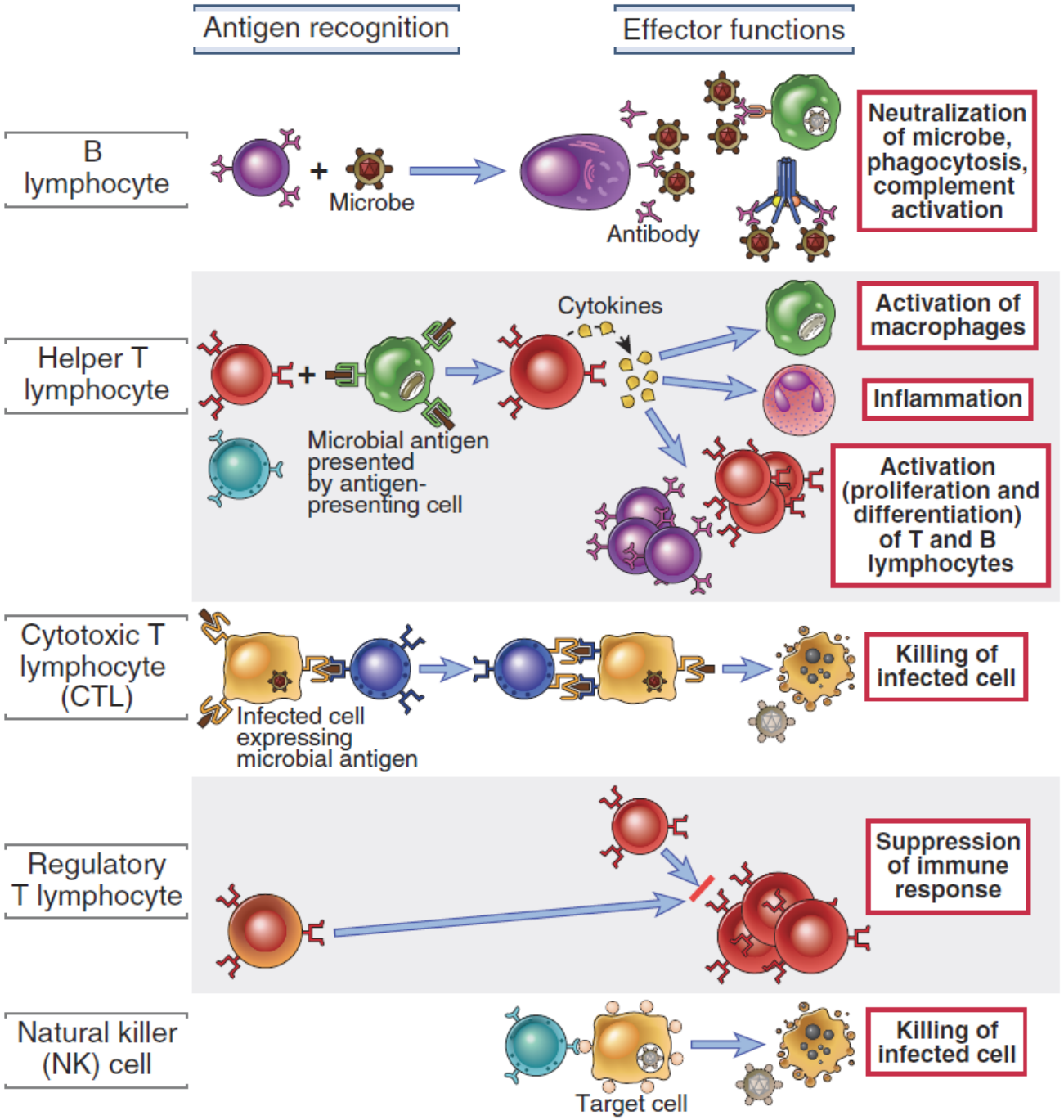


FIGURE 1–4 Types of adaptive immunity. In humoral immunity, B lymphocytes secrete antibodies that eliminate extracellular microbes. In cell-mediated immunity, different types of T lymphocytes recruit and activate phagocytes to destroy ingested microbes and kill infected cells.

Abbas AK, Lichtman AH, Pillai S. Basic Immunolgy, 2014



Abbas AK, Lichtman AH, Pillai S. Basic Immunolgy, 2014

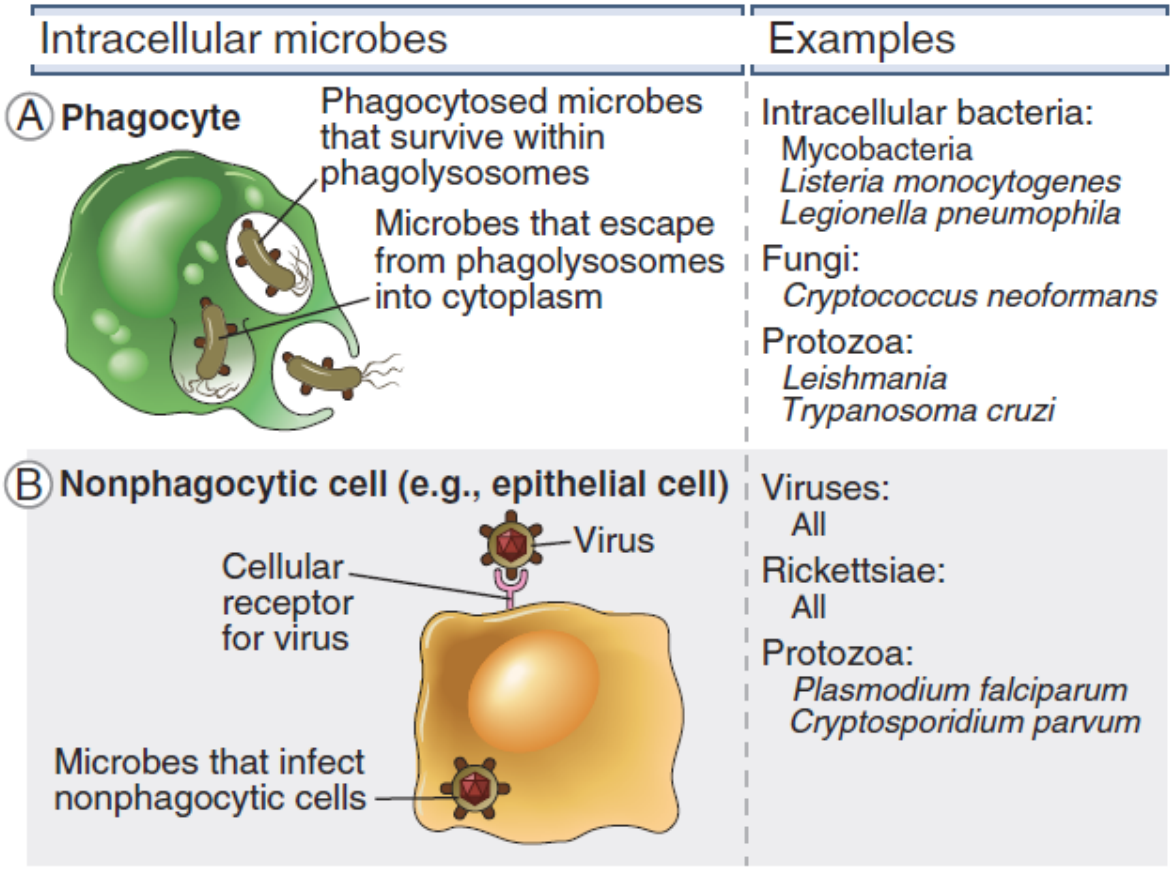


FIGURE 5–1 Types of intracellular microbes combated by T cell–mediated immunity. A, Microbes may be ingested by phagocytes and may survive within vesicles (phagolysosomes) or escape into the cytoplasm, where they are not susceptible to the microbicidal mechanisms of the phagocytes. **B,** Viruses may bind to receptors on many cell types, including nonphagocytic cells, and may replicate in the cytoplasm of the infected cells. Some viruses establish latent infections, in which viral proteins are produced in infected cells (not shown).

Abbas AK, Lichtman AH, Pillai S. Basic Immunolgy, 2014

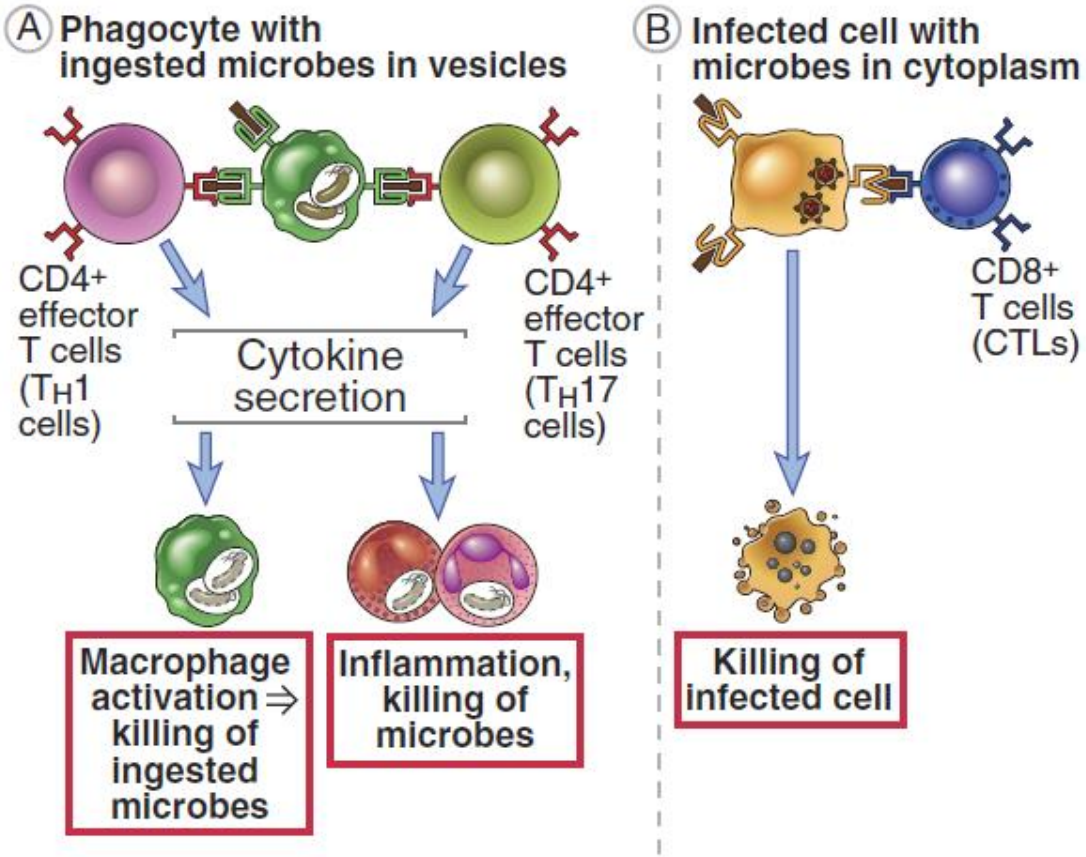


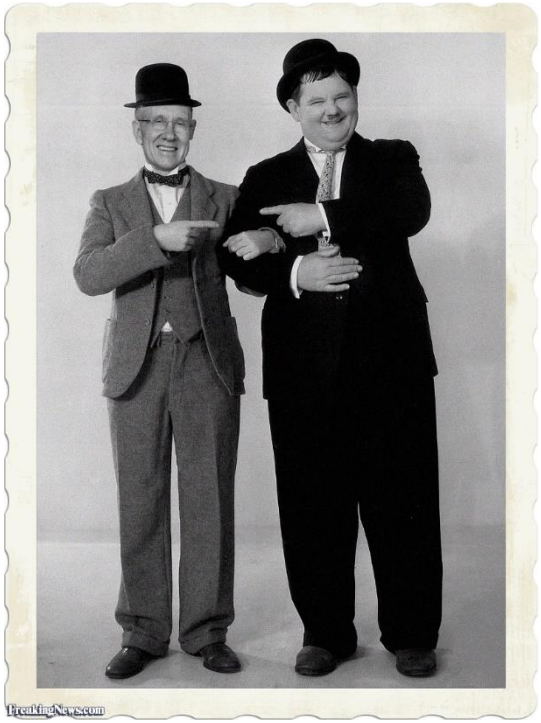
FIGURE 6–1 Cell-mediated immunity against intracellular microbes. A, Effector T helper cells of the $CD4^+$ T_H1 and T_H17 subsets recognize microbial antigens and secrete cytokines that recruit leukocytes (inflammation) and activate phagocytes to kill the microbes. $CD8^+$ T cells also produce cytokines that induce inflammation and activate macrophages (not shown). **B,** $CD8^+$ cytotoxic T lymphocytes (CTLs) kill infected cells with microbes in the cytoplasm.

Hücresel İmmün Yetmezlik ve İnfeksiyonlar

- Fırsatçı infeksiyonlar
- Hücre içi bakteriler
  - Ağır mikobakteri infeksiyonları
- Kronik mukokutanöz kandidiyaz
- P. jirovecii
- Yaygın fungal infeksiyonlar
- Yaygın ve kronik viral infeksiyonlar

Erişkinlerde İmmün Yetmezlikler

- Sekonder
- Primer



Hücresel İmmün Yetmezlikler

- Kalıtsal genetik bozukluklar
- **Sekonder immün yetmezlik**
- Geç ortaya çıkan primer immün yetmezlikler
  - Hipogamaglobulinemi ile birlikte CVID
  - (IFN)-γ ‘ye karşı antikor gelişimi
- IL-12 veya IFN-γ tip 1 sitokin yolağı defekti (yaygın *Mycobacterium avium* veya *Salmonella* infeksiyonları[1]

Current Allergy & Clinical Immunology, March 2008 Vol 21, No. 1

Ajanlar	Etki	İlişkili patojen
Kortikosteroid	Kemotaksis azalma, fagositoz ve mikrobisidal fonk. inhibisyonu	Herpes virus, *Candida* spp. bacteriler, *P. jirovecii*
Sitotoksik ilaçlar: methotreksat, f-florourasil, siklofosfamid, ……	Kemik iliği supresyonu, bazıları lenfopeni, mukozit	Gram-pozitif ve negatif bakteriler, Candida, invasive küfler, Cryptoco.
Purin analogları	Neutropenia, lymphopenia, ± hypogammaglobulinemia	Kapsüllü bakteriler Herpes virusler, Mikobakteri, Candida, Aspergillus, Cryptococcus
Azathioprin	B- ve T hücre proliferasyonunun inhibisyonu, Ak. üretiminde azalma, myelosupresyon	Bakteriler, herpes zoster, CMV, JC virus (PML), HBV, HCV alevlenme, P*. jirovecii, Nocardia*
Siklosporin, takrolimus	T hücrelerinden IL-2 ve diğer sitokin salınım inhibisyonu	CMV, EBV PTLD, JC virus (PML),BK polyomavirus nephropathy, HCV reakt.
Mikofenolat mofetil	B ve T hücre proliferasyon inhibisyonu, Ak. üretiminde azalma, lökopeni	Herpesvirus, HCV, HBV reakt., JC virus (PML),Candida , *P. jirovecii, Cryptococcus, Aspergillus, Mucor*
Rapamisin (sirolimus), everolimus	T hücre proliferasyon –aktivasyon inhibisyonu, Ak. Üretiminde azalma,	Herpesvirus, P. jirovecii, EBV-ilişkili PTLD, BK polyomavirus nefropati, JC virus(PML), mikobakteri inf.

TABLE 5 Biologic immune response modulators targeting lymphocytes

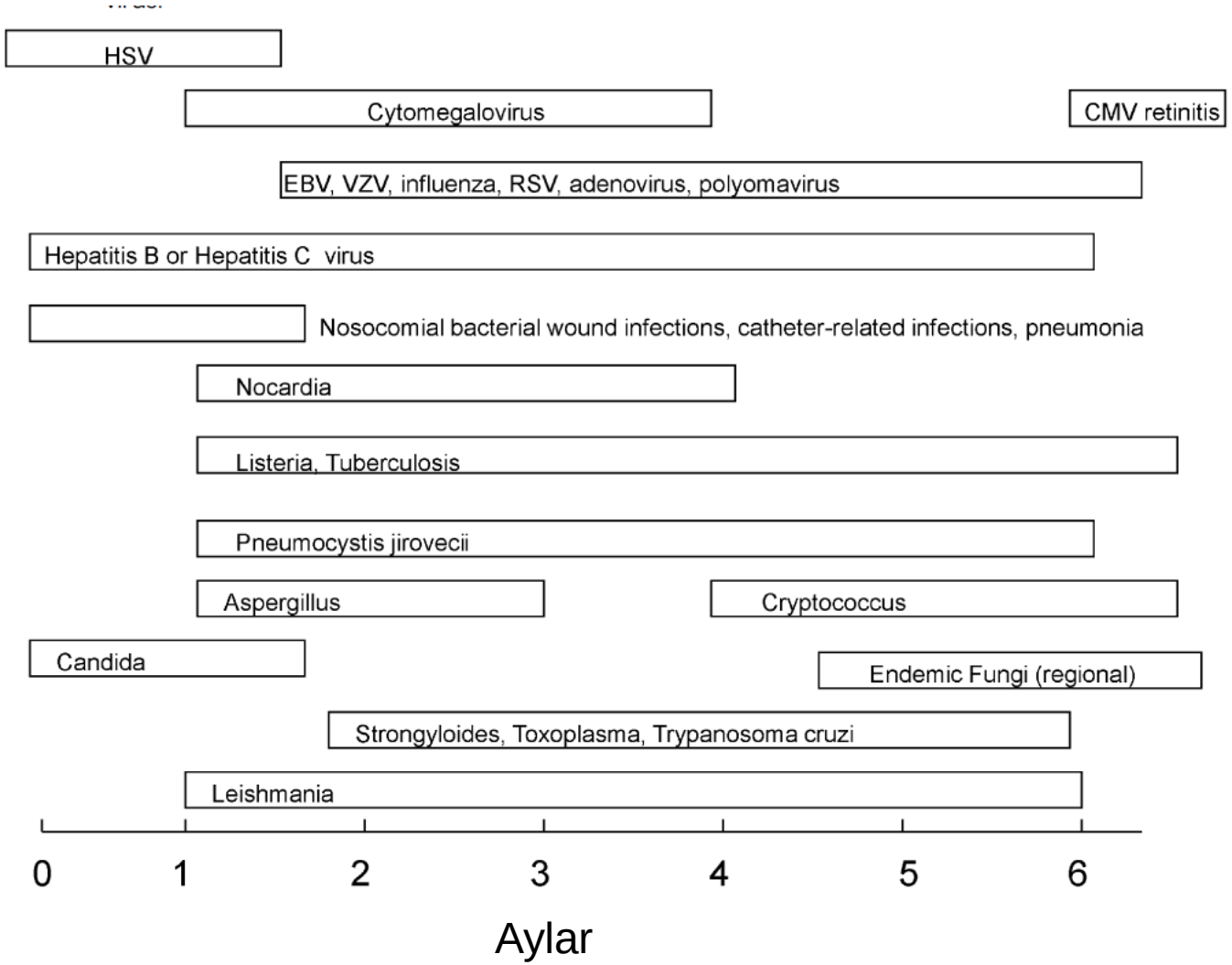
Immune response modulator	Agent(s)	Target cell	Mechanism(s)	Immunologic effects	Reported infectious complications[a]	Treatment indications
Anti-thymocyte globulin	ATG: Thymoglobulin (rabbit), Atgam (equine)	T lymphocyte	Polyclonal immunoglobulin against human T-cell markers; T-cell depletion by cell death; disruption of T-cell/antigen-presenting cell interaction	Depletion of circulating lymphocytes; alters function of T cells involved in humoral and cell-mediated immunity	Herpesvirus infections, particularly CMV, also HSV, EBV	Organ transplant rejection; graft-versus-host disease prophylaxis; aplastic anemia
Monoclonal antibodies to T cells	OKT3	T lymphocyte	Binds to TCR-CD3 complex on T cells and blocks T-cell proliferation and function	Profound T-cell lymphopenia and poor function	Herpesviruses (HSV, CMV, EBV-associated LPD); *P. jirovecii*, *Listeria*; *Mycobacteria*; *Nocardia*; *Toxoplasma*	Acute organ transplant rejection
	Basiliximab	T lymphocyte	Binds to IL-2 receptor alpha chain (CD25), inhibiting lymphocyte activation	Impairment of antigen-specific cytotoxic T-cell response	Incidence of infections not increased when added to dual immunosuppression regimens (steroids/ cyclosporine)	Organ transplant rejection; graft-versus-host disease
Monoclonal antibody to B cells	Rituximab Ofatumumab	B-cell from pre-B cell to pre-plasma cell stage	B-cell death by complement-, cell mediated-, and antibody-dependent cellular cytotoxicity	Peripheral B-cell depletion for 6 to 9 months or longer; hypogammaglobulinemia	Hepatitis B virus; hepatitis C virus, JC virus (PML), herpesviruses (HSV, VZV, CMV), parvovirus B19, West Nile virus, enteroviral encephalitis, if hypogammaglobulinemia severe; viral and bacterial sinusitis and pneumonia	B-cell non-Hodgkin's lymphoma; CLL; autoimmune disorders: RA, Wegener's granulomatosis, microscopic polyangiitis
	Belimumab	B-lymphocytes	Inhibits the binding of soluble human B-lymphocyte stimulator protein (BLyS) to its receptors on B cells	Inhibits the survival of B cells; reduces differentiation of B cells into immunoglobulin-producing plasma cells	Cellulitis; pneumonia; JC virus (PML); CMV pneumonia; *coccidiomycosis*	Systemic lupus erythematosus
Monoclonal antibody to T and B cells	Alemtuzumab (Campath and Lemtrada)	T and B lymphocytes, plus monocytes, macrophages, and natural killer cells	Antibody-dependent and complement-mediated cell lysis after binding to CD52	Profound and prolonged depletion of T and B lymphocytes, natural killer cells, and monocytes	Bacterial sepsis; pneumonia; herpesviruses (HSV, CMV, VZV, EBV-associated LPD); hepatitis B virus, hepatitis C virus; adenovirus; JC virus; PML; IFI: aspergillosis, mucormycosis, histoplasmosis, cryptococcosis, pneumocystosis; *Nocardia*; *Mycobacteria*; *Toxoplasma*	Campath for B cell chronic lymphocytic leukemia; Lemtrada for relapsing, remitting multiple sclerosis
Fusion proteins disrupting T-cell costimulation	Abatacept	T lymphocyte	Binds to CD80 and CD86 antigen-presenting cells	Suppresses T-cell activation	Bacterial pneumonia; cellulitis; urinary tract infection	Refractory rheumatoid arthritis; juvenile idiopathic arthritis

TABLE 6 Biologic immune response modulators targeting cytokines and other immune mediators

Immune response modulator	Agent	Targeted immune mediator	Mechanism(s)	Immunologic effects	Reported infectious complications	Treatment indications[a]
Anticytokine therapies	Anakinra	IL-1 receptor	Recombinant human IL-1 receptor antagonist protein (IL-1Ra) competitively binds to IL-1 receptor	Inhibits immune and proinflammatory actions of IL-1	Increased risk of serious bacterial infection with doses ≥100 mg/day (cellulitis, pneumonia)	Moderate to severe rheumatoid arthritis; NOMID; TRAPS
	Tocilizumab	IL-6 receptor	Competitively blocks interaction of IL-6 with its receptor	Interferes with proliferation and differentiation of T cells and terminal differentiation of B cells	Bacterial pneumonia, cellulitis, sepsis; herpes zoster virus; tuberculous and nontuberculous mycobacteria; *P. jirovecii* pneumonia; invasive fungal infections	Moderate to severe rheumatoid arthritis; juvenile rheumatoid and idiopathic arthritis
	Infliximab (chimeric human mouse anti-TNFα mAb); Adalimumab (human anti-TNFα mAb); Golimumab (human anti-TNFα mAb); Etanercept (soluble TNFα receptor fusion protein); Certolizumab (pegol-pegylated Fab fragment of human mAb)	TNF	Bind to TNF-α	Impairment of differentiation of monocytes to macrophages; macrophage and phagosome activation; recruitment of neutrophils and macrophages; formation and maintenance of granulomas	Active and latent tuberculosis; bacterial pneumonia; herpes zoster virus; tuberculosis; nontuberculous mycobacteria; *Listeria*, *Legionella*, *Nocardia*, hepatitis B virus; hepatitis C virus; invasive fungal infections	Rheumatoid arthritis; psoriatic arthritis; seronegative spondyloarthropathies; inflammatory bowel disease; sarcoidosis
Inhibitors of leukocyte migration	Natalizumab	Alpha 4 integrin	Blocks integrin association with vascular receptors, limiting adhesion and transmigration of leukocytes from vasculature into tissues	Reduction of specific inflammatory cell populations in target tissues	PML; HSV and VZV encephalitis and meningitis	Multiple sclerosis; Crohn's disease; chronic moderate to severe plaque psoriasis
	Fingolimod	Sphingosine phosphate 1, 3, 4, and 5 receptors	Fingolimod-phosphate binds to sphingosine phosphate 1, 3, 4, and 5 receptors	Blocks lymphocyte egress from lymph nodes	PML; cryptococcal meningitis; disseminated primary herpes zoster virus; herpes simplex virus encephalitis	Multiple sclerosis
JAK Inhibitor	Tofacitinib	Janus-associated kinase (JAK) inhibitor	Inhibition of JAK prevents the phosphorylation and activation of signal transducers and activators of transcription (STATs)	Prevents cytokine and growth factor-mediated gene expression and intracellular activity of immune cells; reduces circulating NK cells and serum immunoglobulin levels	Bacterial pneumonia and cellulitis; TB; herpes zoster; EBV PTLD (in renal transplant); *Cryptococcus*; PCP; CMV; BK virus	Moderate to severe rheumatoid arthritis for patients with inadequate response to or intolerant of methotrexate
Monoclonal antibodies to complement	Eculizumab	C5	Binds complement protein C5, preventing cleavage into C5a and C5b	Inhibits terminal complement activation	Bacteremia/sepsis: meningococcal infections (*Neisseria meningitidis*), *S. pneumoniae*, *H. influenzae*	Atypical hemolytic uremic syndrome; paroxysmal nocturnal hemoglobinuria

[a]NOMID, neonatal onset multisystem inflammatory disease; TRAPS, tumor necrosis receptor-1-associated periodic syndrome.

Solid Organ Transplantasyonu Sonrası İnfeksiyon Riskleri

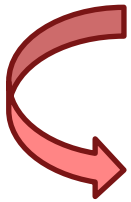


Hücresel İmmüniteyi Etkileyen Diğer Koşullar

- HIV
- EBV, Kızamık
- Kronik lenfositik lösemi
- Protein kaybettiren enteropati
- Yaş
  - Timik involüsyon >40 Y
  - Naif T hücrede azalma
  - Bellek hücre replikasyonunda azalma
  - Th2 yanıtına doğru kayma
  - CD4+/CD8+ oranında azalma
- Majör cerrahi, yanık
- SLE
- Siroz
- Son dönem böbrek yetmezliği

Hücresel İmmünitenin Değerlendirilmesi

- İyi bir öykü,
- Fizik İnceleme
- Periferik kan yayması
- Akış sitometrisinde CD3+, CD+,CD8+ hücre sayımı
- Deri testleri: Önerilmez
- İn vitro T hücre proliferasyon testleri



HIV antikor testi
T hücre sayımları
NK sayımı

Drobulic, Lederman. ASMscience.org/MicrobiolSpectrum,2016

Hücresel İmmün Yanıt Ölçümü

- Ne zaman
- Ağır viral, bakteriyel, fungal ve fırsatçı infeksiyonlarda
- Bir yaştan küçüklerde primer immün yetmezlikler
- Daha büyüklerde HIV infeksiyonu, iyatrojenik immün supresyon (otoimmün hst.lar, malignansi, transplantasyon)
- Nadiren hafif form primer kombine immün yetmezlik veya DiGeorge Sendromu

İleri Testler

- Flow sitometri de monoklonal antikor kullanarak aktive hücreler, regulator T hücreler, naif ya da bellek hücreler, B hücrelerinin gelişim aşamaları..
- T hücre reseptör excision circles (TRECs) ; timik fonksiyon ölçmede
- Sitotoksisite testleri: Sitotoksik T hücre ve NK hücrelerin fonksiyonunu ölçmekte
- Hücre, doku ve vücut sekresyonlarında sitokin ölçümü.
- Mutasyon analizleri (T hücre ve kombine defektlerde)
- Kromozom analizi (DiGeorge sendomu)
- HLA tiplendirme (SCID).
- ●CD3/T hücre reseptör analiz ve fonksiyonu

ÖZET

- Erişkinlerde sekonder T hücre yetmezliği/fonksiyon bozukluğu fazla
- Riskli popülasyon gün geçtikçe artıyor
- Hastaların dikkatle izlemi önemli

- **TEŞEKKÜRLER….**