Immunomodulatory Agents: What Can Be Tested

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5/29/26

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Disclosures of Financial Relationships with Relevant Commercial Interests

- Royalties from UpToDate

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General Principles

Immunomodulatory Agents

- **Why important**
  - Rapidly expanding therapeutics and applications
  - Mechanism of action => immune defect => distinct infection risks
- **High-yield board concepts**
  - Identify the immune deficit
  - Recognize classic infection associations
  - Known relevant screening and prophylaxis
  - Understand vaccine needs → timing, types, and contraindications
  - Recognize mimics → immunomodulatory toxicities vs underlying disease(s) vs infection
  - Be cognizant of FDA black-box warnings

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Key Immunomodulatory Agents*

- Lymphoid-cell targeted monoclonal antibodies (anti-CD20, anti-CD52)
- Tumor necrosis factor (TNF)-alpha inhibitors
- Janus kinase (JAK) inhibitors
- Interleukin (IL) inhibitors (IL-6 and IL-17 inhibitors)
- Complement inhibitors
- Sphingosine-1-phosphate (S1P) receptor modulators
- Immune checkpoint inhibitors (CTLA-4, PD-1, PD-L1 and LAG-3)
- Integrin inhibitors (natalizumab)
- Bruton tyrosine kinase inhibitors

**Note: CAR T-cell and Bispecific T-cell engager therapies discussed separately in the Infections in Neutropenic Cancer Patients Lecture; Lists of Agents/Clinical Uses are not exhaustive*

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General Principles
Immunomodulatory Therapies

SCREENING TESTS

- Viral hepatitis (B and C)
- Human immunodeficiency Virus (HIV)
- Latent tuberculosis
- Other geographic considerations
  - Endemic fungi
  - Strongyloides

VACCINATIONS

- Ensure up-to-date
- Relevant for age and therapy
- Timing pre-therapy
  - Inactivated @ least 2 weeks
  - Live, attenuated @ least 4 weeks
- Contraindications - live vaccines

KEY POINT TO REMEMBER: infection risks depend on multiple factors - age, geographic residence, comorbidities, preceding and concomitant immunosuppressive and immunomodulatory therapies, and time on therapy

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Question #1

68-year-old man, originally from Taiwan, with underlying follicular lymphoma, plans to initiate single-agent **rituximab** therapy.

Which of the baseline serologies would be **most important** when assessing infectious risks and the relevant need for prophylaxis with rituximab therapy?

A. Cytomegalovirus
B. Toxoplasmosis
C. Hepatitis A
D. Hepatitis B
E. Hepatitis C

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Lymphoid-cell Targeted Monoclonal Antibodies
Anti-CD20 Monoclonal Antibodies

- **Agents: *Rituximab*;** others: *obinutuzumab, ocrelizumab,* and *ofatumumab*
- **Uses:** broad - oncologic, autoimmune/inflammatory, hematologic (non-malignant), neurologic, renal, and transplant medicine
- **Infection risks:** prolonged B-cell depletion, hypogammaglobulinemia, and late-onset neutropenia (weeks to months post-exposure)
  - Appreciable impairment in vaccine response (@ least 6-12 months post-use), no LIVE vaccines
  - **Infection Prevention: HBV reactivation** high risk in HBsAg+ and HBcAb+/HBsAg-

Baseline HBV Testing (HBsAg, HBcAb, HBsAb) → Viral Prophylaxis (entecavir, tenofovir) Monitoring → Prophylaxis continued at least 12 months post-cessation

  - Other viruses (herpesvirus, JC virus and PML)
  - *Pneumocystis jirovecii* infection

Hwang JP et al. J Clin Oncol. 2020;38(31):3698.
Tétrault NA et al. Hepatology. 2018;67(4):1560.

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OL10 Immunomodulatory Agents: What Can Be Tested
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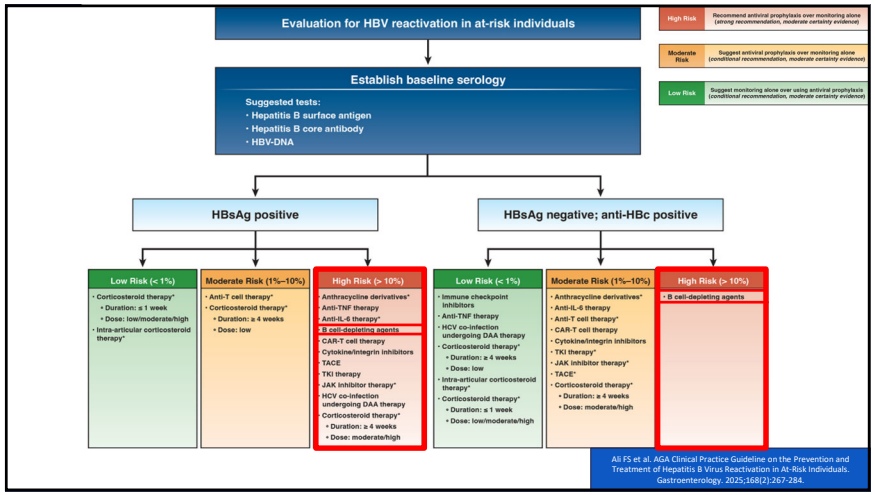

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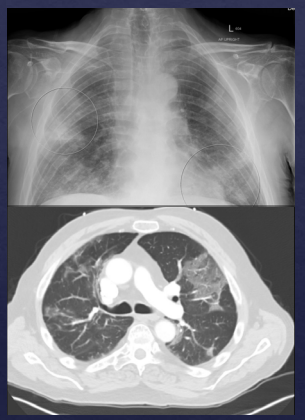
Question #2

63-year-old man with T-cell prolymphocytic leukemia on single-agent **alemtuzumab** therapy. Receiving acyclovir prophylaxis (for HSV/VZV) alongside preemptive therapy for CMV. Serial plasma CMV PCR testing has been negative tc-date.

Presents with a several-week history of slowly progressing shortness of breath and new low-grade non-neutropenic fevers. CXR followed by cross-sectional chest images are shown (R).

This presentation is likely due to the **lack of** which of the following recommended prophylactic therapies?

A. Letermovir
B. Valganciclovir
C. Entecavir
D. Levofloxacin
E. Sulfamethoxazole-Trimethoprim



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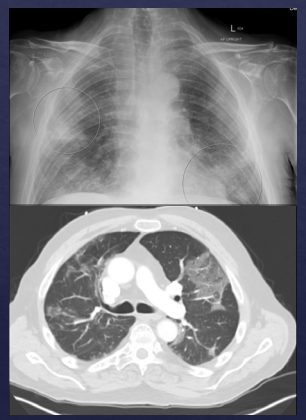

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Lymphoid-cell Targeted Monoclonal Antibodies
Anti-CD52 Monoclonal Antibodies

- **Agent: *Alemtuzumab* -** anti-CD52 Mab, present on B- and T lymphocytes, macrophages, and NK cells
- **Uses**: broad - oncology/hematology (e.g., CLL, T-PLL), transplant medicine, and autoimmune diseases
- **Infection risks:** due to prolonged B- and T-cell depletion, cytopenias
  - Viral infections - especially herpesvirus (e.g. ***CMV**, VZV, HSV), hepatitis B/C, rare JCV PML
  - Mycobacterial and fungal infections (e.g. PJP, *Aspergillus*)
  - Bacterial infections, including *Listeria monocytogenes*
- **Infection prevention:**
  - Viral and PJP prophylaxis – minimum 2 months after alemtuzumab and CD4 ≥ 200 cells/mcL
  - Pre-emptive CMV monitoring – minimum 2 months after alemtuzumab
  - Impaired vaccine response, no LIVE vaccines

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Question #3

A 35-year-old woman with refractory Crohn's disease is to scheduled to begin infliximab. She emigrated from India to the United States at age 14 and has no prior documented tuberculosis (TB) screening or TB infection.

She is currently well, without fevers, chronic cough, or other constitutional symptoms. An interferon-gamma release assay (IGRA) returns positive. What is the most appropriate next best step?

A. Cancel planned infliximab therapy and treat for active tuberculosis infection
B. Delay infliximab, obtain chest imaging and sputum AFB cultures, and if imaging normal, begin infliximab
C. No additional evaluation required, begin infliximab now
D. Delay infliximab, obtain chest imaging, and if normal, start latent TB therapy, then begin infliximab
E. Delay infliximab, obtain chest imaging, and if normal, complete a full course of latent TB therapy before starting infliximab

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Tumor Necrosis Factor (TNF)-Alpha Inhibitors

- **Agents**: **infliximab**, adalimumab, etanercept, certolizumab pegol, and golimumab
  - All are monoclonal Abs, except etanercept, a soluble receptor fusion protein
- **Uses**: autoimmune and inflammatory conditions (e.g., rheumatoid/psoriatic arthritis, inflammatory bowel disease)
- **Mechanism of Action/Immune defects**:

  TNF-α is important for
  - **Formation and maintenance of granulomas**
  - Development of phagosomes
  - Activation and differentiation of macrophages
  - Immune response against viral pathogens

Baddley JW et al. Clin Microbiol Infect. 2018;24 Suppl 2:S10-S20. PMID: 29459143.

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Tumor Necrosis Factor (TNF) Alpha Inhibitors
Infection Risks

- **Bacterial infections**
  - Including *Legionella, Listeria, Nocardia, Actinomyces, Salmonella*
  - *Tropheryma whipplei* (seronegative arthropathy->exacerbation of undiagnosed, subclinical Whipple's disease)
- **Mycobacterial infections:** including tuberculosis and non-tuberculous mycobacteria
  - **TB screening in ALL patients**

Screening: History, Exam, Imaging + IGRA>TST → **Screen POSITIVE:** -Rule out active TB -Initiate LTBI tx → **Timeline for LTBI:** PRIOR to TNF-α inhibitor start*

**Guidelines recommend at least 1-3 weeks of LTBI therapy, do not need to complete prior to start*

- **Viral hepatitis -** hepatitis B and C; (HBsAg+ high risk, HBsAg-/HBcAb+ lower risk)
- **Fungal infections**
  - ***Endemic fungi*** (**histoplasmosis**, blastomycosis, coccidioidomycosis)
  - Aspergillosis, PJP
- **Parasitic infections -** including Leishmaniasis
- **Vaccination status** - update prior to start, no LIVE vaccines

Mimics
-Heart failure
-Demyelinating disease
-Malignancies

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Question #4

What is the most effective first-line prevention strategy for the most common viral infection in patients who are initiating tofacitinib therapy for rheumatoid arthritis?

A. Pre-emptive monitoring with weekly cytomegalovirus plasma PCR
B. Acyclovir prophylaxis
C. Valganciclovir prophylaxis
D. Shingles (recombinant zoster) vaccination
E. Regularly scheduled intravenous immune globulin (IVIG)

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Question #4

What is the most effective first-line prevention strategy for the most common viral infection in patients who are initiating tofacitinib therapy for rheumatoid arthritis?

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B. Acyclovir prophylaxis
C. Valganciclovir prophylaxis
D. **Shingles (recombinant zoster) vaccination**
E. Regularly scheduled intravenous immune globulin (IVIG)

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Janus-Kinase Inhibitors

AGENTS and USES

- **Autoimmune/inflammatory disease JAK inhibitors** (e.g., rheumatoid and psoriatic arthritis, Crohn's disease, ulcerative colitis, atopic dermatitis, giant cell arteritis)
  - Tofacitinib – JAK1/JAK3
  - Baricitinib - JAK1/JAK2
  - Upadacitinib and Abrocitinib - JAK1-selective
- **Hematology-Oncology JAK inhibitors** [e.g., myelo, myelofibrosis, polycythemia vera, graft-versus-host disease (GVHD)]
  - Ruxolitinib – JAK1/JAK2
  - Fedratinib – JAK2-selective, used for myelofibrosis

MECHANISM/IMMUNE DEFECTS

- Inhibition of JAK-STAT pathways
  - Reduced cytokine production
  - Reduced immune cell development
  - Cytopenias (JAK2 inhibition)
- Impact on both innate and adaptive immunity

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Janus-Kinase Inhibitors
Infection Risks

- Black box warning - bacterial, fungal, viral, and other OIs
- **Bacterial infections** - severe pneumonia/bronchitis, UTI, cellulitis
- **Viral infections**
  - **Herpes zoster reactivation – most common**
  - Other herpes virus, including HSV, CMV; rare JCV – PML
  - Viral hepatitis - HBV, HCV; HBsAg+ high risk, HBsAg-/HBcAb+ moderate risk
- **Fungal infections**
  - PJP (consider concomitant IST for prophylaxis considerations)
  - Endemic fungi (geographic history)
- **Mycobacterial infections** – TB, pre-transplant screening essential

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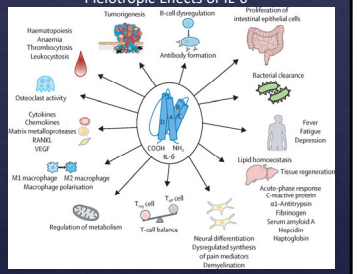
Interleukin-6 Inhibitors

- **Agents**:
  - Tocilizumab – monoclonal Ab targeting IL-6 receptor (others: sarilumab and satralizumab)
  - Siiltuximab – targets IL-6
- **Uses: (tocilizumab, including off-label):** rheumatoid arthritis, giant cell arteritis, COVID-19, cytokine release syndrome (CRS), neuromyelitis optica, Takayasu arteritis
- **Mechanism/immune defect:**
  - IL-6 best known for **prc-inflammatory effects** *(trans-signaling pathway involving gp130)*
  - Pleiotropic cytokine – anti-inflammatory, prc-resolution, and regenerative properties, **important for pathogen clearance** *(classic signaling pathway)*
  - mAbs do not discriminate between pathways – impacts on acute phase responses, neutrophil trafficking, B-cell maturation, and T-cell differentiation

Pleiotropic Effects of IL-6



McElvaney OJ et al. Lancet Respir Med. 2021;9(6):643-654. PMID: 33872590.

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Interleukin-6 Inhibitors
Infection Risks

- **Black box warning (tocilizumab, sarilumab)** – bacterial, mycobacterial, fungal, protozoal / OIs
- **Bacterial infections** – severe pneumonia/bronchitis, UTI, cellulitis
- **Viral infections** – herpesviruses, HBV, HCV; HBsAg+ high risk, HBsAg-/HBcAb+ moderate risk
- **Fungal infections** – PJP, cryptococcus, aspergillosis, candidiasis, endemic fungi
- **Mycobacterial infections** - TB, pre-transplant screening
- **Additional considerations**
  - May **mask typical signs and symptoms of infection** (fever, elevated inflammatory markers – CRP)
  - Consider the possibility of disseminated infections
  - **GI perforation risk** – distinct risk with IL-6 inhibitors, particularly in patients with diverticulitis +/- concurrent corticosteroids

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Question #5

A 55-year-old female started a new therapy for psoriasis 3 months ago. She presents with recurrent oral pain and tenderness alongside white plaques on the tongue and palate.

Which of the following was the most likely agent she was started on?

A. Acitretin
B. Cyclosporine
C. Infliximab
D. Etanercept
E. Bimekizumab

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C. Infliximab
D. Etanercept
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IL-17 Inhibitors

- **Agents:**
  - Monoclonal Abs targeting IL-17
  - Bimekizumab (dual IL-17A/IL17-F), ixekizumab (IL-17A), and secukinumab (IL-17A)
- **Uses:** autoimmune and inflammatory diseases – including psoriasis, ankylosing spondyloarthritis, hidradenitis suppurativa
- **Mechanism/immune defects:** reduces neutrophil recruitment and antimicrobial peptide production at mucosal/skin surfaces + gut epithelial barrier protection

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IL-17 Inhibitors
Infection Risks

- **Candidiasis** – oral, vaginal, typically mild-moderate, responsive to topical/oral antifungals
- **Bacterial infections** – primarily respiratory tract infections
- **Mycobacterial infections** – TB risk low overall, labeling still recommends screening*
- **Viral** – herpes viruses (HSV, VZV), hepatitis B/C screening; overall lower rates of HBV infection/reactivation
- **Other OIs** – uncommon
- **Potential mimic for inflammatory bowel disease (IBD)** – do not use in patients with active IBD, can cause new-onset or exacerbation of IBD

*Blauvelt A et al. Joint position statement from National Psoriasis Foundation Medical Board and the International Psoriasis Council on routine testing for latent tuberculosis infection prior to and during treatment of psoriasis patients with interleukin 17 or interleukin 23 inhibitors. J Am Acad Dermatol. 2026;94(3):802-809.

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Question #6

A 35-year-old female presents with fevers, headache, confusion, and a diffuse petechial rash. Four months ago, she was diagnosed with paroxysmal nocturnal hemoglobinuria after evaluation for abdominal pain, dark urine, hemolytic anemia, and portal vein thrombosis. She was started on eculizumab with improvement in symptoms.

On examination, temperature is 39.4°C (102.9°F), blood pressure is 86/52 mm Hg, and neck stiffness is present. Blood cultures grow gram-negative diplococci.

This patient's infection is most likely due to impaired:

A. Neutrophil respiratory burst
B. Terminal complement-mediated bacterial lysis
C. Interleukin-6 activity
D. Interleukin-17 activity
E. C3b-mediated opsonization

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Complement Inhibitors

- **Agents:**
  - mAbs (eg, eculizumab, ravulizumab, and crovalimab)
  - Peptides/macrocycles (eg, pegcetacoplan and zilucoplan)
  - Small molecule inhibitors (eg, avacopan, danicopan, and iptacopan)
- **Uses:** paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), generalized myasthenia gravis (gMG), neuromyelitis optica spectrum disorder (NMOSD), C3 glomerulopathy, immune complex–mediated membranoproliferative glomerulonephritis (IC-MPGN), IgA Nephropathy, and ANCA-associated vasculitis

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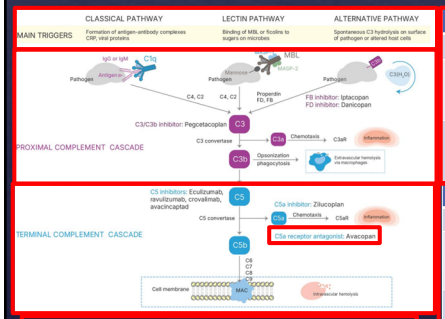
Complement Inhibitors
Mechanism/Immune Defects



PROXIMAL Cascade Inhibition	
Targets	C3, Factor B, Factor D
Therapies	C3/C3b inhibitor: pegcetacopan FB inhibitor: ipacopan FD inhibitor: danicopan
Infection Risk	Susceptibility to encapsulated bacteria, including *Neisseria*, *Streptococcus pneumoniae*, *Haemophilus influenzae*
TERMINAL Cascade Inhibition	
Targets	C5, C5a, or C5-C9 assembly
Therapies	C5 inhibitors: eculizumab, ravulizumab (mAb) C5a inhibitor: zilucoplan *C5a receptor antagonist: avacopan**
Infection Risk* (for C5/C5a inhibitors only)	-Markedly increased risk of *N. meningitidis* and other *Neisseria* spp -Some increased risk for *H. influenzae* and *Moraxella catarrhalis* -Encapsulated bacteria risk theoretically less than proximal inhibition

*Note that **avacopan** (C5a receptor antagonist) preserves MAC formation and does not carry meningococcal risk

Subramanian AK et al. Clin Infect Dis. 2026; PMID: 41711415

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Complement Inhibitors
Infection Prevention

- *Neisseria* infections
  - Meningococcal ACWY (quadrivalent) and B serogroup vaccines – initial series and boosters
    - At least 2 weeks prior to therapy start
    - If unable, antibiotic prophylaxis at least 2 weeks post-vaccination
    - Many experts continue antibiotic prophylaxis for duration of complement inhibitor therapy – *current practice is provider-dependent*
  - Recognize pre-treatment risks for **gonorrhea infection and test**
  - **Vaccination + antibiotic prophylaxis will not prevent all cases**
    - Non-vaccine-covered strains
    - Inadequate response to vaccine
    - Antimicrobial resistance
- **Other encapsulated bacteria** – ensure pneumococcal and *H. influenzae* vaccinations are also up-to-date, particularly with proximal complement inhibitors
- Education paramount – signs/symptoms of infection, when to seek immediate attention

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Sphingosine-1-phosphate (S1P) Receptor Modulators

- **Agents:** fingolimod, siponomod, ozanimod, and ponesimod
- **Uses**: multiple sclerosis, ulcerative colitis
- **Mechanism/Immune Defects**
  - Binds to S1P receptor on lymphocyte → receptor internalized → lymphocytes unable to follow S1P gradient to egress from lymph nodes
  - Essentially **sequesters lymphocytes in the lymph nodes**
- **Infection risks**
  - Bacterial (respiratory tract, skin/soft tissue, UTI)
  - **Viral (most common *VZV, including disseminated, *HSV**; rare PML – late onset 18 + months)
  - Fungal infections, including cryptococcus
  - Mycobacterial infections
- Potential mimics (PRES, hepatotoxicity, bradycardia)
- **Infection Prevention: VZV Ab screening – if seronegative, vaccinate (complete 1 month before start); recombinant zoster vaccine in immune patients**

McGinley MP, Cohen JA. Lancet. 2021 Sep;398(10306):1184-1194. PMID: 34175020.

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Question #7

A 35-year-old woman with relapsing remitting multiple sclerosis has been receiving natalizumab for 20 months.

Which of the following are not considered relevant for risk estimation for Progressive Multifocal Leukoencephalopathy (PML) to guide decisions regarding use of natalizumab therapy?

A. JCV antibody status
B. History of prior immunosuppressive therapies
C. Duration of natalizumab therapy
D. JCV antibody index
E. JCV plasma PCR

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Integrin Inhibitors
Natalizumab

Mechanism of action/immune defects

- Humanized IgG4 monoclonal antibody targeting the **α4 subunit of integrin**
  - Blocks T-cell, B-cell, and monocyte trafficking, adhesion and migration across the **blood-brain barrier**
  - Also binds MadCAm-1 on **gut endothelium**, decreasing migration of memory T cells.

Special Mention: differentiation of risk for integrin inhibitors

Agent	Target	Indication	High Yield Board Buzz
Natalizumab	α4 integrin	Multiple sclerosis, Crohn	PML – PML – PML
Vedolizumab*	α4β7 integrin	Ulcerative colitis, Crohn	Lower risk of infection

*decreases migration of memory T cells to GI tract only, as opposed to the CNS (natalizumab)

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Natalizumab
Infection Risks

- **JCV-associated progressive multifocal leukoencephalopathy**
- Herpesvirus infection
  - HSV, VZV
  - Particularly meningitis/encephalitis
  - Acute retinal necrosis
- General infection and opportunistic infections reported, often dependent on concomitant therapeutics

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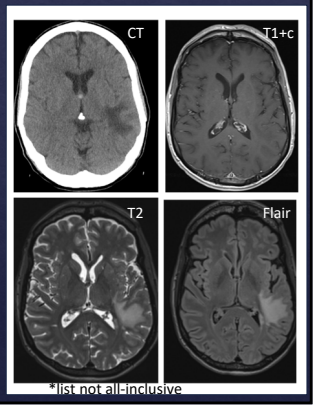
Progressive Multifocal Leukoencephalopathy (PML)

- Demyelinating CNS infection – associated with JC virus
- **Risk factors – presence of anti-JCV antibodies, duration of therapy, and prior use of immunosuppressants**
- Risk management program enrollment is required for use
- Clinical presentation
  - With close monitoring → goal is early detection when asymptomatic
  - Symptoms – progressive, subacute neurological deficits with cognitive impairment, limb and gait ataxia, weakness, visual changes, hemiparesis, aphasia
- Diagnostics - CNS imaging (*asymmetry, periventricular/subcortical, non-contrast enhancing, spares grey matter), CSF PCR, brain biopsy
- Treatment - no effective treatment; immune restoration key; immediate cessation of therapy and PLEX considered for removal of drug
- Risk for post-cessation immune reconstitution inflammatory syndrome (IRIS)



*list not all-inclusive

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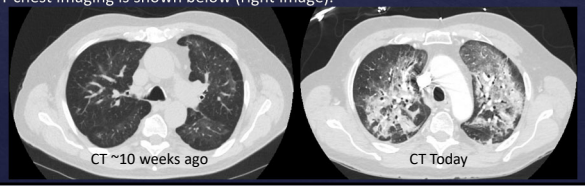
Question #8

A 54-year-old man with metastatic non-small cell lung cancer (NSCLC) on 3 months of combination therapy with nivolumab and ipilimumab presented with several weeks of progressing dyspnea and cough. CT chest showed diffuse ground-glass opacities (bottom left image). He was diagnosed with grade-2 immune checkpoint inhibitor-related pneumonitis. Prednisone 1mg/kg/day initiated with relatively rapid improvement. Plans were made for a slow steroid taper.

He now presents 8 weeks into his steroid taper (current dose: prednisone 30mg/day) with recurrent cough, dyspnea, new fevers to 38.6°C, and marked fatigue.

- Laboratory studies show a WBC of 12,000/µL with lymphopenia (absolute lymphocyte count 300/µL) and normal hepatic and renal indices.
- Repeat CT chest imaging is shown below (right image).



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Question #8 (continued)

Which of the following is the most appropriate next step?

A. Resume oral prednisone at 2mg/kg/day
B. Add infliximab 5mg/kg intravenous therapy
C. Add mycophenolate mofetil 1 g twice daily
D. Add trimethoprim-sulfamethoxazole (TMP-SMX) double strength three times weekly
E. Perform bronchoscopy with bronchoalveolar lavage (BAL) for bacterial, fungal, and AFB cultures, and PJP PCR

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Checkpoint Inhibitors

❖ **Agents**

Target	Example
PD-1	Pembrolizumab**, nivolumab**, cemiplimab
PD-L1	Atezolizumab, durvalumab, avelumab
CTLA-4	**Ipilimumab**, tremelimumab
LAG-3	Relatlimib (with nivolumab)

CTLA-4 ,cytotoxic T-lymphocyte–associated protein 4; PD-1, programmed cell death protein 1, PD-L1, programmed death-ligand 1; LAG-3, lymphocyte activation gene 3.

❖ **Uses:** melanoma, solid tumors (e.g., **NSCLC**, RCC, HCC, Bladder Ca), SCC, certain lymphomas

❖ Mechanism
- Target CTLA-4, PD-1, PD-L1 and LAG-3
- Block inhibitory receptors/ligands used by tumors to evade immune surveillance
- Result = **immune activation *(not immunosuppression)***

❖ Immune-Related Adverse Effects (irAEs)
- Autoimmune phenomena
- Can affect any organ system (lungs, GI, skin, endocrine, kidney, CNS, etc)
- Moderate-severe: require IST
  - Typically steroids
  - If refractory, other IST applied (e.g., TNF alpha inhibitors, mycophenolate)

❖ Highly testable
- **Infectious mimics**
- **Infectious complications**
  - Application of IST
  - Dysregulated immunity

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Presentation	irAEs of Checkpoint Inhibitors	Infectious Considerations
Wasting / Asthenia	Hypo-/hyperthyroidism, diabetes, hypophysitis, adrenal insufficiency	Endocarditis, PML, sepsis, colitis, chronic infections (syphilis, viral), thrush
Skin	Maculopapular rash, pruritus, vitiligo, autoimmune (pemphigus, eczema, psoriasis), vasculitis	Sepsis (candidemia, bacteremia), septic emboli (*Staphylococcus, Pseudomonas, Fusarium*), shingles, herpes simplex, cellulitis
Pulmonary	Pneumonitis (and organizing pneumonitis), sarcoidosis, interstitial fibrosis, pericarditis, myocarditis	Pneumonia involving bacteria, fungal (PJP, *Aspergillus*), viral (CMV, community respiratory), mycobacterial pathogens
Gastrointestinal including hepatic	Oral mucositis, enterocolitis, pancreatitis, perforation, hepatitis, cholangitis (primary biliary cholangitis)	Thrush, *Clostridium difficile* colitis, enteric pathogens and parasites, viral (norovirus, CMV), perforation, peritonitis, hepatitis viruses (ABCE), adenovirus, leptospirosis, mycobacteria
Headaches, confusion	Hypophysitis (pituitary enlargement), immune reconstitution, vasculitis (stroke), PRES, hypo-/hyperthyroidism,	Meningitis (bacterial, viral, *Cryptococcus*), encephalitis (HSV/VZV), endocarditis with septic embolus, abscess (*Aspergillus*)

Adapted from: Fishman JA et al. CID 2019 Clin Infect Dis. 2019;69(6):909-920. PMID: 30520987.

Additional Testable Concepts:
1) Opportunistic infections occur due to **immunosuppressive treatment** of IRAEs (e.g., steroids and PJP pneumonia) and/or **dysregulated immunity pathways (**e.g., latent TB or inflammatory TB presentations, viral reactivation); 2) Checkpoint inhibitors can cause cytokine release syndrome (*less common*)

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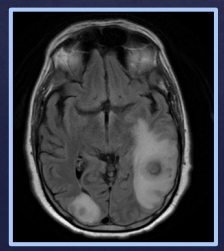
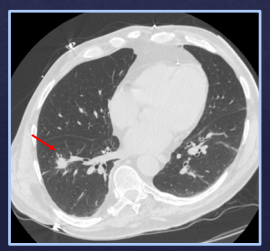
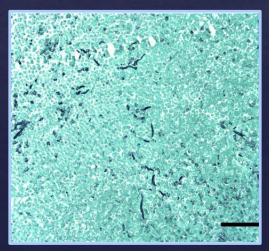
Bruton's Tyrosine Kinase (BTK) Inhibitors

Patient: 62-year-old man, underlying CLL on **single-agent ibrutinib** x 4 months

Presentation: fevers, confusion, dysarthria with significant word finding difficulties

Imaging: brain MRI + chest CT

Histopathology: brain biopsy

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Bruton's Tyrosine Kinase (BTK) Inhibitors

- **Agents**: include - **Ibrutinib**, Acalabrutinib, Zanubrutinib
- **Uses**: most commonly applied in CLL, lymphoma
- **Mechanism/Immune defects**: key enzyme in B-cell receptor signaling→ block downstream activation of B-cell receptor pathway, cell growth, macrophage function
- **Infectious risks**
  - Bacterial infections (most common)
  - Opportunistic fungal infections, inclusive of CNS involvement (e.g. *Aspergillus, Cryptococcus*, PJP)
- **Infection prevention**
  - Consider fungal (mold, PJP) and HSV/VZV prophylaxis if additional risk factors (inclusive of concomitant therapies)

Shah M et al. Transpl Infect Dis. 2024:e14283.

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Immunomodulatory Therapy	Examples	Board Buzz - Infection Risk
CD20 inhibitors	Rituximab, obintuzumab	Hepatitis B reactivation, impaired vaccine response, hypogammaglobulinemia, rare JCV PML
CD52 inhibitors	Alemtuzumab	PJP, CMV, HSV/VZV, other invasive fungal and opportunistic infections
TNF-alpha inhibitors	Infliximab, adalimumab	Tuberculosis, endemic fungi, other intracellular pathogens
Janus kinase inhibitors	Tofacitinib, ruxolitinib	Herpes zoster, TB, other opportunists
Interleukin-6 inhibitors	Tocilizumab, sarilumab	Severe infections, masked infectious signs/symptoms – normal CRP, GI perforation
Interleukin-17 inhibitors	Bimekizumab, secukinumab	Mucocutaneous candidiasis
Complement inhibitors	Eculizumab, ravulizumab	Severe/disseminated *Neisseria meningitis*, Gonococcal infections, other encapsulated bacteremia (Pneumococcus, *H. influenzae*)
Sphingosine 1-phosphate receptor modulators	Fingolimod, Siponimod	VZV infections, other viral infections (HSV, rare CMV, JCV-associated PML)
Integrin inhibitors	Natalizumab	PML (JC Virus)
Checkpoint inhibitors	Pembrolizumab, nivolumab, ipilimumab	PJP when treated for iRAEs and no prophylaxis, mimics from iRAEs (pneumonitis, colitis)
Bruton's tyrosine kinase inhibitors	Ibrutinib, acalabrutinib	Invasive fungal infections (aspergillosis, cryptococcosis), including CNS involvement/dissemination

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Questions / Comments

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