Infectious Diseases in Immunosuppressed Patients

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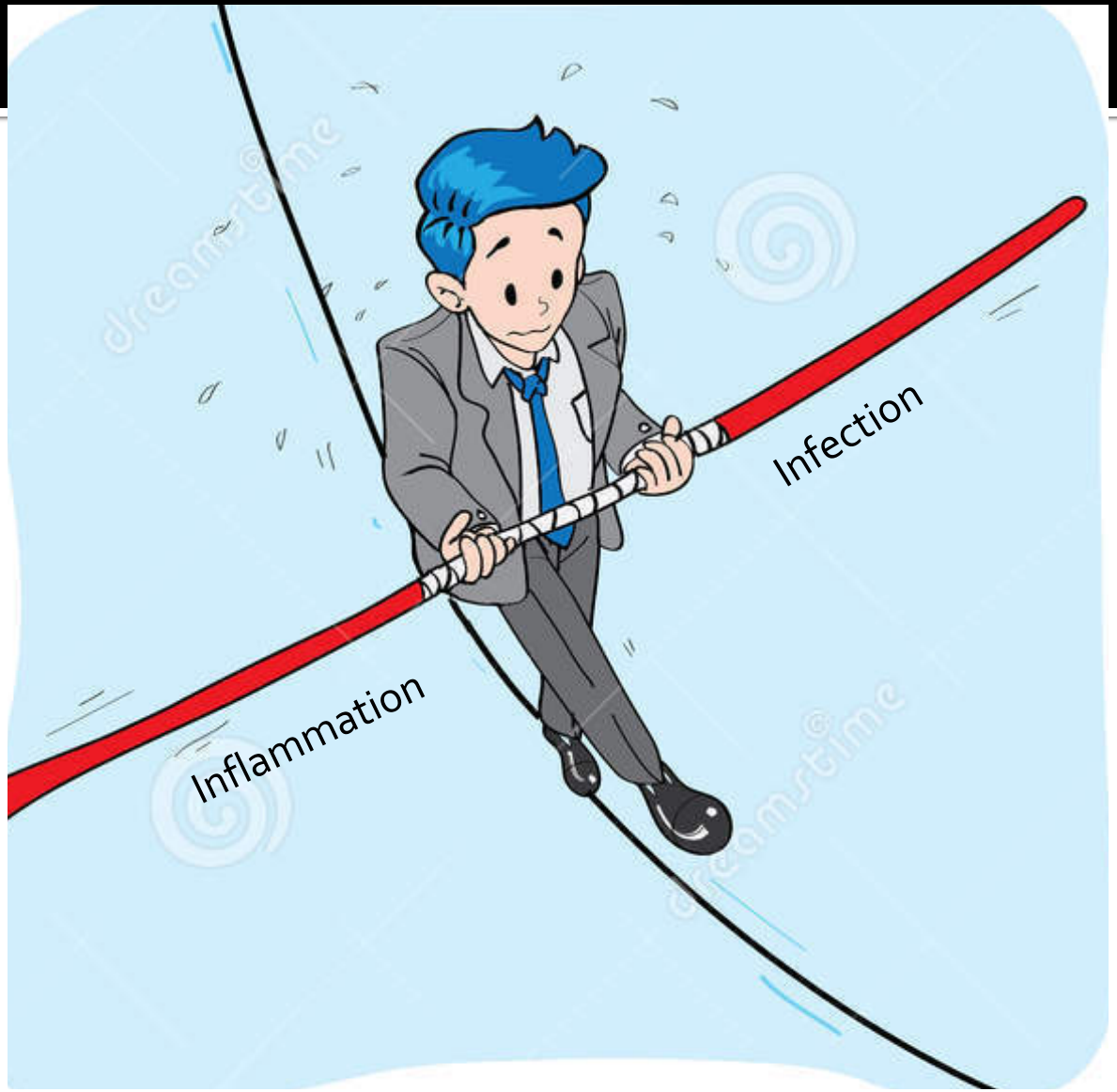

Infection
Inflammation

Infectious risk not all the same

Topics to Discuss

- Glucocorticosteroids
- Methotrexate
- TNF-inhibitors
- IL-inhibitors
- B cell depletion therapy
- Kinase inhibitors
- PML
- Herpes Zoster
- Histoplasmosis
- Cryptococcus
- PJP
- Tuberculosis
- Hepatitis B

Glucocorticosteroids and Immunity

- Inhibitory effects on broad range of specific immune responses mediated by T & B cells
- Suppressive effects on effector functions of phagocytes
- < 10 mg qd prednisone, little or no infection risk
- > 40 mg qd prednisone, eight fold rise in infection risk

Methotrexate

- DNA synthesis inhibitor
- As monotherapy, not associated with opportunistic infection in most patients
- Used in combination with other immunosuppressants… serious and opportunistic infections encountered

Rheumatoid Arthritis and Infection Risk

Infection Type	Rate ration (RA/Non-RA)	95% CI
Total	1.53	1.41-1.65
Bacteremia/septicemia	1.50	1.10-2.08
Septic arthritis	14.89	6.12-73.71
Osteomyelitis	10.63	3.39-126.81
Lower respiratory tract	1.88	1.41-2.53
Skin/soft tissue	3.28	2.67-4.07
Intra-abdominal	2.76	1.39-6.22

Arthritis & Rheumatism 2002; 46(9)

Rheumatoid Arthritis and Infection Risk

Drug	Hazard ratio	95% CI
MTX	0.91	.57-1.45
Aza	1.24	.7-2.2
Cyclosporine	1.99	1.25-3.16
Cyclophosphamide	6.14	3.12-11.8
Glucocorticoids	1.90	1.47-2.47

Arthritis & Rheumatism 2002; 46(9)

TNF-Inhibitors

- Infliximab (Remicade)
- Adalimumab (Humira)
- Etanercept (Enbrel)
- Certolizumab pegol (Cimzia)
- Golimumab (Simponi)

TNF-alpha aids in macrophage and phagosome activation and recruitment, granuloma formation

All the following pathogens can be controlled via granuloma sequestration except…?

A. *Toxoplasma gondii*
B. *Legionella pneumonia*
C. *Mycobacterium tuberculosis*
D. *Aspergillus fumigatus*
E. *Histoplasma capsulatum*

Pathogens Controlled via Granuloma Sequestration

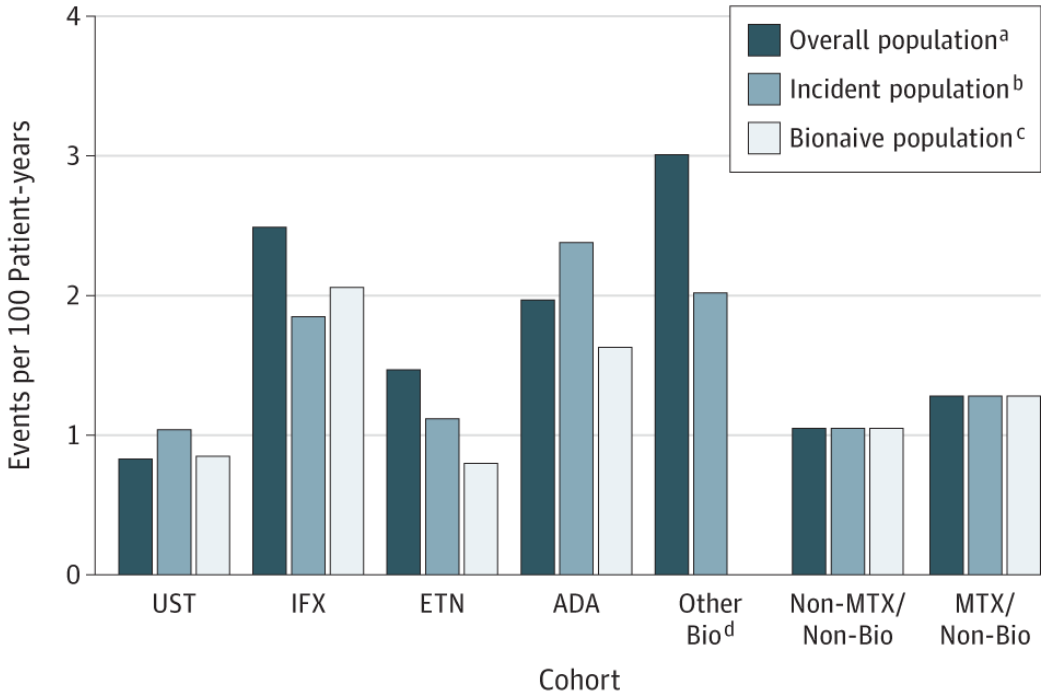
- *Mycobacterium tuberculosis*
- *Mycobacterium avium*
- *Histoplasma capsulatum*
- *Cryptococcus neoformans*
- *Coccidioides immitis*
- *Toxoplasma gondii*
- *Aspergillus fumigatus*

Other Pathogens

- *Legionella pneumonia*
- *Listeria monocytogenes*
- Herpes Zoster
- Hepatitis B/C

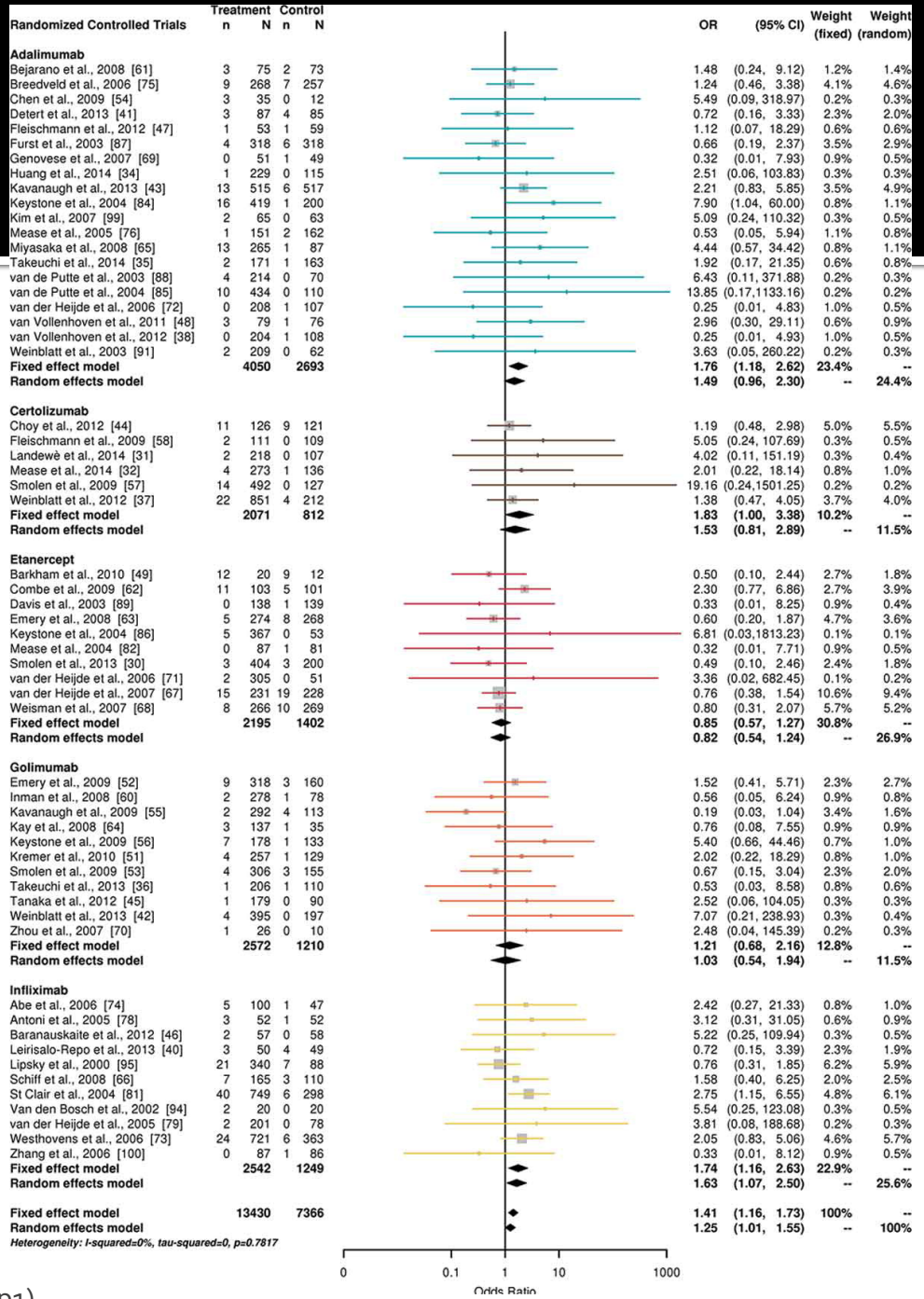
TNF-inhibitors

Cumulative Incidence of Serious Infections (PSOLAR)



JAMA Dermatol 2015;151(9)

TNF-inhibitors: Risk of serious infection



Expert Opin Drug Saf 2016;15(sup1)

Which biological agent has been associated with PML?

A. Infliximab (Remicade)
B. Rituximab (Rituxan)
C. Ustekinumab (Stelara)
D. Natalizumab (Tysabri)
E. Secukinumab (Cosentyx)
F. B and D
G. All of the above

IL-inhibitors

IL-inhibitors	Infectious Risk
IL-6 inhibitor Tocilizumab (Actemra) Sarilumab (Kevzara	Serious and fatal infections reported, bacterial, viral infections. Opportunistic infections probably not increased.
IL-17 inhibitor Secukinumab (Cosentyx)	Small increase in risk of infections. Higher rates of rhinitis, pharyngitis, URIs. TB screening recommended, though little evidence of increased TB risk
IL-12/23 inhibitor Ustekinumab (Stelera)	Lower infectious risk than TNF inhibitors, mostly bacterial (pneumonia, cellulitis)

Rheumatology 2012;51(5), Rheumatology 2010;50(3)

Other Biologics

Agent	Infectious Risk
Costimulation blocker Abatacept (Orencia)	Little or no increased risk for serious or opportunistic infections
Kinase inhibitor Tofacitinib (Xeljanz)	Increase in both serious and opportunistic infections: TB, fungal (cryptococcus, PJP), viral (CMV, BK virus, zoster)
B cell depleting Rituximab (Rituxan) Belimumab (Benlysta) Ocrelizumab (Ocrevus)	Little or no increased risk for serious or opportunistic infections Hepatitis B reactivation (rituximab) Cases of PML
Alpha-4 integrin antibody Natalizumab	PML (1:132 in JCV+)

Ann Rheum Dis 2009;68

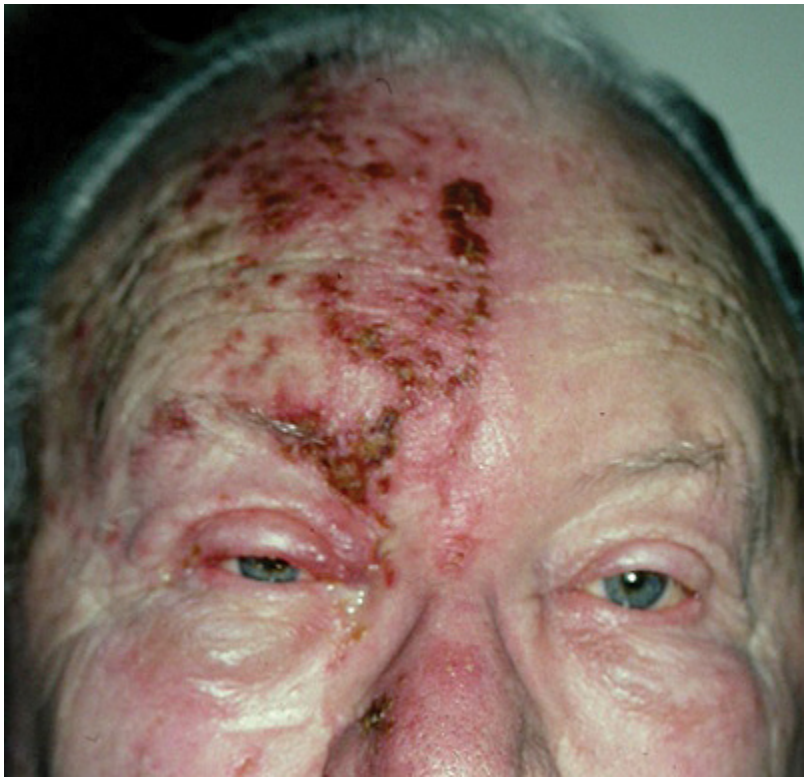
PML

- Progressive multifocal leukoencephalopathy (PML) caused by JC virus
- Most cases in RA/SLE with rituximab + other immunosuppressant therapy (MTX, steroids, leflunomide)
- Natalizumab (MS patients + for JCV antibodies)
- Motor deficits predominated

Arch Neurol. 2011 Sep;68(9)

Herpes Zoster

- Most common OI in RA patients
- 3.2-9.1/1000 person years
- Older age, female gender



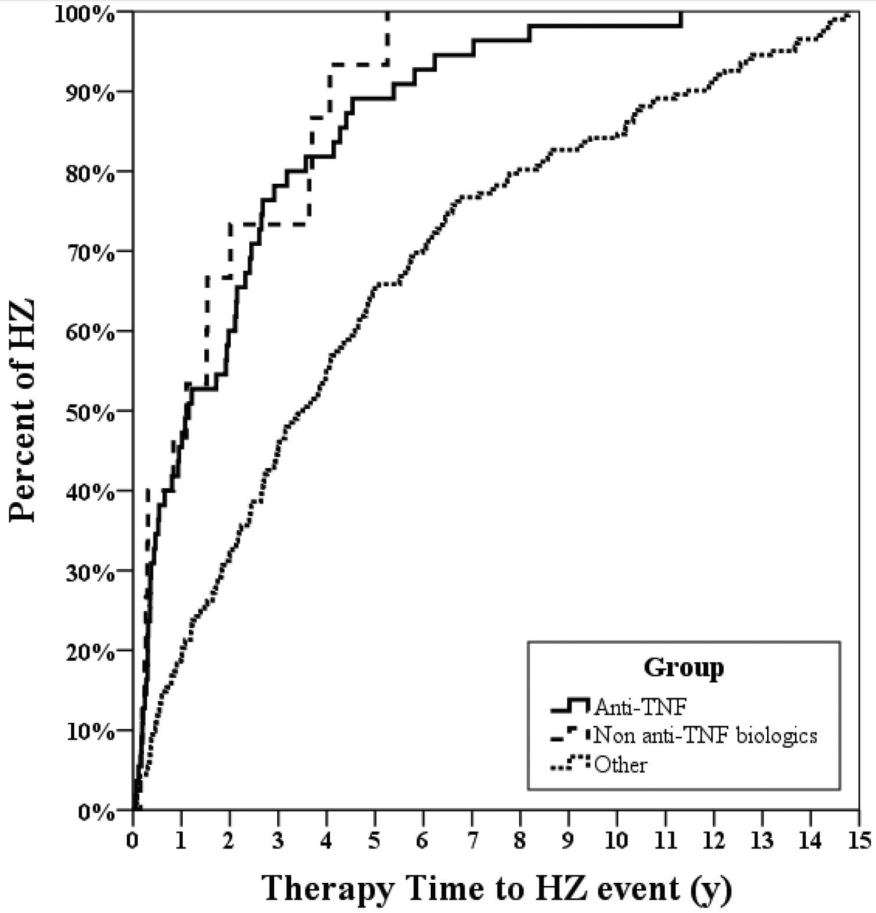
Herpes Zoster: RA

Drug	Adjusted OR €	95% CI
MTX	1.98	1.43-2.76
Anti-TNF	2.07	1.34-3.19
Non-anti-TNF¥	1.05	0.54-2.03
Corticosteroids		
<5mg	1.28	1.17-1.47
5-10mg	1.73	1.34-2.32
≥10mg	2.30	1.25-4.22

€ Adjusted by comorbidities (HTN, CKD, DM) and other rheumatic medications
¥ Includes rituximab, tocilizumab, abatacept

BMJ Open 2017;7(1)

HZ and RA



Test method	P for log rank	Pair comparison		
		(Anti-TNF, Non anti-TNF biologics)	(Anti-TNF, Other)	(Non anti-TNF biologics, Other)
Log Rank test	**<0.001****	0.41	**<0.001****	**<0.001****

HZ and RA

	Anti-TNF	Non-anti-TNF	Non Biologicals
Intravenous antiviral	26%	40%	5%
Opthalmic HZ	2%	20%	2%
HZ neuralgia	36%	27%	24%

BMJ Open 2017;7(1)

Zoster Vaccine

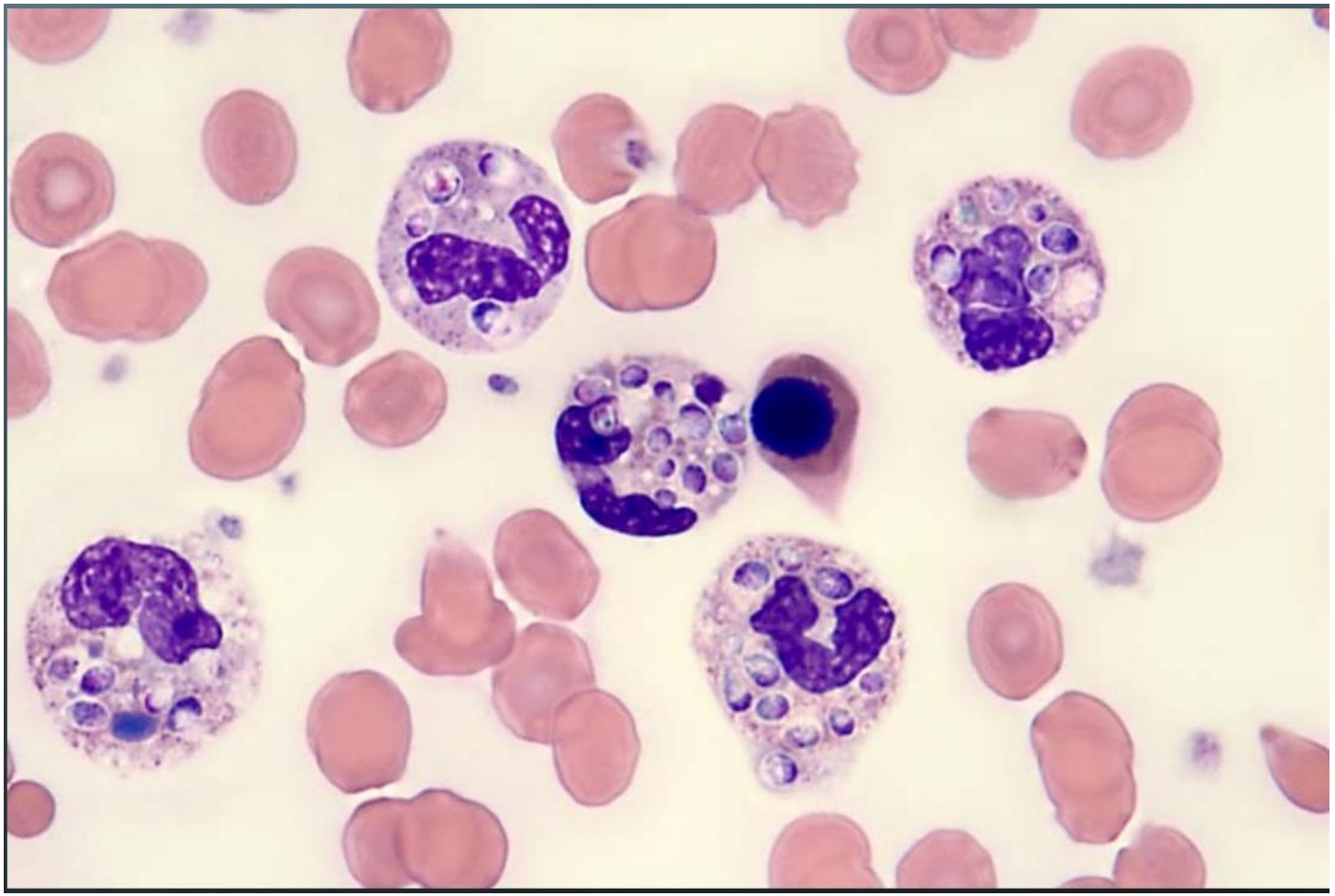
- Live attenuated zoster vaccine (Zostavax) not recommended for immunosuppressed patients
- Defer live vaccination for > 1 month after discontinuation (or initiation)
- Recombinant zoster vaccine (Shingrix) can be used in immunosuppressed patients
- Shingrix adjuvant (AS01B): unknown if safe in autoimmune or transplant patients

JAMA 2012;308(1)

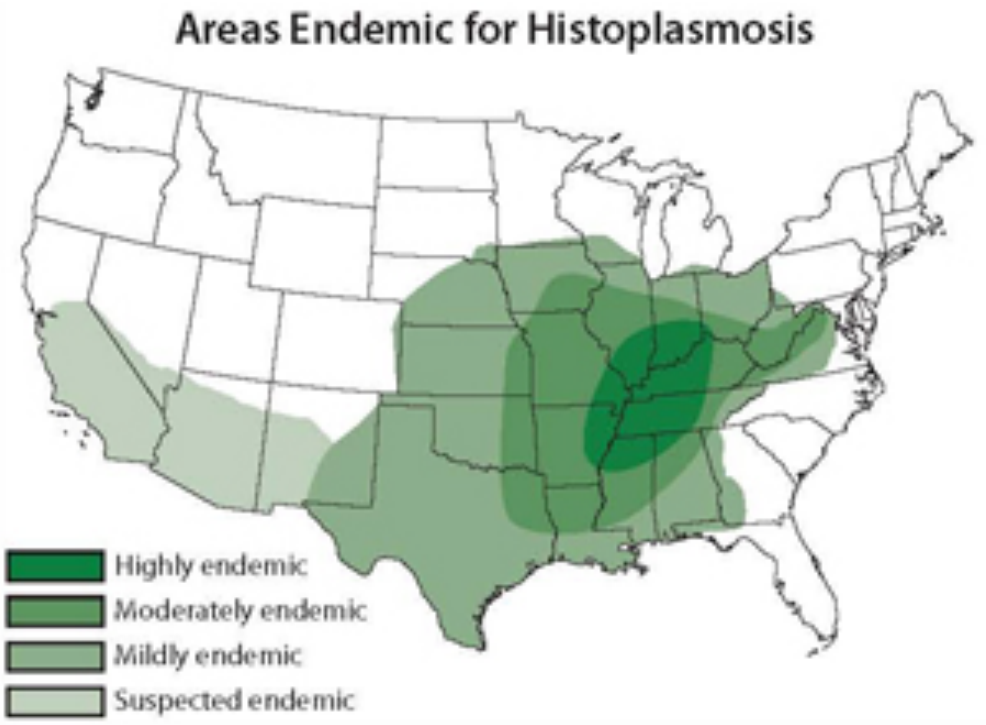
Histoplasmosis

- Soil fungus seen mostly in south central USA. Occurs in about 0.5-1% in endemic areas
- Most common fungal infection in TNF-inhibitor users
- Multisystem disease with fever, pneumonia, lymph node enlargement, low blood counts and liver and spleen enlargement
- Diagnosis by culture (slow), urine or blood antigen (few days) and in sickest pts by blood smear

Histoplasma in Blood Smear



Histoplasmosis Map



cdc.gov

Histoplasmosis at VUMC

- 11 cases of disseminated histoplasmosis in TNF-inhibitor users reviewed

	N (%)
Male	7 (64%)
Age (median)	43 (23-65)
Rural Environment	5(45%)
IBD	6 (55%)
RA	2 (18%)
Psoriasis	2 (18%)
Seronegative spondylarthropathy	1 (9%)
Median time on biologic	26 months
Adalimumab	7 (64%)
Infliximab	4 (36%)

Open Forum Infect Dis 2015;2(1)

Histoplasmosis: Presentation

Variable	
Severity	
Mild	27%
Moderate	45%
Severe	27%
Fever	82%
Cough	64%
Symptom Duration (median)	14 days
+ Urine Ag	91%
Chest CT abnormality (n=9)	
Adenopathy	22%
Miliary	44%
Interstitial infiltrates	44%
Alveolar infiltrates	33%
LDH (median, U/L)	682

Common Question

- When can we resume TNF-inhibitor in patient with histoplasmosis?

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No definitive consensus, but if patient is adequately being treated with resolution of symptoms and improvement in antigen levels, could consider restarting TNF-inhibitor

Common Question

- This patient has a history of infection with histoplasmosis, can we use TNF-inhibitor?

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Yes…

If active infection in past 2 years, could consider itraconazole prophylaxis or monitor urine histo antigen levels q2-3 months

CID 2007;45:807-25

Cryptococcal Infection

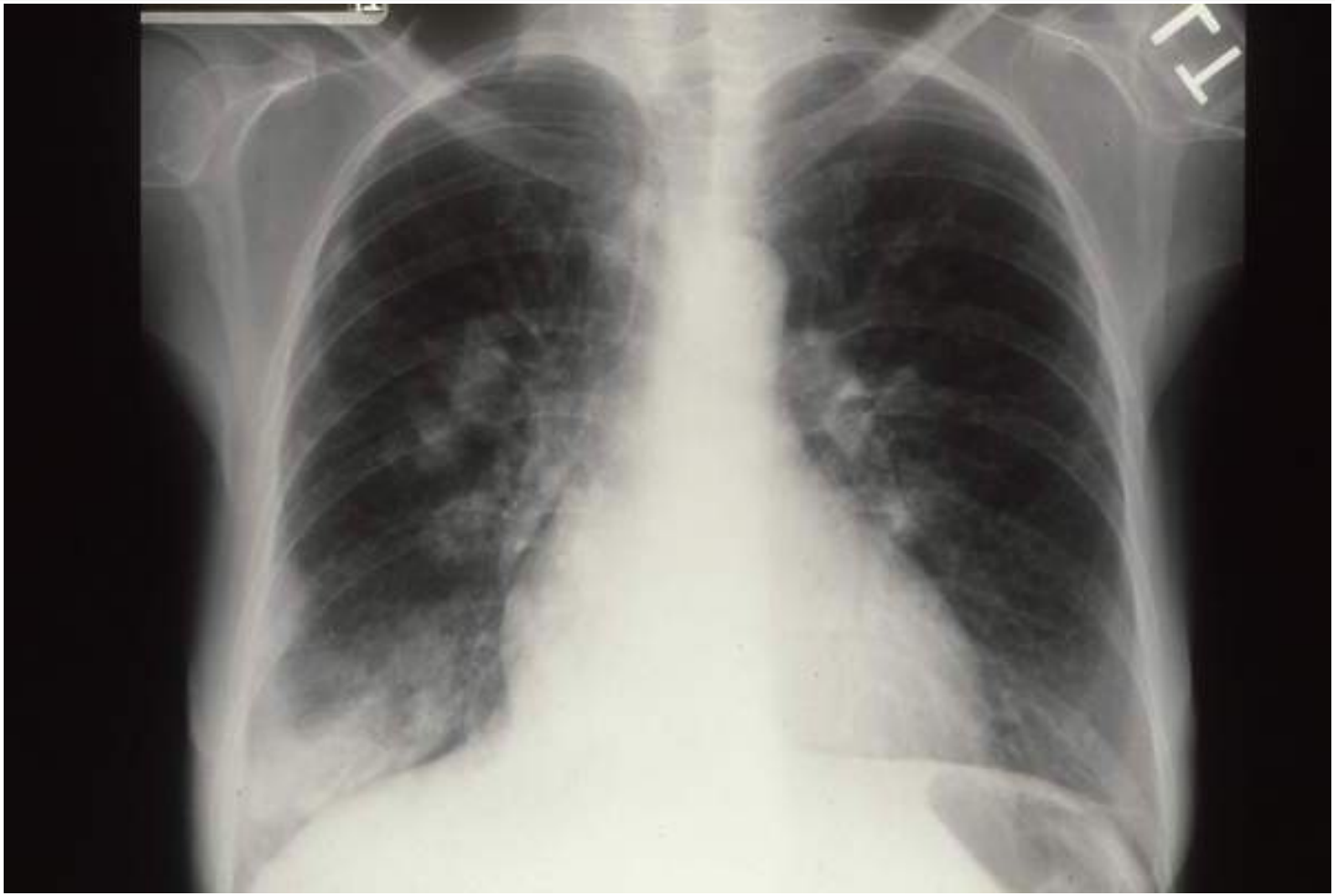
- Common soil fungus with worldwide distribution, higher concentrations near bird roosts
- Commonly presents either with lung or central nervous system disease
- Pulmonary: usually lung nodule(s) on CXR with mild pulmonary symptoms

Cryptococcal Infection

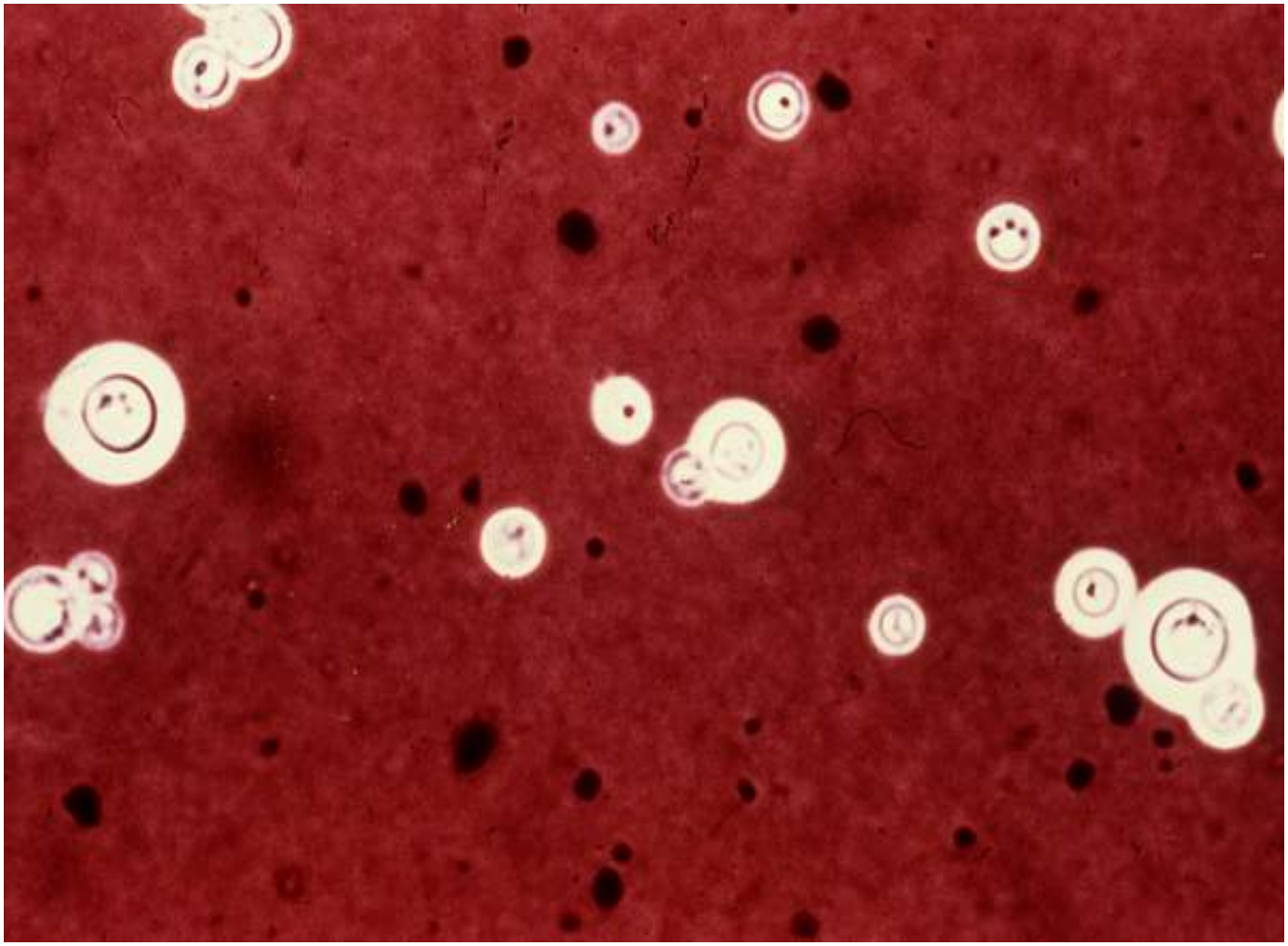
- CNS disease: meningitis with gradual evolution of headache and subtle neurological findings
- Cutaneous lesions sometimes occur
- Diagnosis with invasive procedures (bronchoscopy, lumbar puncture) with culture and cryptococcal antigen
- Prognosis: patients do well unless diagnosis is delayed until there is severe neurological disease

CID 2010;50:291-322

Pulmonary Cryptococcosis



Positive India Ink Smear



Beware…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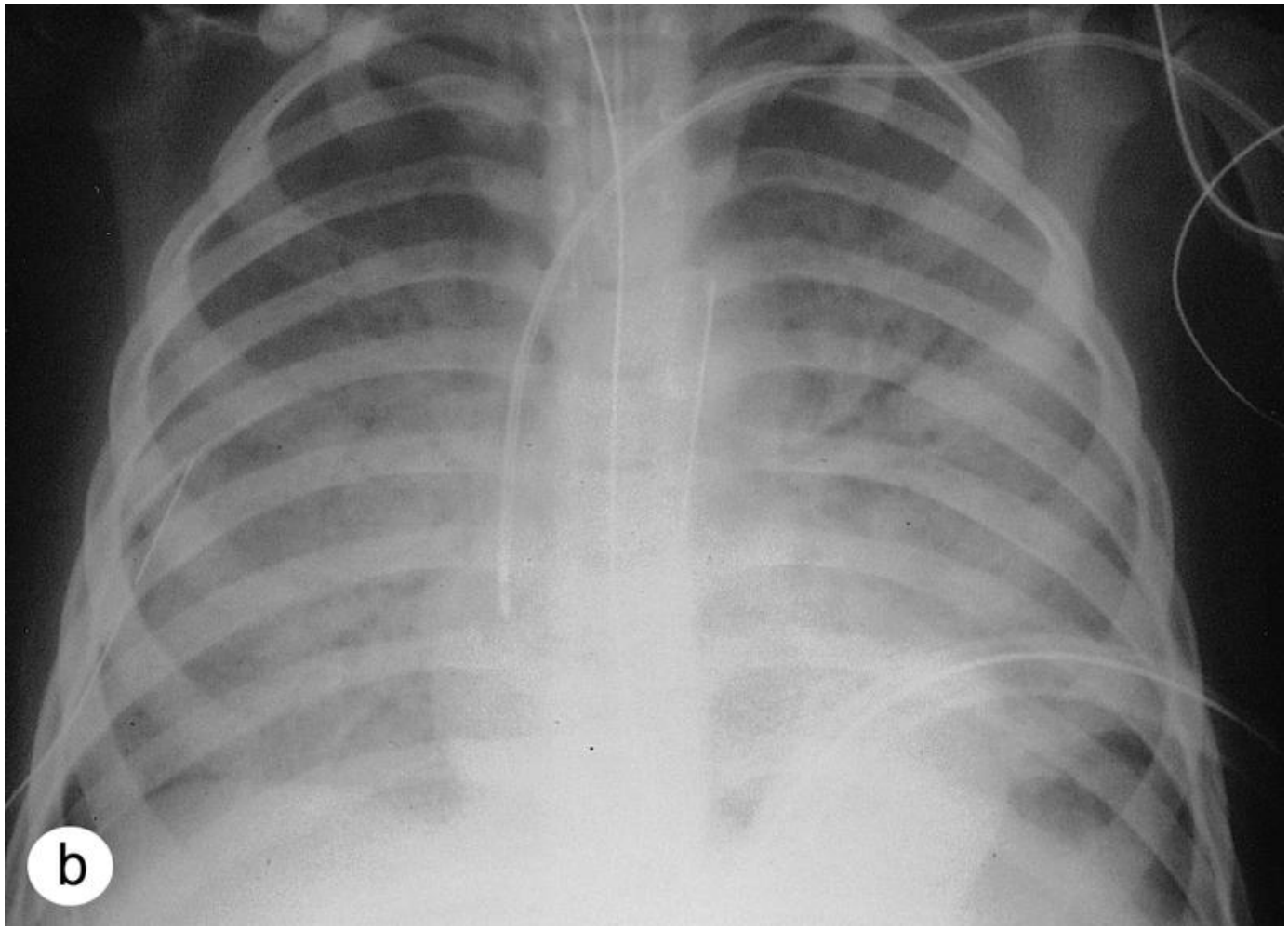
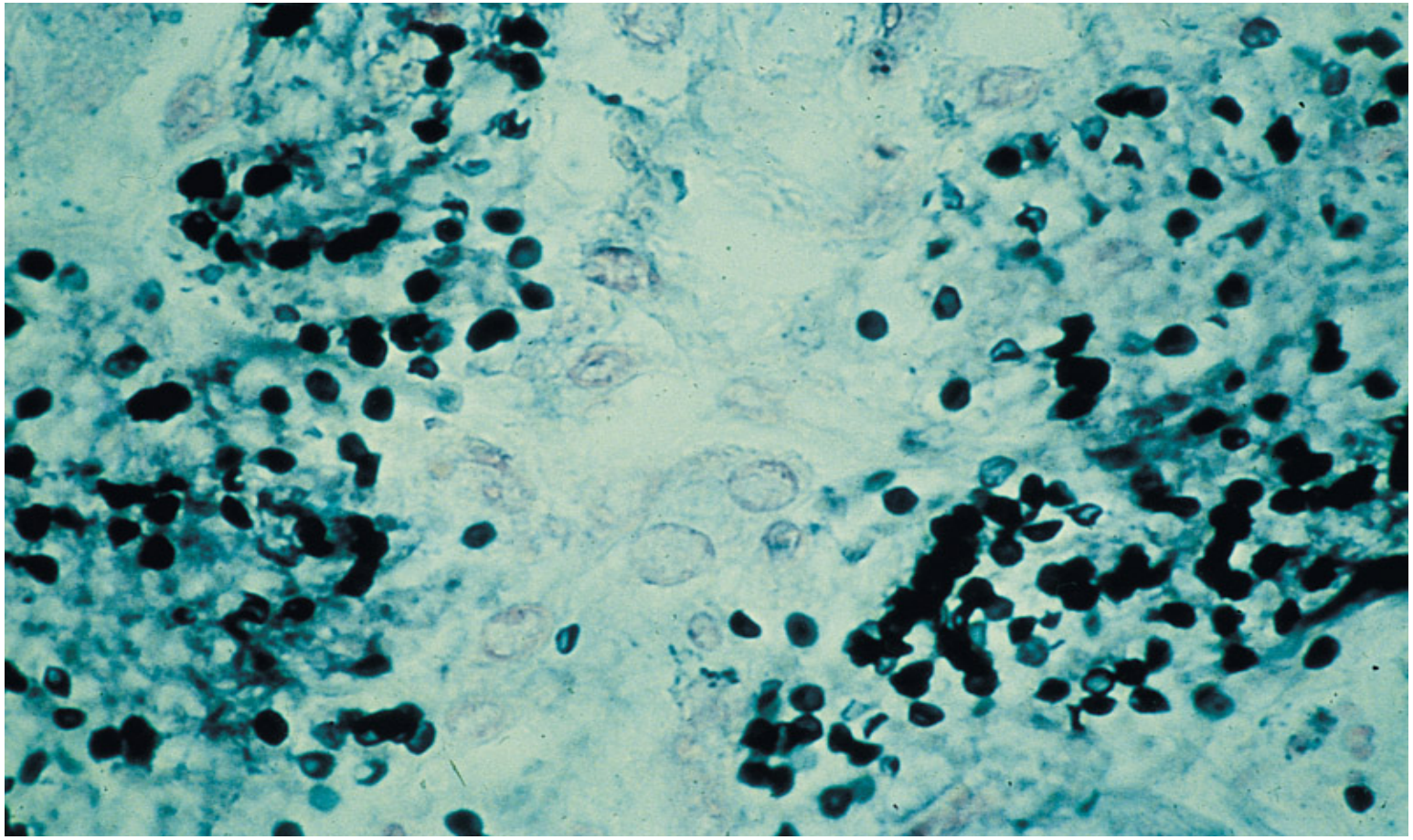
Pneumocystis jirovecii Pneumonia (PJP)

- Typically presents with fever, hypoxia, and diffuse pneumonia
- Diagnosis usually required bronchoscopy with lavage of lung alveoli (BAL GMS not as sensitive as with HIV patients)
- 1,3 beta D glucan also helpful in diagnosis, or PJP pcr of BAL fluid
- Treatment with sulfa-trimethoprim or pentamadine is usually successful in clearing the organism but some patients die during period of hypoxia

Radiographic Picture of Pneumocystis Pneumonia



Cysts of Pneumocystis



When to Consider PJP Prophylaxis

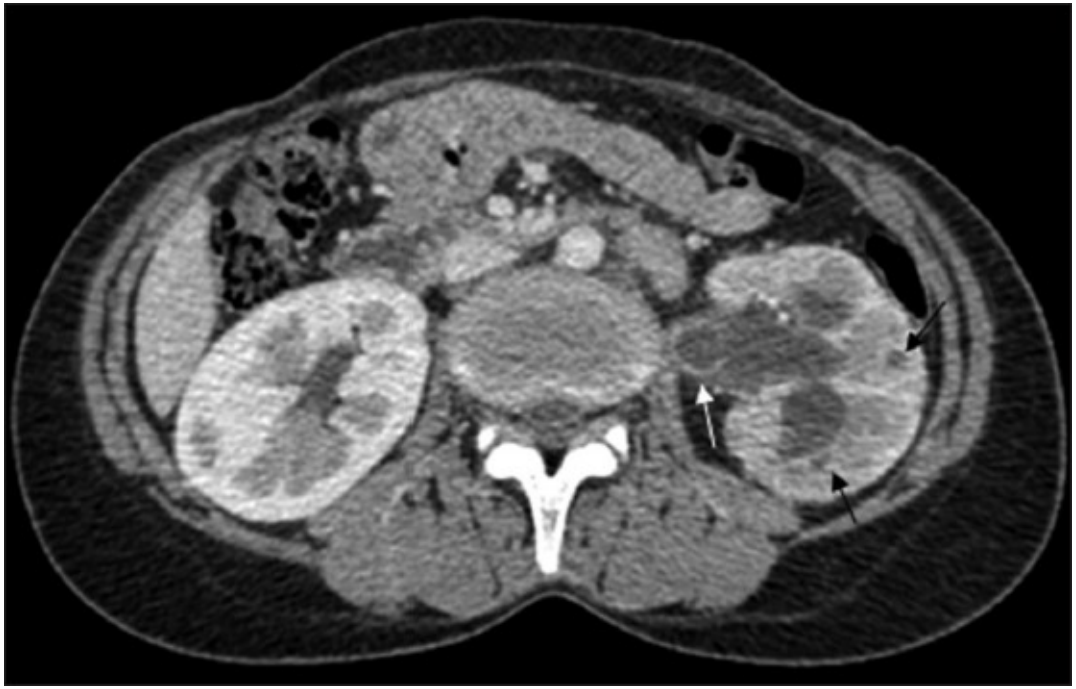
- ≥ 20mg of prednisone daily for one month or longer and on second immunosuppressive drug
- TNF inhibitors plus high dose glucocorticoids or other intensive immunosuppression
- TMP-SMX, dapsone, or inhaled pentamidine most commonly used

Tuberculosis

- Rate of TB: 4-10 X higher in TNF-inhibitor therapy
- Rates highest with adalimumab or infliximab
- Extrapulmonary disease occurs in majority of cases (disseminated, lymph node, pleural, vertebral, GU)

Expert Opin Drug Saf 2016;15(sup1)

GU tuberculosis



TB screening

- TST (tuberculin skin test) or interferon-gamma release assay (IGRA) should be performed prior to initiation of TNF-inhibitor therapy and yearly

- Latent TB therapy should be offered to the following:
  - + TST ≥ 5mm
  - + IGRA
  - Evidence of remote TB disease on CXR
  - Evidence of prior TB exposure

When can TNF-α inhibitor therapy be used in a patient with latent TB?

A. Contraindicated in patients with latent TB

B. Only in latent TB patients who have completed entire LTBI treatment course

C. Those who are taking LTBI treatment and have completed at least 1 month

Rituximab & Hepatitis B

- Increased risk of hepatitis B reactivation
- HBsAg+: 30-60%
- HBsAg-/HBcAb+:>10% in lymphoma patients
- HBsAg-/HBcAb+ RA patients: of 131 patients, none developed HBVr

Ann Rheum Dis. 2009 Jan; 68(1), Gastroenterology. 2015;148(1)

Hepatitis B

- Screen HBsAg, HBcAb, +/-HBsAb
- If HBsAg+: antiviral prophylaxis (tenofovir or entecavir) recommended
- If HBcAb + (sAg-): consider prophylaxis (rituximab) or viral load monitoring

Take Home Points…

- Just because a patient is immunosuppressed does not mean they are necessarily susceptible to all opportunistic infections
- Being an immunosuppressed patient does not make one immune to common diseases (i. e. influenza): don’t focus all of your energy looking for zebras

Questions?