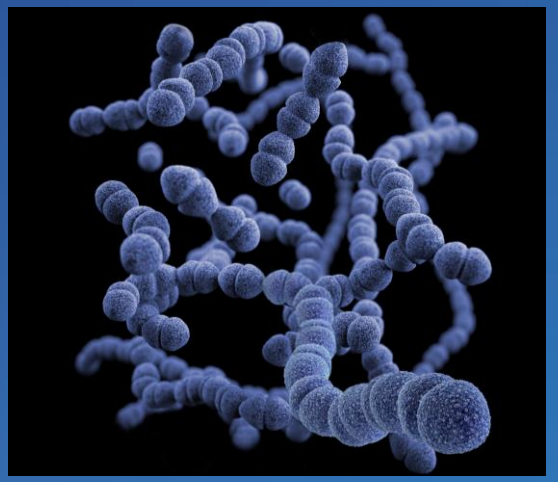
PATHOGENS

Rheums Should Worry About



John J. Cush, MD
RheumNow.com
Dallas, TX

Bad News Bugs

- Infection: most common/concerning adverse events in RCTs of new Rx
- Some infections have high mortality risk
- Metanalysis Biologics in RA (52 studies, 21 countries, 9 biologics)
  - Infection rate from 0.9 to 18.0/100 person-years; Fatality rates 2.5% - 22.2%
- Infection (risk) is often ascribed to AIRD & Rheumatic Meds

Makimoto K, et al. JBI Evidence Synthesis ():10.11124/ .

Scope of Infections Associated with Biologic Use

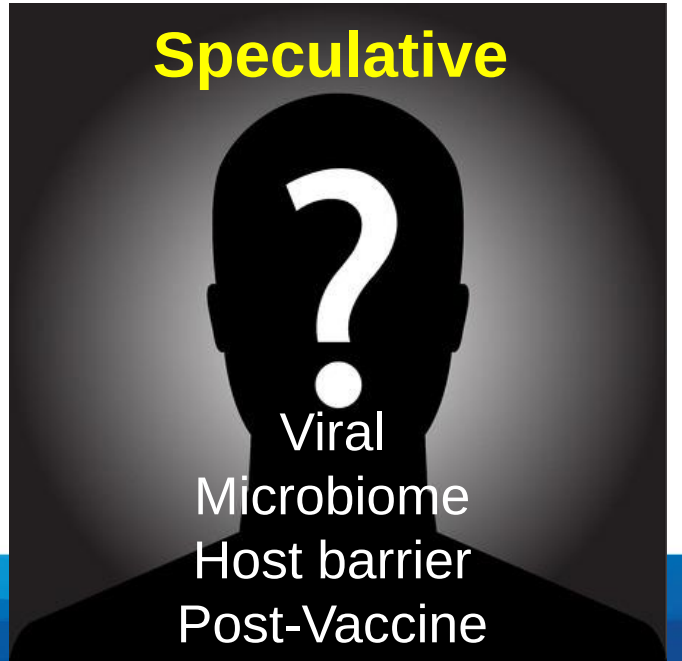
	Anti-TNF	Anakinra	Abatacept	Rituximab	IL-6 Inhibitors	JAK Inhibitors	IL-17 inhibitors
NSIE	✓	✓		✓	✓	✓	
SIE	✓	✓	✓	✓	✓	✓	✓
Bacterial	✓	✓	✓	✓	✓	✓	
TB & NTM	✓✓		*	*	*	*	
Fungal & Opportunistic	✓		*	✓		✓	
Hepatitis B	✓		*	✓	*		
Hepatitis C				*			
H. zoster	✓		*	*	*	✓✓✓	
PML	*			✓			

✓ Increased risk from PI, RCTs & Registries
* Few cases reported

NSIE: nonserious infectious events (URI, etc)
SIE: serious infectious events
NTM: nontuberculous mycobacterial infection
PML: progressive multifocal leukoencephalopathy

Considering Pathogens

- Infections Causing Arthritis
- Infections Complicating AIRD
  - Which disease associates with infection?
- Drug related Infection Risk
  - Is drug use linked to specific infection(s)?

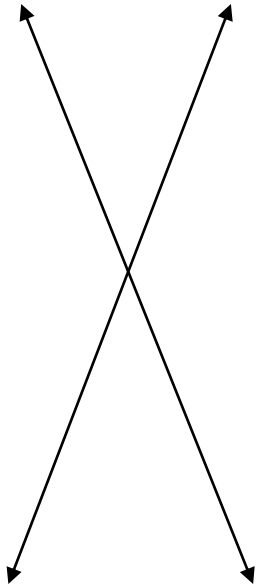


Synovial Fluid Analysis

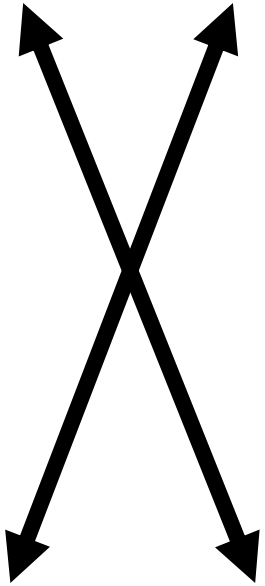
	Noninflammatory Type I	Inflammatory Type II	**Septic Type III**	Hemorrhagic Type IV
Appearance	Amber-yellow	Yellow	**Purulent**	Bloody
Clarity	Clear	Cloudy	**Opaque**	Opaque
Viscosity	High (+ String sign)	Decreased (- string)	**Decreased (- string)**	Variable
Cell Count (%PMN)	200-2000 (< 25% PMN)	2000-75,000 (>50% PMN)	**> 60,000 (>80% PMN)**	RBC >> wbc
Examples	OA Trauma Osteonecrosis SLE	RA, Reactive SLE gout Tbc, fungal	**Bacterial Gout**	Trauma, Fx Ligament tear Charcot Jt. PVS

Infections: Match up with MSK Dx or Drugs?

Rheumatic / MSK Diagnosis
Osteoarthritis
Erosive osteoarthritis
Fibromyalgia
Gout
Pseudogout
Rheumatoid arthritis
Psoriatic arthritis
Spondyloarthritis
Reactive arthritis
Systemic Lupus
Dermatomyositis
Systemic Sclerosis
Granulomatous polyangiitis
Polymyalgia rheumatica



Infection
Gonococcus
Strept
Staph
E. Coli
Shigella
Salmonella
mTB
NTM
Histoplasma
Coccidioides
HIV
HCV/HBV
COVID
H. Zoster



Drugs
Steroids
Methotrexate
Hydroxychloroquine
Leflunomide
Azathioprine
Mycophenolate
TNF inhibitors
αIFN inhibitors
B cell inhibitors
IL-1 inhibitors
IL-6 inhibitors
IL-17 inhibitors
IL-23 inhibitors
JAK Inhibitors

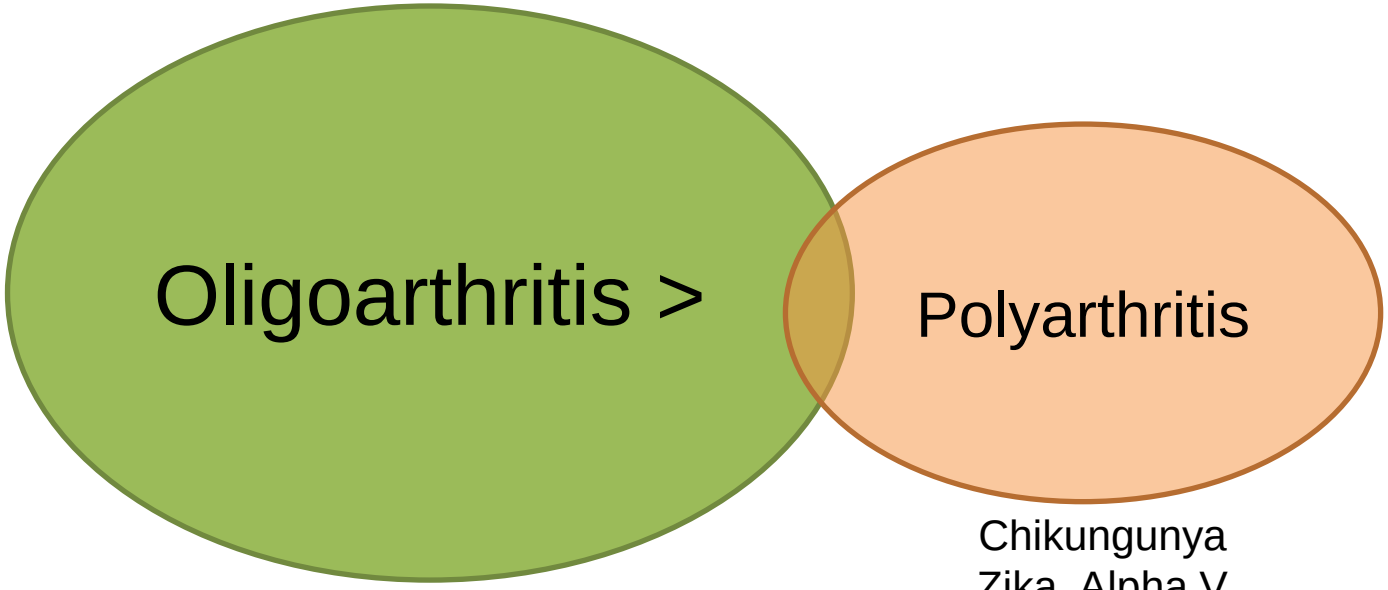
Does MSK Dx Associate with Infection

(not much)

Rheumatic Diagnosis	At Risk For:	Mimickers
Osteoarthritis	Risk of Prosthetic Joint Infx	
Rheumatic fever (post-streptococcal ReA)	Streptococcus	
Gout	Risk of septic joint	Septic joints, GC
Cryglobulinemia (±vasculitis)	1-5% associated with HBV	
Rheumatoid arthritis	Risk of septic joint	Chikungunya; M. leprae; Parvo B19, HBV, HCV
Psoriatic arthritis	Risk of septic joint	
Spondyloarthritis		Brucella, mTB
Reactive arthritis	⇦Chlamydia (etc), mTB, Strept	
Systemic Lupus	(EBV? Gut dysbiosis?)	
Poly/Dermatomyositis		Trichinella, Toxoplasma, M. TB/Leprae, Virus
Systemic Sclerosis		
Granulomatous polyangiitis		Sinusitis

Mazzaro C. Front Oncol. 2023; 13: 1095780.

Infection Related Arthritis - Presentation?



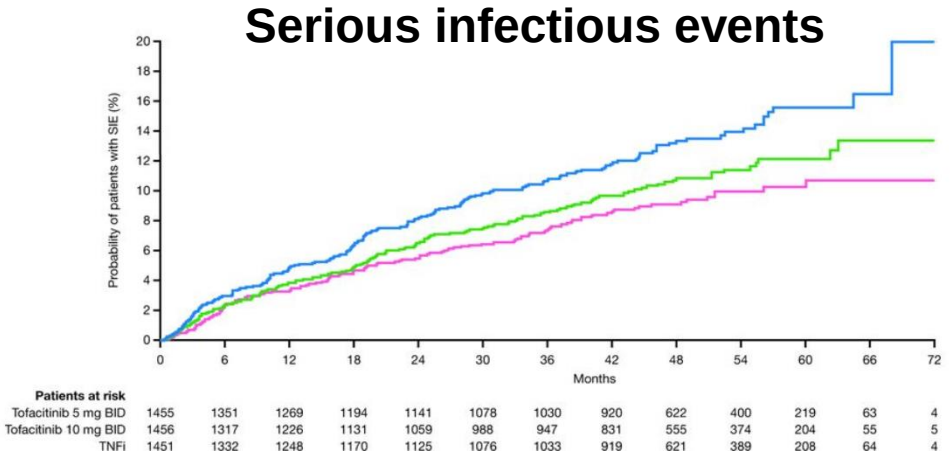
Sonomoto, et al. *Rheumatology 2022:* 61: 1831–1840; Dao KH, Cush JJ. Schlossberg's Clinical Infectious Disease; 3rd Ed. 2022
Fragoulis GE, et al. ARD 2022. doi: 10.1136/ard-2022-223335 Hellmich B, et al. ARD March 2023. doi: 10.1136/ard-2022-223764

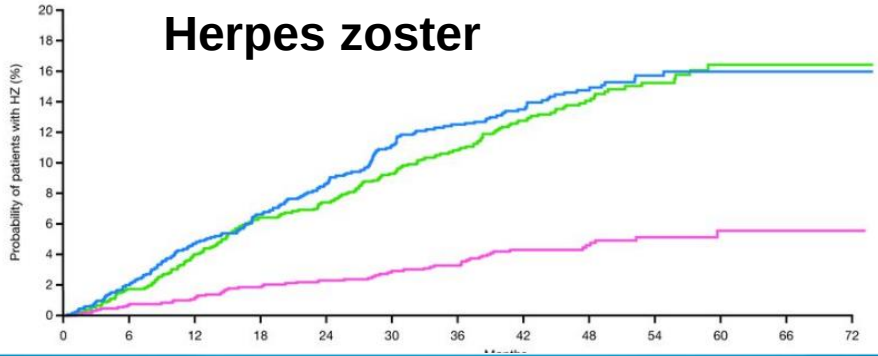
Oral Surveillance – More Infections w/ Tofa

- All infections increased (Tofa v TNFi); esp Tofa 10 mg > 5 mg
  - *All, NSIE, HZ, SIE, fatal SIE*

NNH vs TNFi – overall SIEs
- TOFA 5 mg bid = **283**
- TOFA 10 mg bid = **83**

- SIE Predictors:
  - *age, opioids, chr lung dz, steroids*
  - *Disease activity*





Balanescu A, et al. ARD 2022; 03 August 2022. doi: 10.1136/ard-2022-222405

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Community-Acquired Pneumonia (CAP)

- Leading cause of morbidity and mortality
  - Esp. elderly and patients with comorbidities
  - No. I cause due to infection
- Incidence
  - General pop.: 1–12/1000/year
  - > 65 years: 25–44/1000/year
  - RA: 8-17/ 1000/year
- 5-6 million cases/year
  - Approx. 1 million admissions/year
  - > 75% treated as outpatients
- Cost of treating CAP exceeds $17 billion/year

File T. *Lancet* 2003; File and Tan *JAMA* 2005;
Niederman et al. *Am J Resp Crit Care Med*. 2001; Doran MF. Arthritis Rheum 2002; 46: 2265-2548

Most Common Etiologies of CAP

Ambulatory Patients	Hospitalized (non-ICU)†	Severe (ICU)†
S. pneumoniae	*S. pneumoniae*	*S. pneumoniae*
M. pneumoniae	*M. pneumoniae*	*S. aureus*
H. influenzae	*C. pneumoniae*	*Legionella* spp.
C. pneumoniae	*H. influenzae*	Gram-negative bacilli
Respiratory viruses††	*Legionella* spp.	*H. influenzae*
	Aspiration	
	Respiratory viruses‡	

Based on collective data from recent studies; †Excluding *Pneumocystis* spp.
‡ Influenza A and B, adenovirus, respiratory syncytial virus, parainfluenza

modified from File TM.` *Lancet*. 2003;362:1991-2001.

Community-acquired Pneumonia (CAP) in Elderly

11,241 individuals > 65 yrs (NO ARTHRITIS), followed 2002 - 2005	
	CAP/1000 person-yrs
Elderly	14.0
Immunocompromised	30.9
Chronic lung disease	46.5
Long-term steroid Rx	40.1

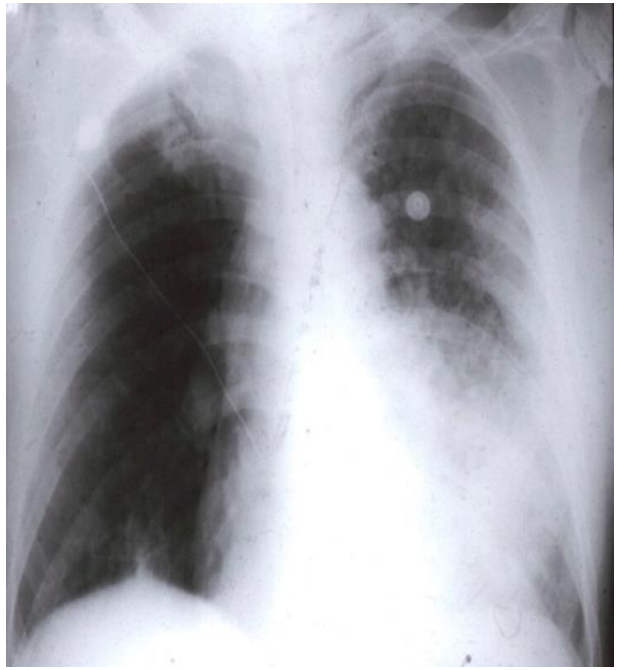
NDB: 16,788 RA pts	17
Risk factors (HR ~2-4)	Age, Pred, DM, MI, Lung Dz

Pneumonia risk is driven by age, severity, steroids, comorbidity

Vila-Corcoles A,; EPIVAC Study Group. Respir Med. 2008
Wolfe F, et al. Arthritis Rheum 54:628-34, 2006

RA and the Risk of Serious Infections

- The best predictors of serious infectious events (SIE) and infectious deaths in RA:
  1. **RA severity/disease activity**
  2. **Corticosteroid** therapy
  3. Comorbidities: **COPD/ILD**, CHF, CRF, DM
  4. Cutaneous breakdown (ulcers, wounds)
  5. Major joint surgery



There is little or no risk imposed by conventional DMARDs
Biologics impose a relatively small but significant risk of SIE

RheumNow Live!

Summary from Product Labels

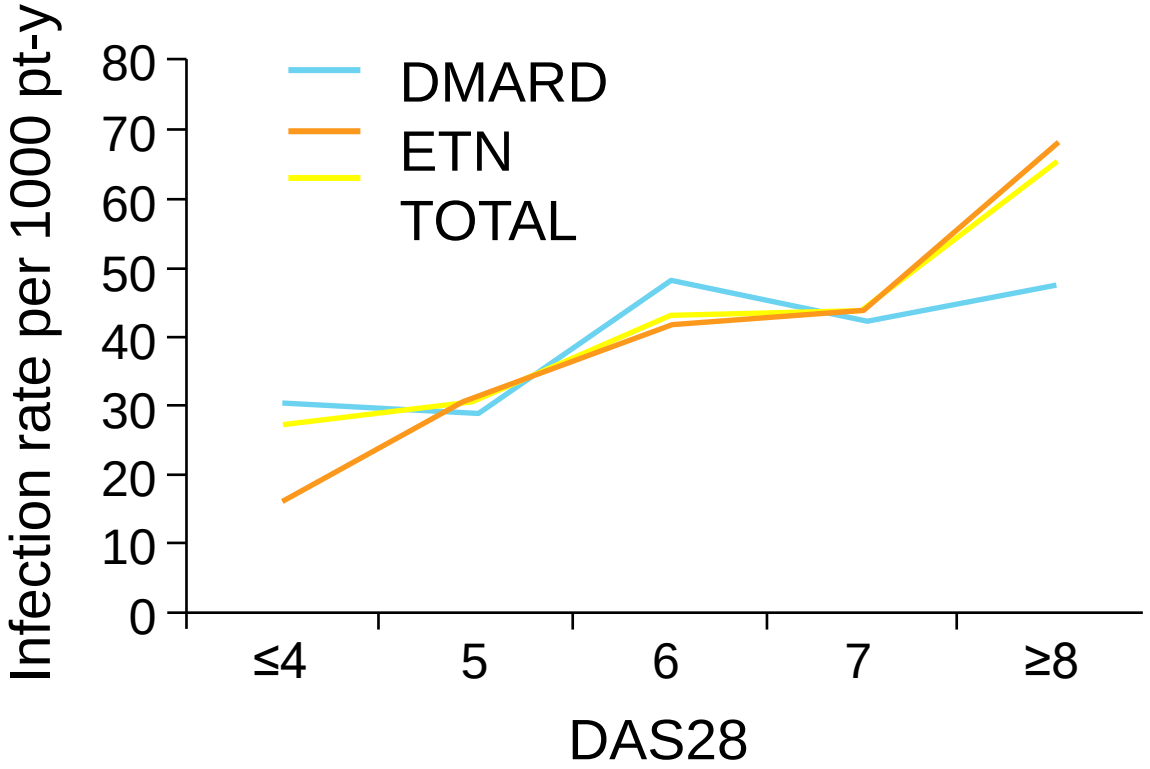
non-Significant Doubling of SIE w/ Biologics

SIE Rates (PI)	Biologic	Placebo
Anakinra	2%	1%
Adalimumab	2%	1%
Etanercept	1%	1%
Infliximab	5.3%	3.4%
Golimumab	1.9%	2.2%
Certolizumab	3%	1%
Abatacept	3%	1.9%
Rituximab	2%	1%
Tocilizumab	3.6 / 100py	1.5 / 100py

HUMIRA (adalimumab) [package insert]. Chicago, IL; Abbott Laboratories; 2008; ENBREL (etanercept) [package insert]. Thousand Oaks, CA; Immunex Corporation; 2006; REMICADE (infliximab) [package insert]. Malvern, PA; Centocor, Inc; 2007.

Serious Infection and Baseline Disease Activity

- Data from BSRBR*
  - DMARD n=1365
  - ETN n=3470
- For every 1 point ↑ DAS28
  - HR for SIE ↑ 17%
  - HR 1.17 (95% CI 1.08–1.27, P<0.001)
  - No difference between ETN or DMARD



Disease activity, not medication, determines risk of SIE

Courtesy
TREG 2012

BSRBR – British Society for Rheumatology Biologics Registers
Emery P, et al. ACR 2011, Chicago, #429

Randomized Controlled Trials in High Risk Populations[#]: SIE Outcomes

Study, yr	Drug	No.	Wks	DMARD +Placebo	DMARD + TNFi
STAR, 2003	Adalimumab	636	24	1.3 %	1.9%
START 2006	Infliximab	1084	22	1.7%	1.7% 3mg (5% 10mg)
Weissman 2007	Etanercept	535*	16	3.9%	3.0%

must have >1 comorbidity (eg, DM, COPD)

*1000 pt study closed enrollment after 3.5 yrs for slow accural

Usual doses did not increase the risk of SIE in patients w/ comorbidities.
Higher dose infliximab significantly increased SIE events

Furst, J Rheumatol. 2003;30:2563. Westhovens Arthritis Rheum. 2006;54:1075 Weissman ME Rheumatology 2007:46:1122

NSIE – URI, etc…..

- Everyone gets NSIE – nonserious infx (475/1000PY)
- Everyone Stops Biologics for NSIE ($T_{1/2}$ >2wks)
  - Most common AE in all trials
  - Don't stop (a long half life biologic) for URI, NSIE

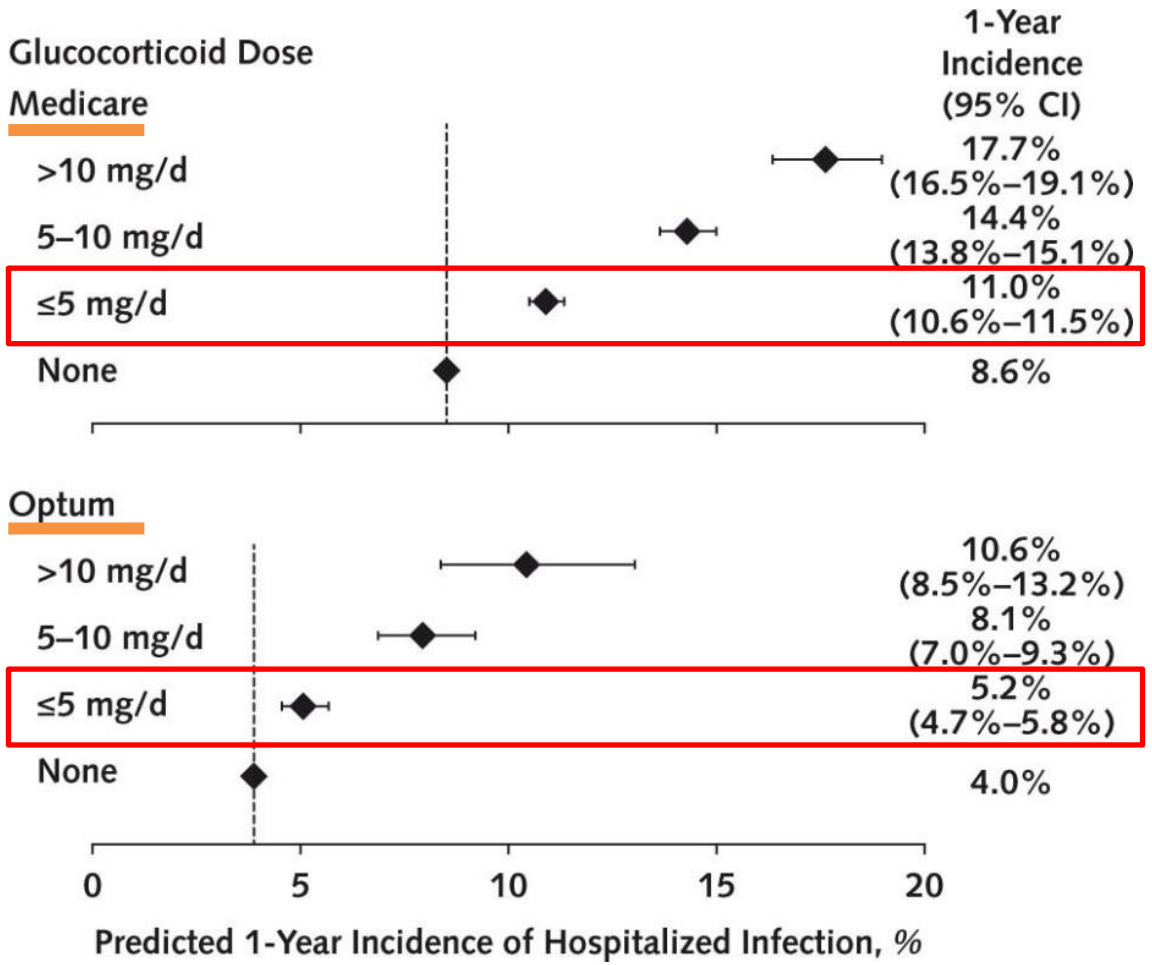
Do Steroids Cause Infection?

- 30-60% of RA patients take prednisone
- Steroids significantly increase the odds of: NSIE, SIE, TB, OI
- Dose-dependent infection risk

	Low Risk Pts	HIGH RISK Pts
Prednisone ≤ 5 mg / day	No increase	Possible
Prednisone 5 - 10 mg / day	Unlikely	Likely
Prednisone > 10 mg / day	Likely	Highly Likely

Rostaing L, Malvezzi P (2016) PLoS Med 13(5): e1002025
Youssef J. Rheum Dis Clin North Am. 2016 Feb;42(1):157-76.

Risk for Serious Infection With Low-Dose Glucocorticoids in Patients With Rheumatoid Arthritis: a Cohort Study



Predicted 1-year incidence of hospitalized infection calculated from inverse probability–weighted cause-specific hazards models. Confidence intervals are not available for the reference group, which represents the baseline incidence at 1 y. Variables that were imbalanced across glucocorticoid categories after inverse probability weighting were added as covariates to weighted models (opioid use, outpatient visits, and hospitalizations in both data sets and emergency department visits in Medicare).

George M, et al. Ann Int Med. Published online: 22 September 2020doi:10.7326/M20-1594

RABBIT: Calculating the Risk of Serious Infection (SIE) in the Next 12 Months

Risk Calculated from Risk Factors				
Age	Pred	# priorDMARDs	Prior SIE	Current Biologic

RA patient #1	RA patient #2
47 yr. old woman has no comorbidities, 2 prior DMARD failures, has 3 tender and 3 swollen joints, HAQ = 0.5, and takes MTX and prednisone 10 mg qday	62 yr. old woman with COPD and prior pneumonia has failed 6 prior DMARDs/biologics, has 6 tender and 6 swollen joints and HAQ=1.2 while taking leflunomide and prednisone15 mg qday
SIE Risk = 1.4%	**SIE Risk = 28.4%**
+TNFi SIE Risk = 2.6%	**+TNFi SIE Risk = 45.2%**

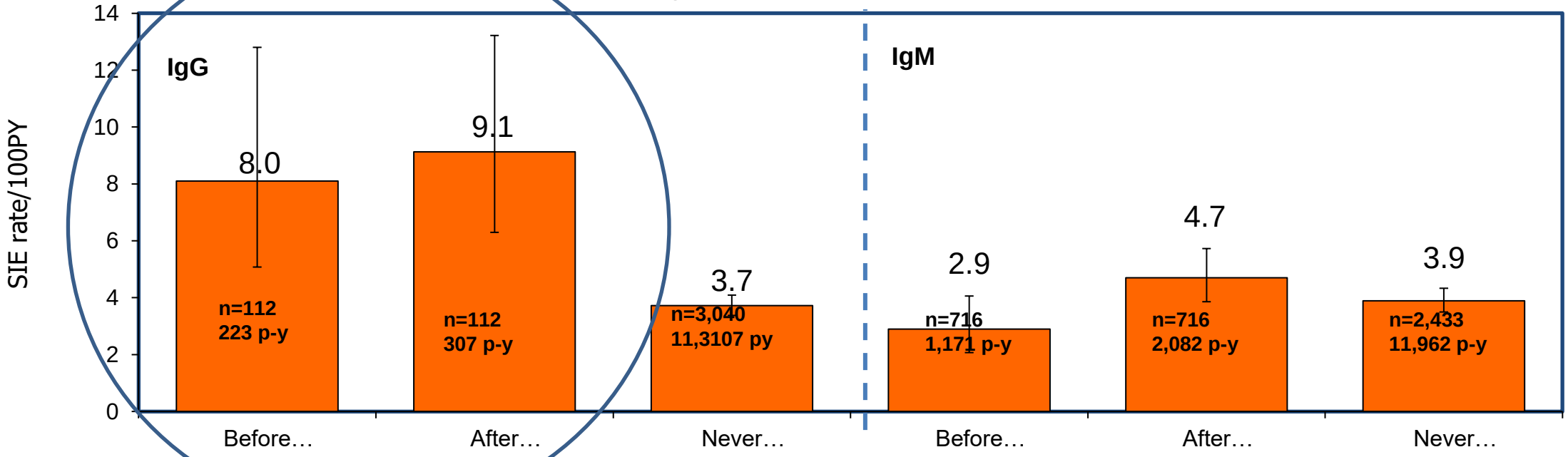
Cush JJ. *ACR Drug Safety Quarterly* 2013; 4 (4):1-3 Zinck A, Ann *Rheum Dis*.2013 Jun 28 Epub

***SIE Risk calculator http://www.biologika-register.de**

RheumNow

RTX: Infection risk based on immunoglobulin levels

- 3,595 pts treated with RTX; over 11 years f/u (14,816 pt-yrs)
- Low IgG or IgM defined as <LLN for ≥4 mos or 2 consecutive visits
  - Low IgM seen in 22.4% and low IgM (>4 mos) in 3.5% overall
- SIE rates estimated before and after low Ig were detected



SIE higher in those with low IgG < LLN before and after RTX use

Van Vollenhoven RF, et al. J Rheumatol.2015 Oct;42(10):1761-6)

Infection & Death in SLE

- Spanish Hospital Discharge Database: 18430 SLE hosp admissions for:
  - SLE activity (19%) vs Suspected infection (15%).
  - Cause of death: Infection 25% (vs 6% from SLE p<0.001) (3x ↑fold over gen. population)
- Swedish Database (2006-2013) - 2378 incident SLE, F/U of 6.4 years
  - Serious infections = 22% SLE vs 6% controls
  - SIE 40 per 1,000 person-years (4x higher than gen population
  - SLE twofold higher risk for recurrent infx hospitalizations (HR 2.22)
- National Medicaid SLE patients at high risk of infection – SIE and mortality did not differ among new users of MMF, AZA, or CYC.

Moreno-Torres V, et al. *Lupus Science & Medicine* 2022;**9:**e000711
Simard J, et al . " Lupus Sci Med 2021; doi:10.1136/lupus-2021-000510. Feldman KH, et al. A&R 2017 Feb;69(2):387-397

Infections in Poly/Dermatomyositis

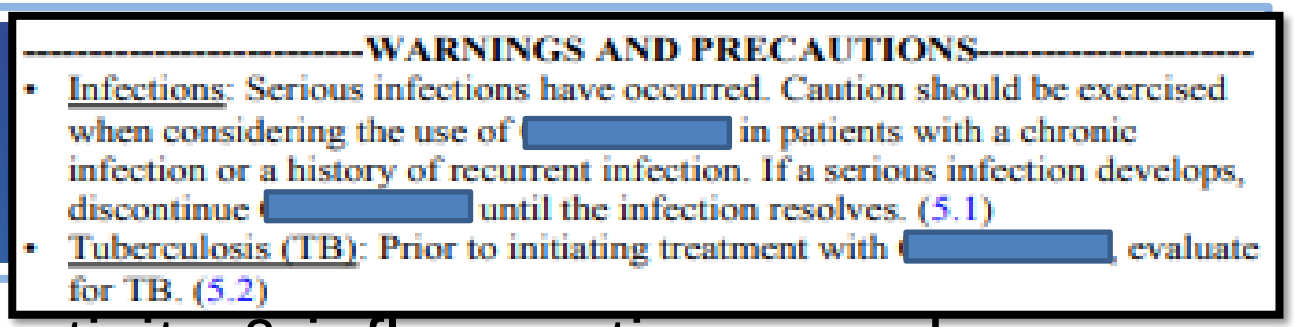
- **Opportunistic infx** in 18/156 pts **(11.1%)** PM/DM pts
  - 69% occurred in 1st year
  - OI: *Candida, Pneumocystis, Aspergillus, Geotrichum capitatum, MAI, M. xenopi, M. marinum, M. Tbc, Helicobacter heilmanii, CMV, HSV.*
  - **Mortality rates 27.7%.** Assoc. w/ high dose steroids, lymphopenia, total protein levels
- 104 Severe Infections in 279 PM/DM pts **(37.3%)**
  - 46/71 Pyogenic infections secondary to Aspiration Pneumonia
  - 33 Pyogenic infx: *Candida, Pneumocystis, Aspergillus, Mycobacterium, CMV, HSV, H. Zoster, HBV, HCV, JC virus, Leishmania, Strongyloides*
  - Risk: Esophageal dysfunction, respiratory insufficiency, malignancy, lymphopenia

Infections in Poly/Dermatomyositis

- 3 large retrospective studies
  - SIE 28-38% (11.1 per 100 pt-yrs)
  - Opportunistic infection in 11-18%; Aspiration pneumonia >20%
  - SIE ↓ survival to 68.3% at 1 year; Mortality rates 20-30%
  - ↑Risk: Age >45 (OR 5.3), Arthritis (2.6), ILD (7.2), AZA IVIG (6.1) *(also MDA5+)*

SIE	N	192 PM/DM pts 1999-2008
Pneumonia	30	Klebsiella (7), S aureus (6), P aeruginosa (4), H influenzae (4), Serratia (1), Acinetobacter (2), Stenotrophomonas (1), Prevotella (1),
Soft Tissue	13	S aureus (5), Klebsiella (2), Bacteroides (2), S pyogenes (1), Group D Strept (1), Enterococcus (1), Proteus (1), Peptostreptococcus (1
UTI	9	E. coli (6), K pneumonia (2), Proteus mirabilis (1),
Bacteremia	8	Salmonella (6), E. coli (1), Streptococcus pneumonia (1
Mycobacterial	7	M. Tuberculosis (6), Mycobacterium avium intracellulare (1)
Opportunistic	8	CMV, Varicella Zoster, Candida albicans

Dealing with Infections



WARNINGS AND PRECAUTIONS

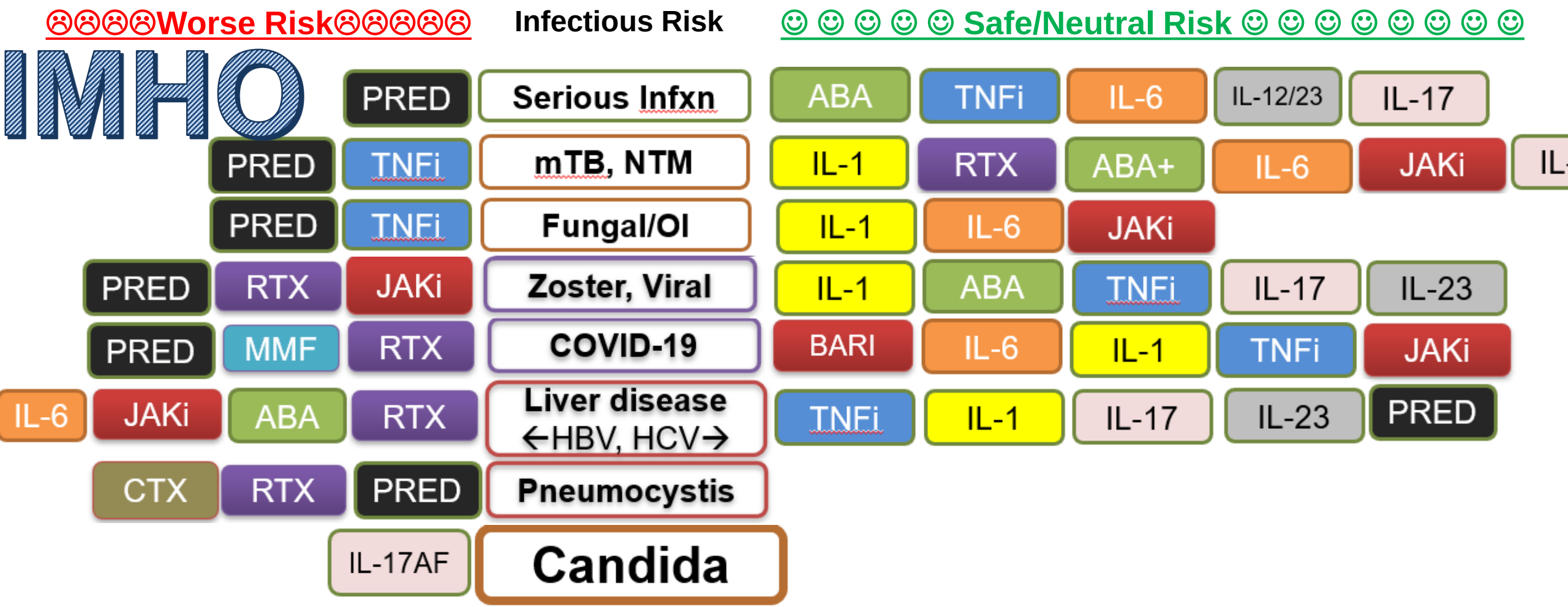
- Infections: Serious infections have occurred. Caution should be exercised when considering the use of [redacted] in patients with a chronic infection or a history of recurrent infection. If a serious infection develops, discontinue [redacted] until the infection resolves. (5.1)
- Tuberculosis (TB): Prior to initiating treatment with [redacted], evaluate for TB. (5.2)

- **Rule #1** - Infection is related to activity & inflammation >>> drug
- **Rule #2** - Everyone gets their education television ads
- **Rule #3** - NSIE's are too common to FREAK OUT over
- **Rule #4** - Steroids are DANGEROUS *(what's the expiration date?)*
- **Rule #5** - Biologics add infection risk mostly in the worse pts
- **Rule #6 –** Pathogen suspicion based on drug target & host factors
- **Rule #7** - ONLY hold a biologic: when hospitalized or w/ fever > 102F

Reduce Infx Risk by: 1) reduce steroids; 2) ⇩Inflammation; 3) control comorbidity

SUSPICION

What Drugs Augment Risk of Which SIE?



Which Drug do you Use vs Avoid?

RheumNow

Opportunistic infections reported

TNF Inhibitors	
mTB, nTM Clostridial Salmonella Nocardia Legionella Listeriosis	**Histoplasmosis** **Coccidioidomycosis** Candidiasis Aspergillosis Cryptococcosis Pneumocystis
Hepatitis B, Hepatitis C Herpes simplex virus HIV Varicella Zoster Cytomegalovirus Ebstein-Barr virus Human papilloma virus	Toxoplasmosis Strongyloidosis Leishmaniasis Pneumocystis jiroveci

Rituximab: Rare TB, mycobacterial
JC Virus (PML)
Reactivation viruses: **HBV**, CMV, HSV, Parvo B19, VZV, W. Nile, Hep C
Pneumocystis jiroveci

Abatacept: Rare TB, Reactivation HBV, Aspergillosis, candidiasis

Tocilizumab: Uncommon TB, reactivation HBV

JAK Inhibitors: **H.Zoster 4-10fold↑**
UncommonTB, BK virus

Ustekinumab: mycobacteria, Salmonella, Bacillus Calmette-Guerin

Ali T, et al. Drug Health Patient Saf. 2013; 5: 79–99.

Opportunistic infections on TNFi: BSRBR

- BSRBR studed RA pts Rx from 2001-2008, F/U to 2010
- Anti-TNF showed a nonsignificant increase in OI: HR 1.5 (0.3, 7.8) (IFX >> ETN, ADA)
- Number needed to harm = 2500

	DMARD	All TNFi	ETN	IFX	ADA
Exposure	**3666**	**11,864**	**4136**	**3472**	**4256**
# OI	**4**	**37**	**9**	**18**	**10**
OI per 100,000 pt-y (95% CI)	**32 (8–81)**	**81 (57–111)**	**45 (21–86)**	**159 (94–251)**	**66 (33–127)**
Fully adj. HR	**Ref**	**1.51 (0.30–7.75)**	**0.72 (0.12–4.40)**	**3.27 (0.64–16.60)**	**1.22 (0.23–6.37)**

- No significant increase in Opportunistic infx in TNFi exposed pts
- IFX cohort accounted for 44% these cases

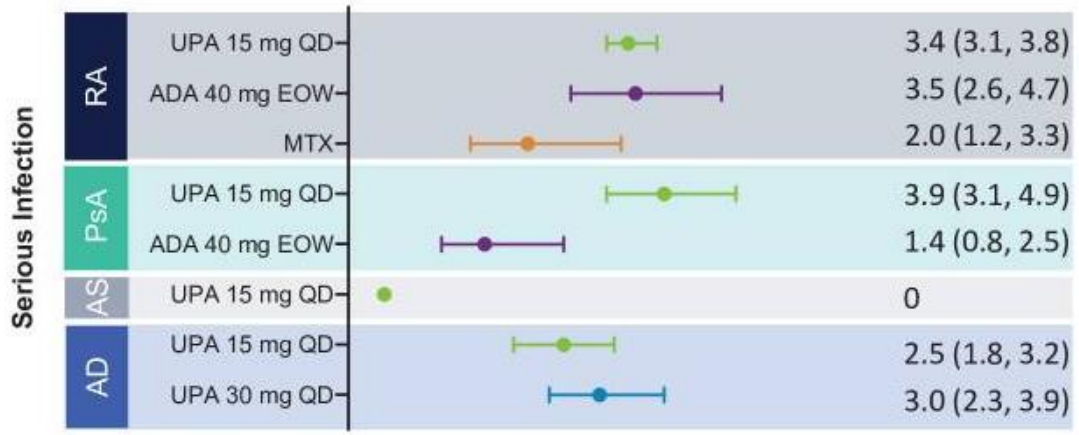
Adalimumab Long-Term Safety Data
(most Serious AE are 1/1000 risk)

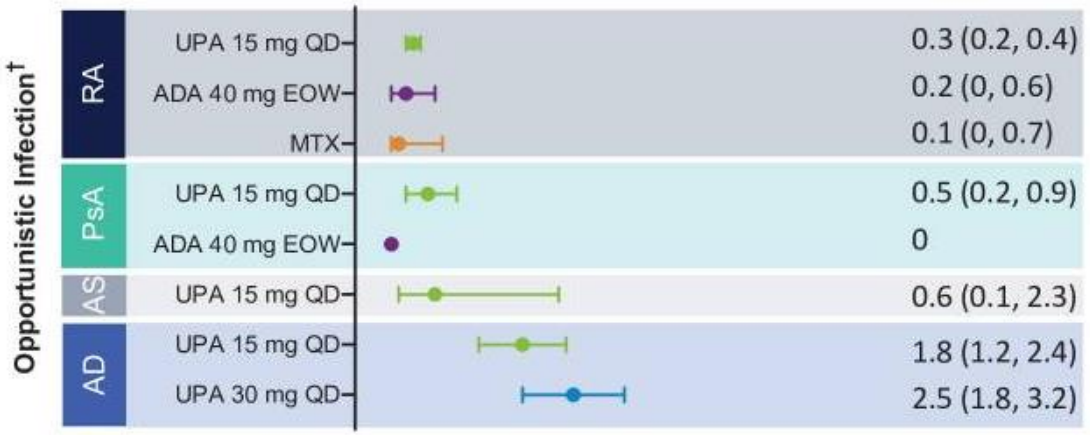
29,987 Patients Representing 56,951 Patient-Years in 10 Indications

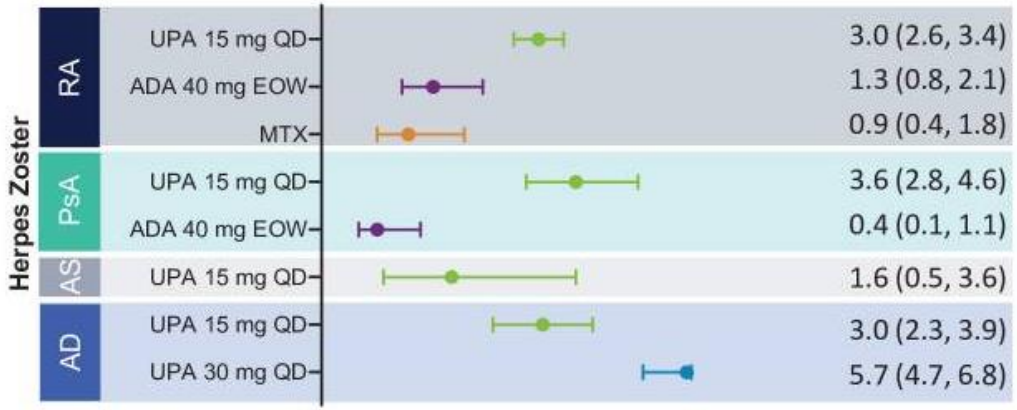
	RA	AS	nr-axSpA	pSpA	PsA	Ps	HS	CD	UC	Uveitis
N	15,512	2026	863	165	837	3732	733	3896	1739	464
Exposure, pt-y	37,106	2120	709	391	998	5479	1198	4359	3407	1151
Serious infection	**3.9**	**1.8**	**2.5**	**1.0**	**2.8**	**1.8**	**2.8**	**6.9**	**3.5**	**4.1**
TB	**0.2**	**0.1**	**0.1**	**1.0**	**0.2**	**0.2**	**0**	**0.2**	**<0.1**	**0.4**
Active	**0.2**	**0.1**	**0.1**	**0.3**	**0.2**	**0.2**	**0**	**0.1**	**<0.1**	**0.2**
Latent	**<0.1**	**0**	**0**	**0**	**0**	**0**	**0**	**<0.1**	**0**	**0.3**
Opportunistic infections	**<0.1**	**0**	**0.1**	**0.3**	**0**	**0**	**0**	**<0.1**	**<0.1**	**0.4**

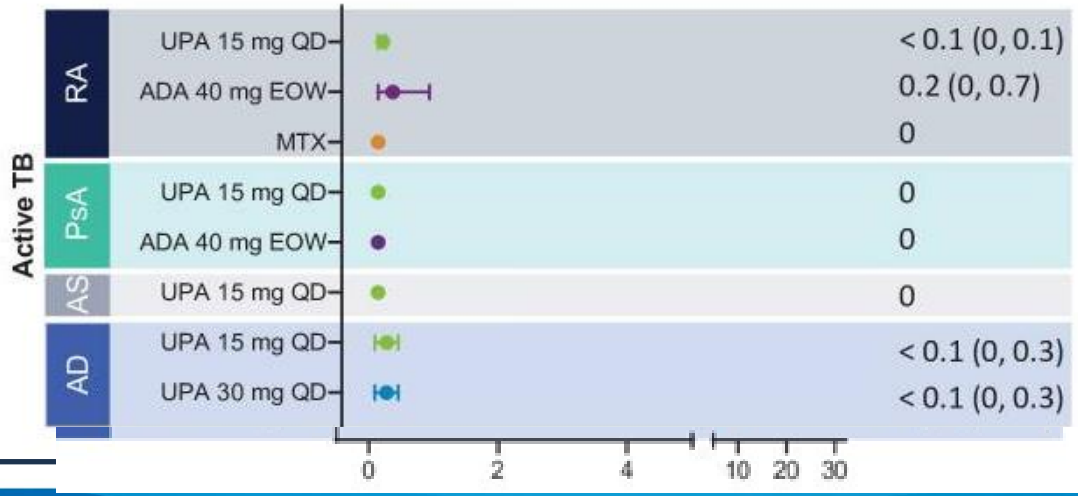
Events reported per 100PYs; Burmester GR, et al. Adv Ther. 2020 Jan;37(1):364-380.

Safety Events with Upadacitinib









Burmester G, et al. RMD Open. 2023; 9(1): e002735.

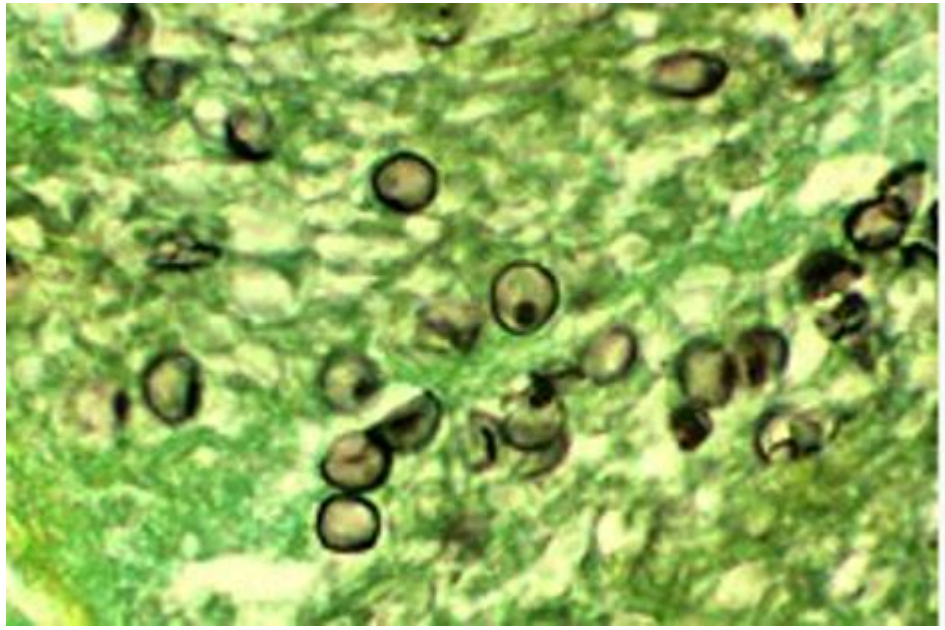
Pneumocystis Jiroveci Pneumonia (PJP) Risk

- **Corticosteroids** (high dose; >15-30 mg)
  - Pred dose predicts mortality risk
- **Rituximab**
- **Cyclophosphamide**

Risk Factors:

- Lymphopenia (HIV, CD4#s)
- Multiple (combo) immunosuppressives
  - CsA, MMF, AZA, CTX
  - MTX?
- Chronic Lung Disease
- Elderly

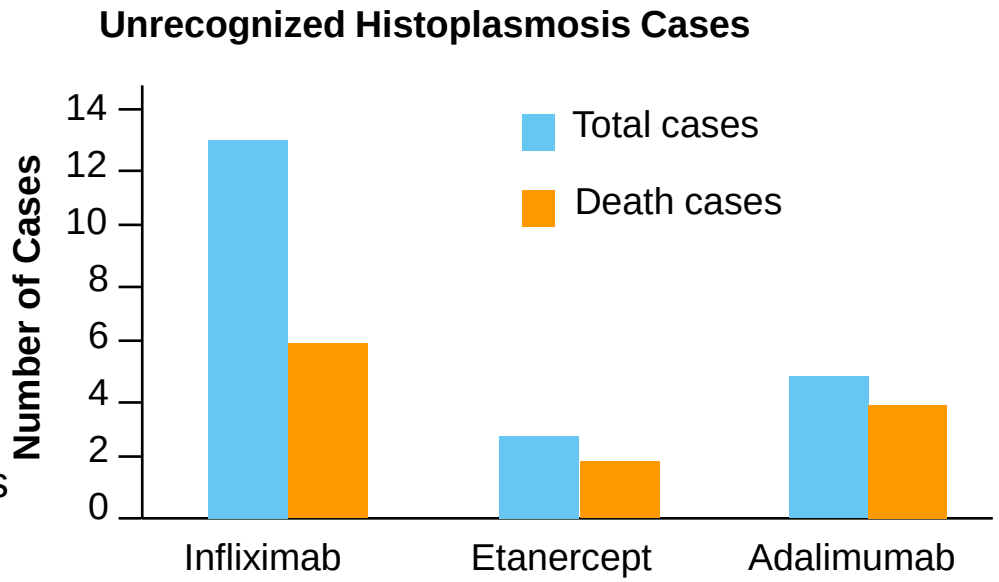
- Not Necessarily: RA, SLE, PMR, Gout



Sonomoto, et al. *Rheumatology 2022:* 61: 1831–1840 Shiba H. et al. Int. J. Mol. Sci. 2023, 24(8), 7399;
Fragoulis GE, et al. ARD 2022. doi: 10.1136/ard-2022-223335 Hellmich B, et al. ARD March 2023. doi: 10.1136/ard-2022-223764

Histoplasmosis Infections with anti-TNF

- FDA analysis prompted by reports of histoplasmosis deaths in patients receiving anti-TNF Rx; Medwatch AERS thru' 2/29/08
- N=240 Historplasmosis FDA Reports
- (207 IFX; 16 ETN; 17 ADA)
  - Pulm. 10%, disseminated 76%
- **Death occurred in 45/240 (19%)**
- 85% of cases occurred in endemic areas (OH/MS river valley)
- Concern about delayed diagnosis of fungal infection in anti-TNF Rx pts



Summary:

- Patients living in endemic areas are at risk
- FDA conclusion: *'Clinicians should consider initiating empiric fungal therapy while evaluating at-risk individuals with undiagnosed systemic illnesses'*

Diak P et al., FDA 2008; 26:854-9.

mTB - Tuberculosis

Tuberculosis and Opportunistic Infections

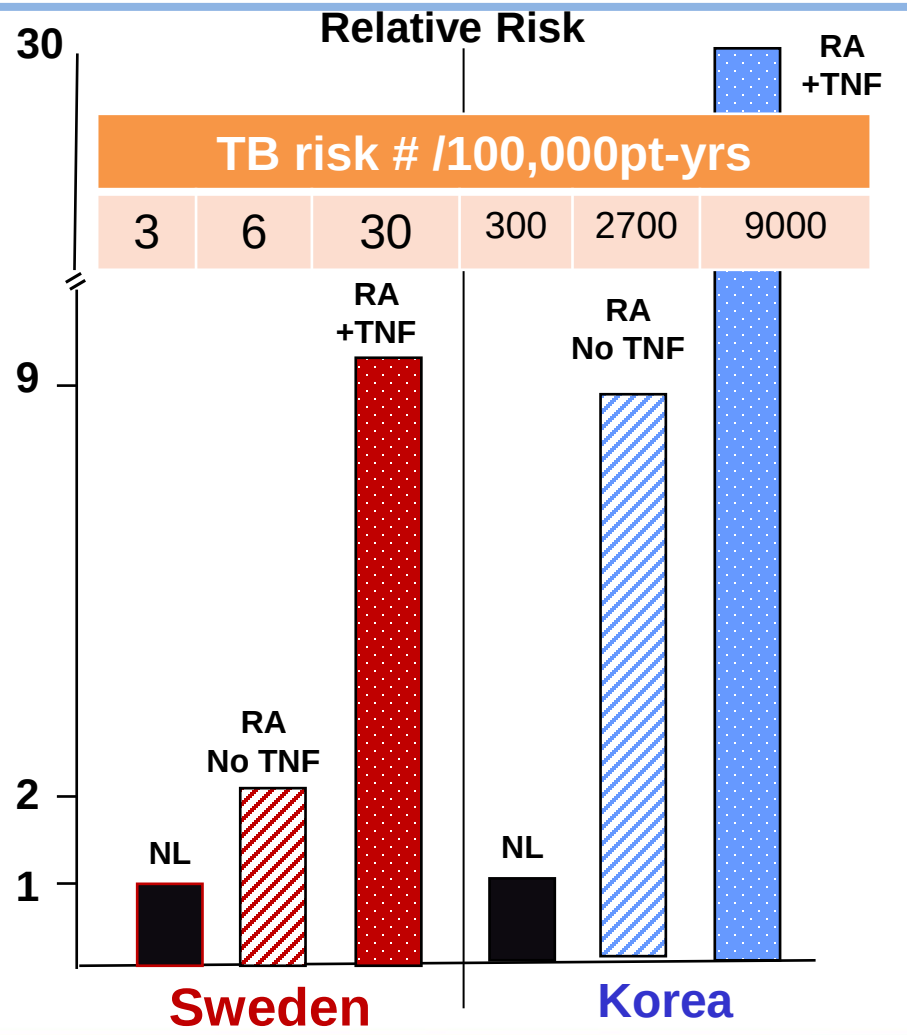
- TB US risk 4 per 100,0000 (RA pt TB risk is 6-7/100,000)
- Foreign Born “TB land” risk is **250 to 12,000/100,000**
- **TB & OI Risk is due to TNFi >>>>>> all other biologics**
- NNH TB with TNFi = 1 in 500-700

- **Boxed Warning for nearly all biologics**
  - **Tuberculosis (TB) Screening required for all JAKi & Biologics (eg canakinumab)**
  - **But not for Methotrexate, Azathioprine, Apremilast, Anakinra, Rilonacept, Rituximab, Belimumab, Pegloticase**

TB Risk with TNF Inhibitors

TB Risk Augmented by:

- Risk of prior TB exposure
  - Prior contact to case
  - Birth or extended living in endemic TB countries
  - Living or working in
    - Homeless shelters
    - Jail/prison
    - Health care settings (where TB is seen)
- Immunosuppressed (HIV)
- Exposure
- TNFi use increased TB risk 5-10+ fold
- Number needed to Harm = 681



1 Winthrop K. EULAR 2005, #SP0005; 2. Askling J, *et al.* Arthritis Rheum 52:1986-92, 2005 3. Seong SS, et al. 2007 Apr;34(4):706-11 4. Singh JA, etl. Cochrane Reviews 2011 Baronnet et al. / Joint Bone Spine 78 (2011) 279–284

Worldwide Distribution of Tuberculosis

L. Baronnet et al. / Joint Bone Spine 78 (2011) 279–284`

Tumor Necrosis Factor-α Is Required in the Protective Immune Response Against Mycobacterium tuberculosis in Mice

JoAnne L. Flynn,[1] Marsha M. Goldstein,[2] John Chan,[3] Karla J. Triebold,[4] Klaus Pfeffer[5,6], Charles J. Lowenstein,[7] Robert Schreiber,[8] Tak W. Mak,[5] and Barry R. Bloom[4]

Understanding the immunological mechanisms of protection and pathogenesis in tuberculosis remains problematic. We have examined the extent to which tumor necrosis factor-α (TNFα) contributes to this disease using murine models in which the action of TNFα is inhibited. TNFα was neutralized in vivo by monoclonal antibody; in addition, a mouse strain with a disruption in the gene for the 55 kDa TNF receptor was used. The data from both models established that TNFα and the 55 kDa TNF receptor are essential for protection against tuberculosis in mice, and for reactive nitrogen production by macrophages early in infection. Granulomas were formed in equal numbers in control and experimental mice, but necrosis was observed only in mice deficient in TNFα or TNF receptor. TNFα and the 55 kDa TNF receptor are necessary conditions for protection against murine *M. tuberculosis* in

tissue

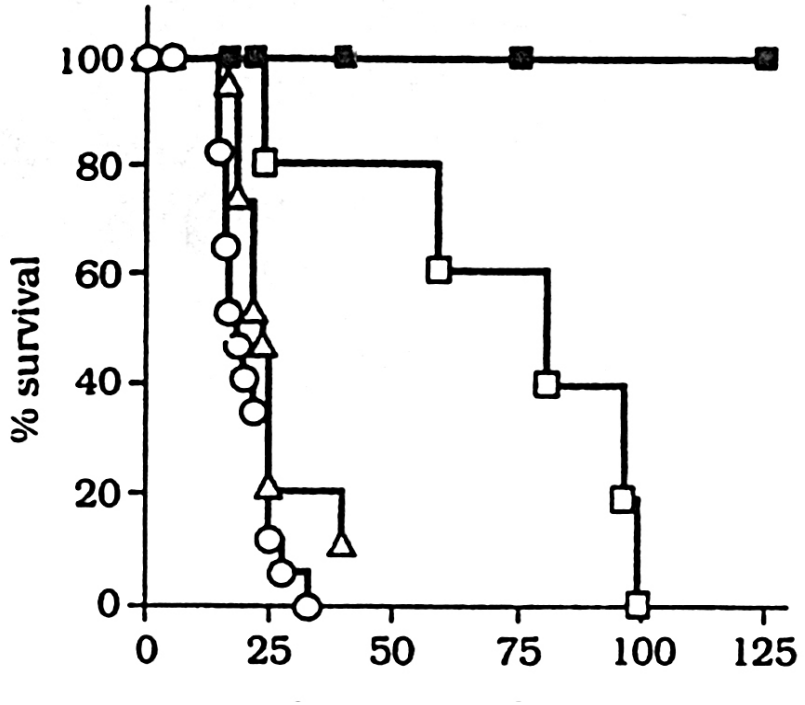


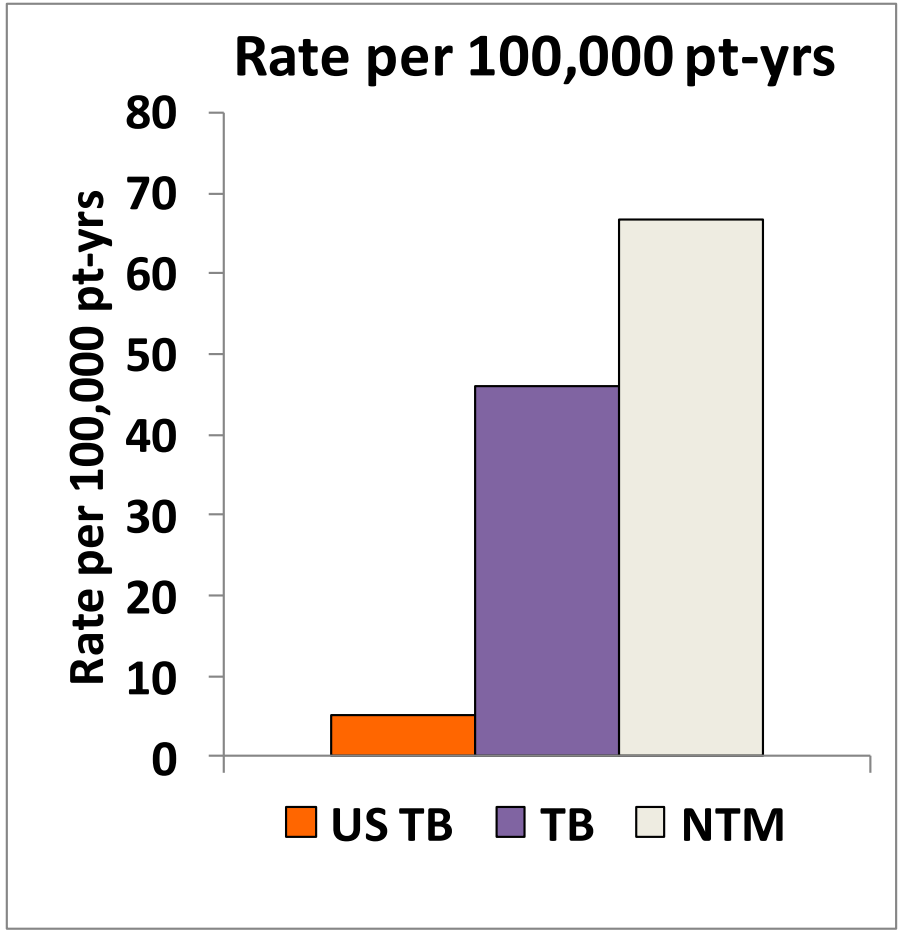
Figure 1. Effect of TNF Neutralization or Lack of TNF p55 Receptor on Survival of M. tuberculosis-infected Mice

C57BL/6 mice treated with anti-TNF Mab (open triangle) or, as controls, hamster IgG (closed square). TNFRp55$^{-/-}$ mice (open circle). Controls for TNFRp55$^{-/-}$ (C57BL/6 mice) showed 100% survival, identical to hamster IgG-treated mice. Data shown are from two experiments each with at least 8 mice per group per experiment. C57BL/6 mice (open square) were previously immunized with BCG, and treated with anti-TNF Mab at time of challenge with M. tuberculosis.

Flynn JL, et al. Immunity. 1995 Jun;2(6):561-72.

Non-Tuberculous Mycobacterial (NTM) Infections are More Common than mTB

- Among 29,500 new users of TNF inhibitors in 3 databases followed from 2000-07
- More new NTM (24) than TB (11) cases identified
- NTM Sx: fever cough malaise
- Most common sites: pulm, LN, skin, soft tissues
- NTM,aka atypical mycobacteria, is more common than TB among RA, elderly and sick patients



Treatment of Latent TB infection

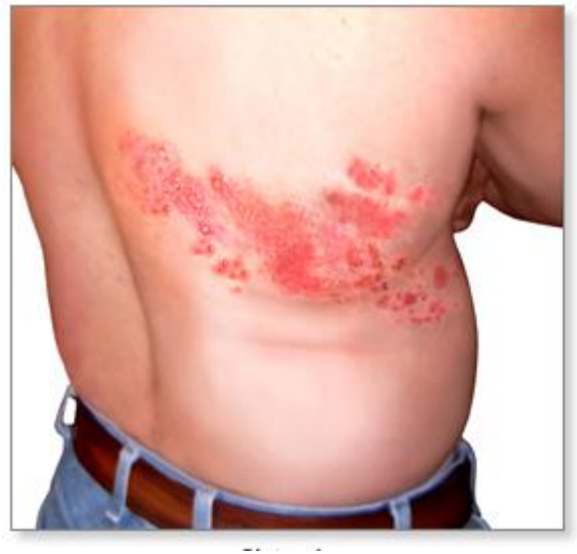
Rx / mg	Regimen	Duration (mos)	Evidence	Completion	Hepatitis Risk
INH 300	Qd	9	A	45-60%	3.8%
INH 300	Qd	6	B	55-57%	
RIF 600	Qd	4	B	69-78%	0.7%
INH/RIF	Qd	3	B	75%	Unknown
Rifapentin/ INH 900	Q Wk	3	B	75%	2.7%

INH: Isoniazid; RIF: Rifampin

Horsburgh CR, Rubin EJ, NEJM 2011: 364: 15 Sterling TR NEJM 2011; 365:23

Shingles – Fear the Infection, Value the Solution!

- Reactivation of varicella zoster virus (VZV)
  - 1 / 3 Lifetime risk of reactivation
  - 4 -11 per 1000 Pt-Yrs
- Acute and chronic pain, dermatomal rash
  - Post-herpetic neuralgia (15%), visual loss rare
  - Disseminated disease (1%)
- RA patients: Risk elevated <2 fold Vs. non-RA



Risk per 1000 Pt-Years						
Nl	OA	RA	SLE	GPA	TOFA	Bari
4	10	14	20	43	45	35

Herpes Zoster and Tofacitinib

Crude incidence rates of HZ overall and by geographic region of Enrollment in the phase II, phase III, and long-term extension studies

	HZ events	Patient-years of exposure	HZ incidence rate (95% CI)*
Global rheumatoid arthritis program	239	5,482	4.4 (3.8-4.9)
By region			
US/Canada/Australia	40	1,216	3.3 (2.4-4.5)
Western Europe	12	450	2.7 (1.5-4.7)
Eastern Europe	43	1,425	3.0 (2.2-4.1)
Latin America	37	991	3.7 (2.7-5.2)
Asia	107	1,388	7.7 (6.4-9.3)
Within Asian countries			
Japan/Korea	85	920	9.2 (7.5-11.4)
India	8	90	8.9 (4.4-17.7)
Thailand/Malaysia/Philippines	3	137	2.2 (0.7-6.8)
China/Taiwan	11	241	4.6 (2.5-8.2)

*The crude incidence rates of herpes zoster (HZ) events, with 95% confidence intervals (95% CIs), are expressed per 100 patient-years.

Winthrop et al Arth and Rheumatol 2014
Winthrop K et al Arth and Rheumatol 2014 November; pp 2924–2937

Shingrix - Herpes Zoster subunit vaccine

- FDA Approved - 2017
- Prevention of H zoster and related complications 50 years and older.
- Phase III RCTs w/ 38k adults – ZOE50 & ZOE70
- > 90% Efficacy all ages; sustained efficacy over 4 yrs
  - reduced risk (>90%) of postherpetic neuralgia (PHN)
- AE: ISR (pain, redness, swelling), muscle pain, tiredness, headache, shivering, fever, GI upset (Systemic sxs 53% v 25%)
- Administer 2 doses (0.5 mL each) at 0 and 2 to 6 months.
- Cost: $280-320 for the two shots
- Low risk of flare in RA

Med Lett Drugs Ther. 2017;59(1535):195-196
Cunningham N Engl J Med 2016; 375:1019-1032.
Stevens E, Weinblatt M, et al. ACR 2019; Abstrct #1804
Acharya ACR 2019 abstr#2093

Common Vaccines

Inactive Vaccines*	Live Vaccines
Influenza (IM) (A/B/H1N1)	Influenza (nasal)
Typhoid (IM)	Typhoid (oral)
Tetanus/Diptheria/Pertussis (Tdap)	Yellow fever
Recombinant zoster subunit vaccine (Shingrix)	**Varicella [Varivax] [Zostavax#]**
Pneumococcal (23/7valent)	Measles, mumps, rubella (MMR)
Human papilloma virus (HPV)	BCG (bacillus Calmette-Guerin)
Hepatitis B (HBV), Hepatitis A (HAV)	Polio (oral)
Hemophilus influenza B (HIB)	Smallpox (vaccinia)
Meningococcus	Rotavirus
Rabies, Anthrax, Lyme	Adenovirus type 4, 7 (oral)

#H. Zoster: Ok give if ≥60 yrs on MTX, AZA, pred, but avoid w/ biologics. Give before biologic or give 4wks after biologic stop; vaccinate; wait ≥2wks before biologic restart

*component / toxoids / inactivated / killed)

Kavanaugh, A Curr Opin Rheumatol 2009 Cush JJ Drug Safety Quarterly 2013; 4:1

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Effects of Immunomodulatory Agents on Vaccine Efficacy[a]

Treatment	Inactivated Influenza Vaccine	Pneumococcal Vaccine
Nonbiologic DMARDs		
Antimalarials	No effect[1]	NA
Azathioprine	No effect[2]	Reduced response[2]
Corticosteroids	No effect[1]	No effect[8]
Leflunomide	No effect[1]	Reduced response[2]
Methotrexate	**Reduced response[1]**	**Reduced response[8]**
Sulfasalazine	No effect[3]	NA
Biologics and targeted immunomodulators		
Abatacept	No effect[4]	Reduced response[9]
Rituximab	**Markedly reduced response[5]**	**Markedly reduced response[9]**
TNF inhibitors	No effect[1]	No effect[8]
Tocilizumab	No effect[6]	No effect[9]
Tofacitinib	No effect[7]	Reduced response[7]

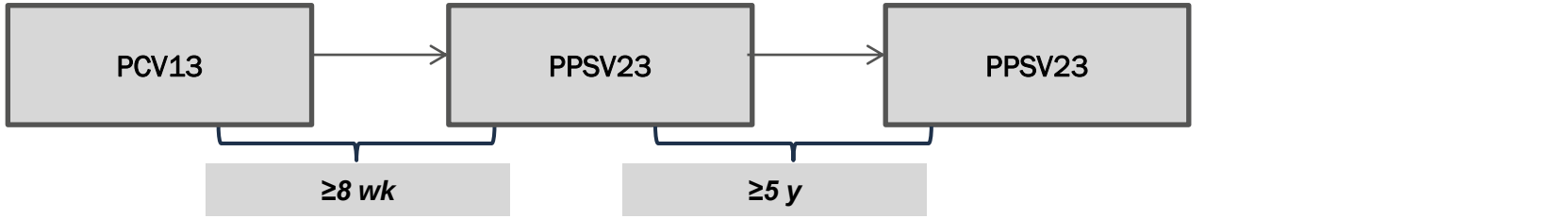
[a]As measured by immunologic responses, not clinical events.

1. Ribeiro AC et al. *Ann Rheum Dis.* 2011;70(12):2144-2147. **2.** Sowden E, Mitchell WS. *BMC Musculoskelet Disord.* 2007;8:58. **3.** Trollmo C et al. *Ann Rheum Dis.* 2007;66(4):481-185. **4.** Milanetti F et al. *Clin Exp Immunol.* 2014;177(1):287-294. **5.** van Assen S et al. *Arthritis Rheum.* 2010;62(1):75-81. **6.** Mori S et al. *Ann Rheum Dis.* 2012;71(12):2006-2010. **7.** Winthrop KL et al. [Epub March 20, 2015]. *Ann Rheum Dis.* doi: 10.1136/annrheumdis-2014-207191.
8. Kapetanovic MC et al. *Arthritis* . 2011;63(12):3723-3732. **9.** Kapetanovic MC et al. *Arthritis Res Ther.* 2013;15(5):R171.

ACIP Vaccination Recommendations PCV13 & PPSV23 in Immunocompromised Adults

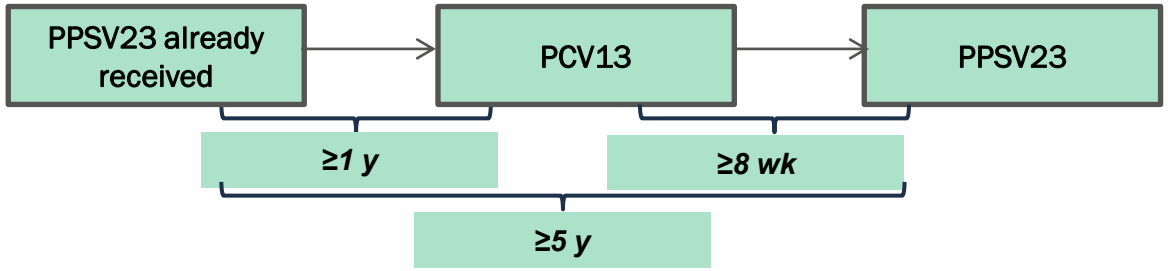
- **Immunocompromised adults should be vaccinated 1st with PCV13 then PPSV23 8 weeks later**

Pneumococcal vaccine-naïve aged ≥19 y with immunocompromising conditions[a]



- **Prior PPSV23 should receive another PPSV23 dose at 65 yrs, or after 5 yrs have elapsed previous dose**

Previously received PPSV23 aged ≥19 y with immunocompromising conditions[b]



1st PCV13
PPSV - 8wk later
PPSV23 - 5 yrs later

RheumNow Live!

Centers for Disease Control and Prevention. *MMWR Mortal Wkly Rep*. 2012;61(40):816-819.

Seasonal Flu Vaccination in RA Patients on MTX

2 Wk

- Study based on a pilot effort
- RCT N=316 MTX pts.
- Seasonal quadrivalent flu vaccine
- RCT: continued MTX vs Hold MTX x 2wks
- Seroconversion higher in MTX-held
  - 75% vs. 54%

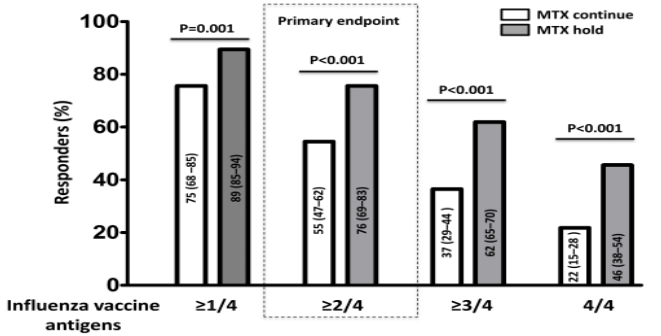


Figure. Frequency of satisfactory vaccine response to 4 influenza antigen

1 Wk

- OL prospective study
- N = 184 MTX pts.
- RCT: 1 vs 2 week MTX hold vs continued MTX
- Humoral responses @ wk 4, 16
- Equivalent Seroconversion 1 vs 2 wk

Seroconversion at:	1 Week	2 Week
Week 4	68.9%	75%
Week 16	78.4%	79.1%

1 or 2 wk MTX discontinuation after vaccination improves the immunogenicity of seasonal influenza vaccination in RA patients without increasing RA disease activity.

Park JK, et al. ACR 2017, Ann Rheum Dis. 2018 Mar 23. Park JK, et al A&R July 2023 doi.org/10.1002/art.42644

High Dose Superior to Standard Dose Influenza Vaccine in RA

- Rheumatoid arthritis patients have a 2-3 fold increase risk of influenza
- McGill Study - done over 2016-17 and 2017-2018 flu seasons.
- N = 279 RA patients with a mean age of 59-62 years.
- Randomized to standard dose vs high-dose quadrivalent flu vaccine.
- Primary endpoint was seroconversion/seroprotection at day 28
- **High dose vaccine pts showed 2-3 fold higher seroconversion rates**
- All DMARD groups - although **lower responses were seen in those on rituximab.**
- Cost and availabilityof the high dose vaccine.
  - The quadrivalent vaccine is 4 to 10 times the cost of the standard influenza vaccine

Patients who should NOT receive TNF inhibitors!

Infectious Scenario	Comment
1. Active Hepatitis*	HBsAg+ at greatest risk
2. Nontuberculous mycobacterial (NTM) infection*	Despite anti-mycobact. Rx, never fully eradicate NTM
3. Invasive fungal infection*	Difficult to fully eradicate, reactivation common
4. Intravesicular BCG treatment	TNF inhibitor use may potentially lead to mycobacterial infection

** if absolutely necessary, consider chronic prophylaxis w/ biologic*

World Map of HBV Prevalence

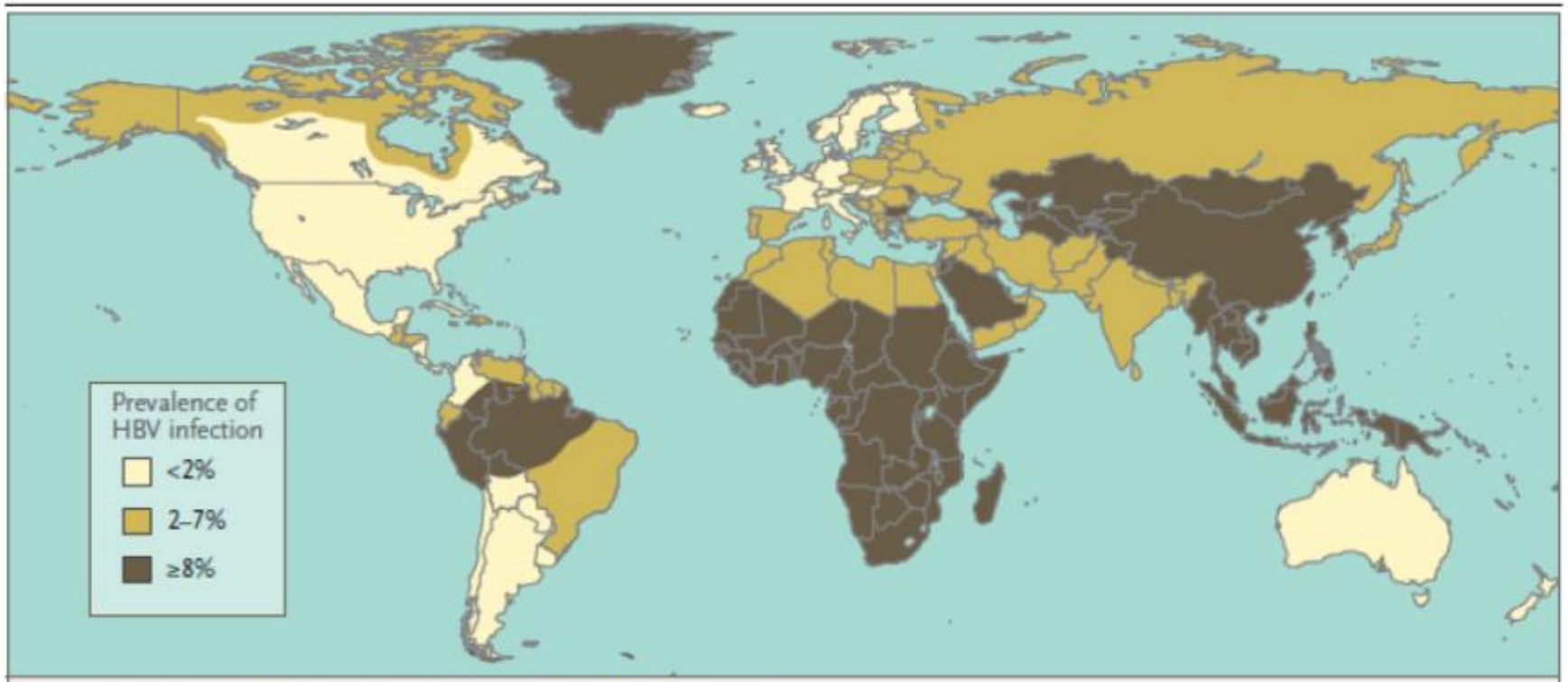
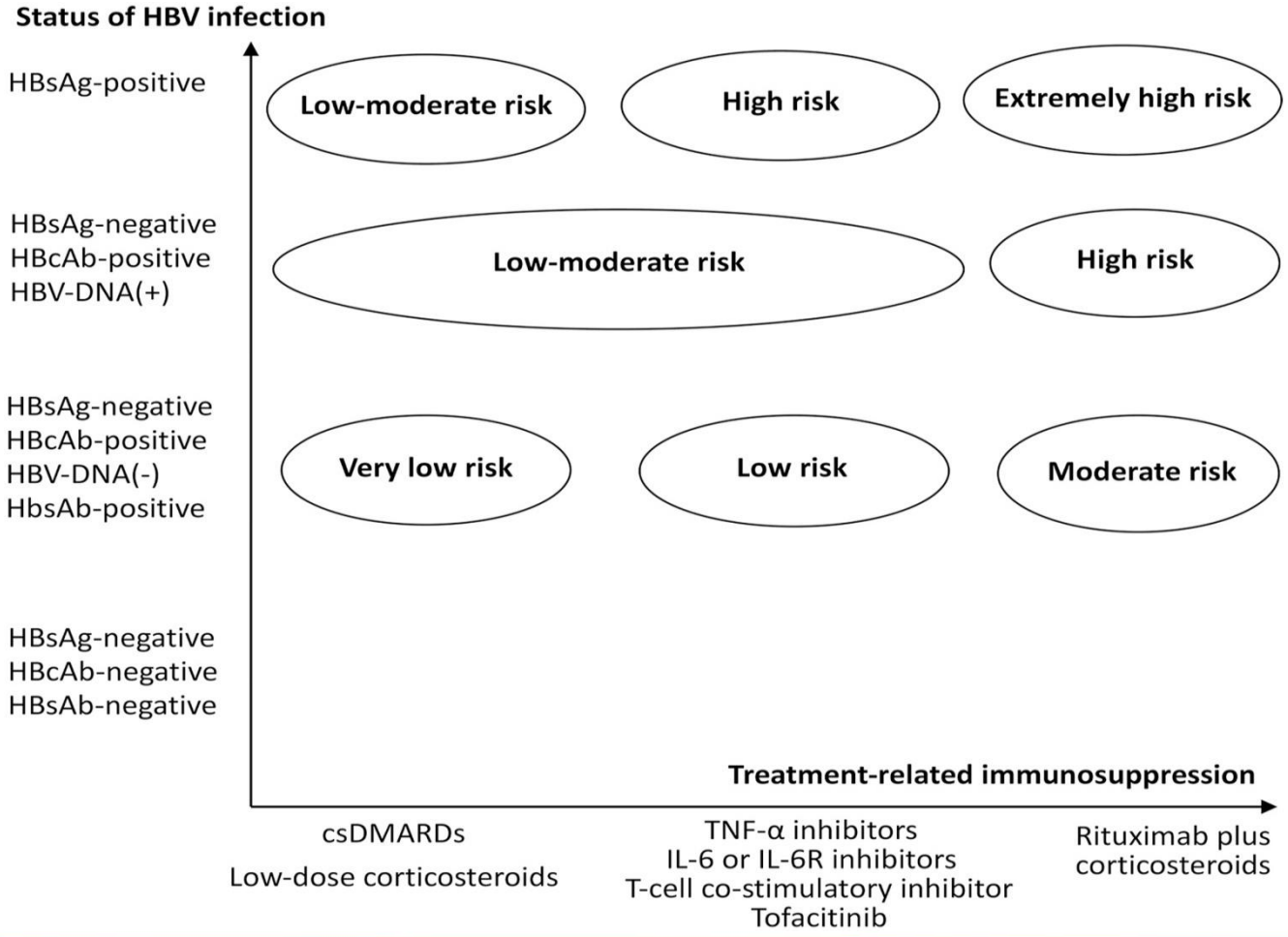


Figure 2. Clinical and Epidemiologic Correlations in HBV Infection.

The clinical expression of HBV infection depends on the time of life when the infection is acquired. In Asian countries with a high prevalence of HBV infection, HBV is acquired perinatally from infected mothers. It is not accompanied by acute hepatitis, but it results in chronic infection in more than 90% of patients. Later in life, cirrhosis and hepatocellular carcinoma account for up to a 40% lifetime risk of death. In contrast, in Western countries with a low prevalence of HBV infection, HBV is rarely acquired perinatally but instead is acquired during adolescence and early adulthood; infections acquired in adulthood usually cause a clinically apparent acute hepatitis, but progression to chronic hepatitis is rare, as is the risk of hepatocellular carcinoma.

HBV Reactive Risk Stratification



- According to serology and treatment in RA

Chen YM, et al. J Micro Immunolo Infection, 2019; 52: 1-8

Reactivation Risk with Resolved HBV (HBsAg-, HBcAb+) and TNF Inhibitors

- TNFi Rx pts not adequately HBV tested (~25%)
- HBV activation occurs w/ HBsAg+ (12-40%);
  - But NOT if on anti-viral prophylaxis
- TNFi can be used with low (1%) risk in pts with resolved HBV
- Reactivation of HBcAb+ pts also reported with RTX, TCZ, ABA
- Biologic Rx: Screening for HBV, HCV and monitoring of LFTs is strongly advised .

Reactivation risk in inactive HBV (HBsAg-, HBcAb+)	
Author/ year	Reactivation
Charpin 2009	0/21
Bobbio 2009	0/69
Chung 2009	1/8
Vassilopoulous 2010	1/19
Caporali 2010	0/67
Cassano 2011	0/62
Mori 2011	1/31
Tamori 2011	1/45
Ye 2014	0/50

= 4/372 (1%) risk of reactivation with resolved HBV and TNFi Rx

Adapted from Nard FD, et al. World J Hepatol. 2015 Mar 27;7(3):344-61

Progressive Multifocal Leukoencephalopathy (PML)

- Rare, less fatal, demyelinating disorder → JC polyomavirus
- PML Sxs: hemiparesis, cognitive/AMS, discoordination, apathy. (Dx: MRI lesions, PCR of CSF)
- @risk: conditions that affect cell-mediated immunity
  - AIDS, Leukemia/lymphoma, organ transplantation, chemotherapy
  - FDA (PI) Warnings for **Rituximab**, Efalizumab, Natalizumab, **Mycophenolate**
- Autoimmune pts (noHIV/Cancer), incidence = 0.2 per 100,000
  - Rheumatoid arthritis = 0.4 per 100,000 (**RTX RA: 6/168,000**)
  - SLE = 4.0 per 100,000
- Study 34 confirmed cases of PML in IMID
  - 17 SLE, 10 RA, 7 other
  - 14 RTX, 6 TNFi
- JC Virus serological should not be used to screening prior to biologic use

Exposed	N	Rx	Death
Biologics	15	14 RTX (4 mono) 6 TNF inhibitors*	7/10
DMARDs	19	14 Alkylating Rx 14/34 AZA 6/34MMF	10/19

* 5 prior to RTX use

Bharat A et al. Arth Res Care 2012; Molloy ES et al Arth Rheum 2012; 64:3043-3051

Questions?

Email : jackcush@rheumnow.com

Questions?

- Does infection amplify autoimmune disease activity
- Does AIRD Dx increase/decrease infection mortality risk
  - Do steroids/DMARDs decrease or reduce mortality risk

Email : jackcush@rheumnow.com

2022 EULAR Recommendations on Screening and Prophylaxis for Opportunistic Infections

- AIIRD Pts are at increased risk for infections due to both immune dysregulation and immunosuppressive, immunomodulating and anti-inflammatory treatments
- AIIRD pts should undergo screening & preventive measures

Four Overarching principles

- Infecion Risks should be assessed and discussed with patients.
- Collaboration between rheumatologists and other specialists is important.
- Consider Patient-specific risks in screening and prophylaxis decisions.
- National and regional guidelines/recommendations should be considered when making decisions regarding opportunistic and chronic infections.

Fragoulis GE, et al. *Annals of the Rheumatic Diseases* 2023;**82**:742-753.

2022 EULAR Recommendations on Screening and Prophylaxis for Opportunistic Infections

1. Screening for LTBI is recommended in prior to starting bDMARDs or tsDMARDs* (consider in those starting csDMARDs, immunosuppressants* and/or glucocorticoids)
2. Screening for LTBI should follow national guidelines (CXR, IGRA, TST or PPD where available)
3. LTBI therapy should be guided by national and/or international guidelines. (beware of drug interactions)
4. HBV screening considered with: csDMARDs, bDMARDs, tsDMARDs*, immunosuppressants* and steroids
5. HCV screening considered prior to csDMARDs, bDMARDs, tsDMARDs*, immunosuppressants & steroids
6. HIV is recommended prior to bDMARDs (maybe with csDMARDs, tsDMARDs, immunosupp. & steroids)
7. With Varicella zoster virus (VZV) exposure, post-exposure prophylaxis should be considered in patients starting csDMARDs, bDMARDs, tsDMARDs, immunosuppressants and/or glucocorticoids
8. PJP prophylaxis should be considered in AIIRD patients on high doses of glucocorticoids, especially in combination with immunosuppressants

Fragoulis GE, et al. *Annals of the Rheumatic Diseases* 2023;**82**:742-753.

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Peter Merkel, MD: AN
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PODCAST

In RA TNF

Scie

man, MD

Patients with rheumatoid arthritis (RA) were less likely to discontinue their first biologic when that treatment was a tumor necrosis factor (TNF) inhibitor than if it was a non-TNF biologic, and especially if treatment was initiated prior to 2005 [...]

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04 Dec 2015

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Physician Burnout on the Rise

By Jack Cush, MD

Burnout among U.S. doctors affects more than half of practicing physicians, according to a new study published in Mayo Clinic Proceedings.

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RA TNF-Inhibitors Prove To Be Durable Choice

Patients with rheumatoid arthritis (RA) were less likely to discontinue their first biologic when that

SOCIAL

Physician Burnout is a rising concern. But is it happening in Rheumatology too? https://t.co/XeYJeCLZrz

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In a placebo controlled RCT, 3 mg/kg infliximab injx fails to improve Sciatica from PostOp peridural lumbar fibrosis https://t.co/4dnmhLOZ4F

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Drug use decreases in the Yr following Hip Replacement 14% decrease in opioids, 18% NSAIDS, & 13% drop in analgesics https://t.co/1rJ8iZel8k

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RT @DrPetryna: @RheumNow NOREPOS study: combination of low serum VitK1 and VitD associated with

Drug use decreases in the Yr following Hip Replacement 14% decrease in opioids, 18% NSAIDS, & 13% drop in analgesics https://t.co/1rJ8iZel8k

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