Sistema Socio Sanitario
Ospedale Niguarda
Regione Lombardia

Massimo Puoti

Dept. of Infectious Diseases

ASST GOM Ospedale Niguarda

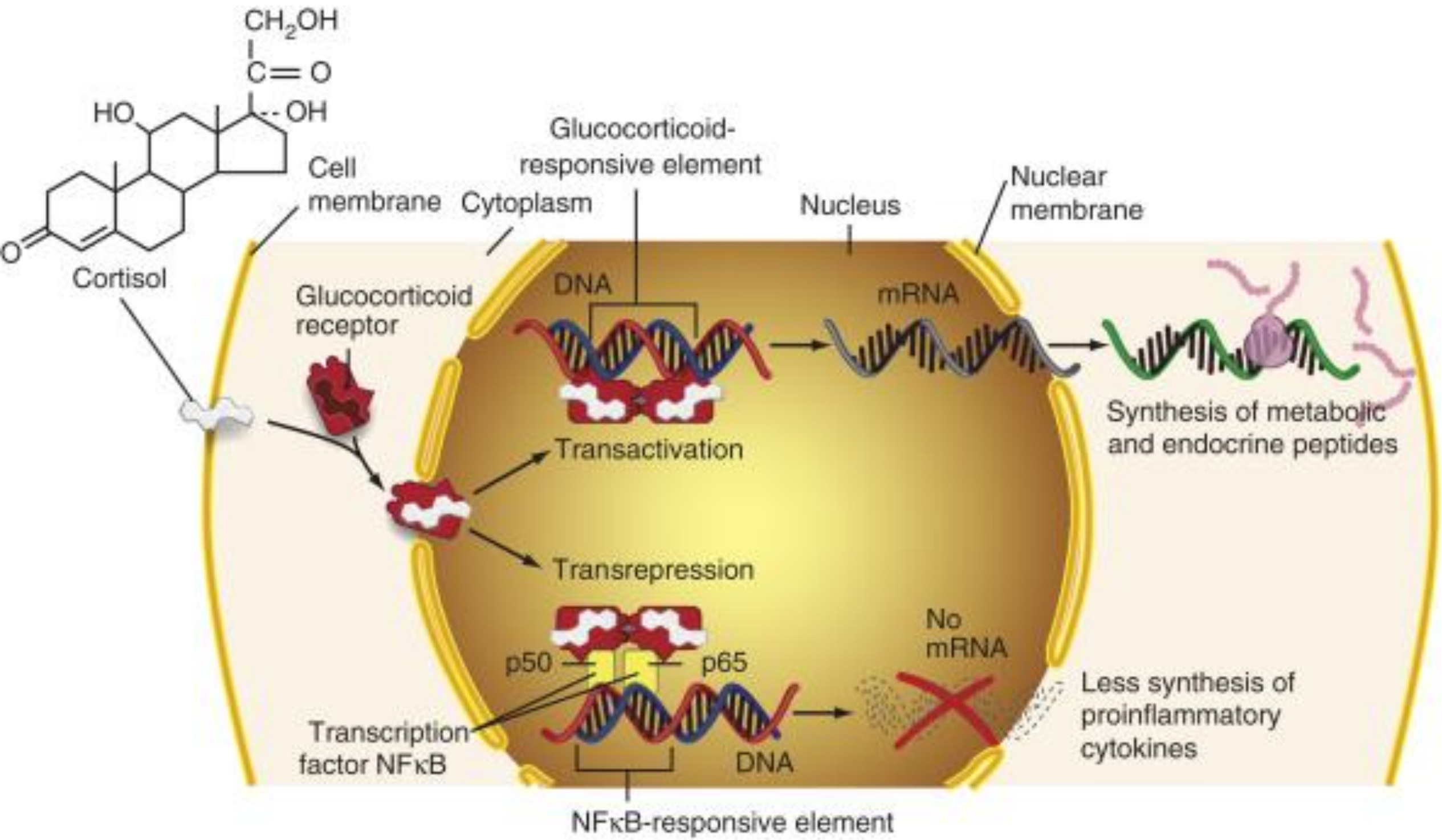
Milan, Italy

Management of Infections in RA

Incidence of infectious diseases in patients with RA

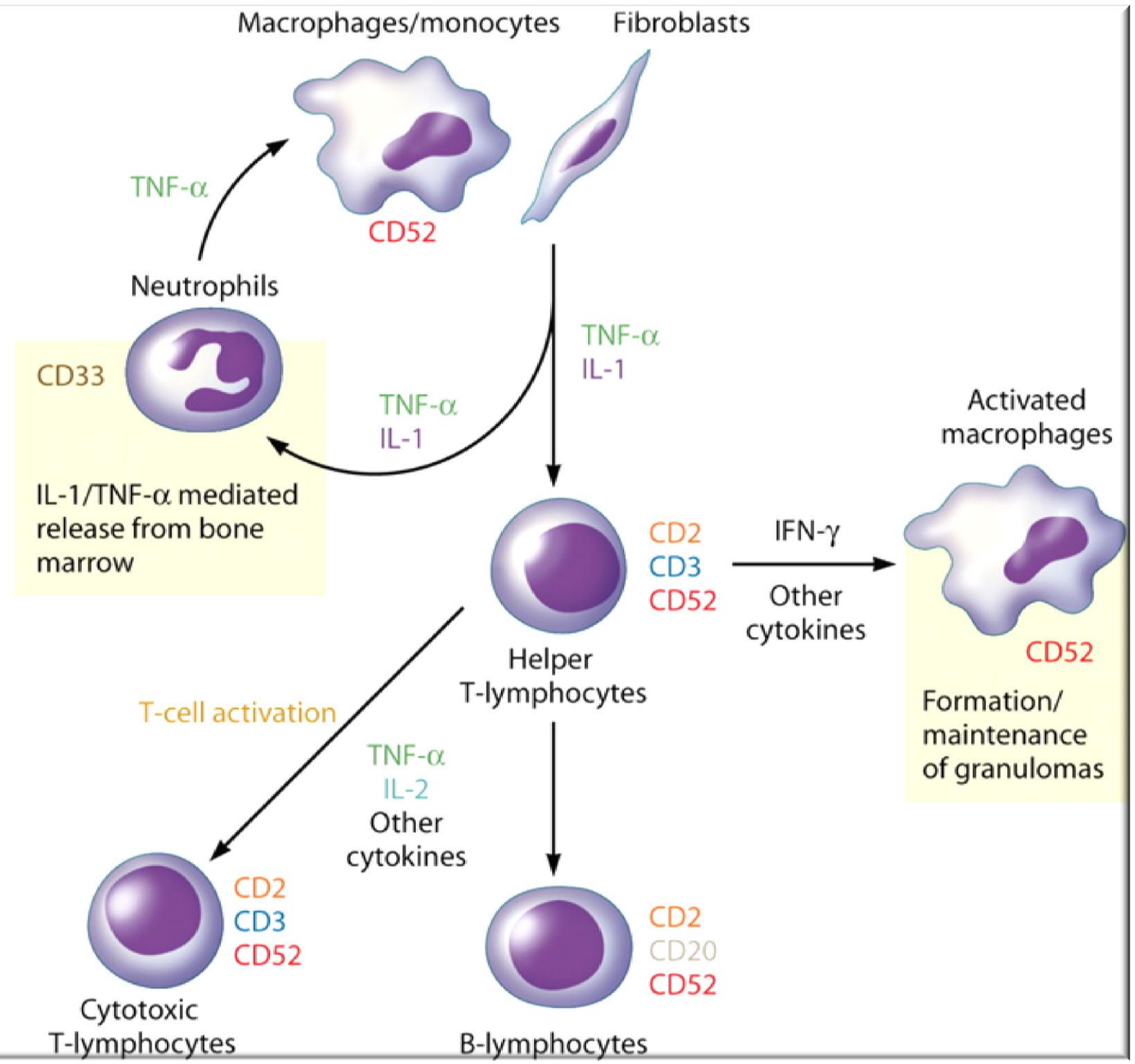
- Since the 1950s, observational studies → risk of infectious diseases[1]
  - joint damage, immobility amyloidosis with subsequent renal failure.
  - Increased risk of septic arthritis related[2] or not[3] to surgical procedures
- In the last decades of the '900 age adjusted mortality in RA patients 2 x general population → infectious diseases were one of the three leading causes of premature death
  - Rate of infections requiring hospitalizations *9.6 infections/100 person/years in 609 patients with established RA* **HR=1.9; 95% CI 1.7-2.1** vs 609 age & gender matched controls[4]
  - 2108 inflammatory polyarthritis: infection in Norwich UK > **2.5 x general population**[5]
- The pathogens: Pneumococcal infection
  - RA patients hospitalized between 1963 and 1998, **pneumococcal infection 2 x hospitalized pts with other chronic disease**[6]

1. Cobb S, et al. N Engl J Med 1953;249: 5533-6. 2.Goldenberg DL. Arthritis Rheum 1989;32:496-502. 3. Reilly PA. Ann Rheum Dis 1990; 49:36-39. 4. Doran Arthritis Rheum 2002;46: 2287-93 5. Franklin. Ann Rheum Dis 2007;66:308-12. 6. Wotton CJ, J Epidemiol Community Health 2012 Apr 6. [Epub ahead of print]


CH2OH
C=O
HO
OH
O
Cortisol
Cell membrane
Cytoplasm
Glucocorticoid-responsive element
Nucleus
Nuclear membrane
Glucocorticoid receptor
DNA
mRNA
Synthesis of metabolic and endocrine peptides
Transactivation
Transrepression
No mRNA
p50
p65
Less synthesis of proinflammatory cytokines
Transcription factor NFκB
DNA
NFκB-responsive element

Outline of human immunologic responses showing key targets of monoclonal antibodies that may suppress immune responses and enhance the risk for infection.

Therapeutic monoclonal antibodies	Key targets
Alemtuzamab	CD52
Adalimumab, Infliximab, Certolizumab pegol, Etanercept	TNF-α
Anakinra, Rilonacept	IL-1
Gemtuzumab ozogamicin	CD33
Alefacept	CD2
Muromonab	CD3
Abatacept, Efalizumab	T-cell activation
Basiliximab, Daclizumab	IL-2
^{90}Y-Ibritumomab tiuxetan, Rituximab, ^{131}I-Tositumomab	CD20



Salvana E M T , and Salata R A Clin. Microbiol. Rev. 2009;22:274-290

Clinical Microbiology Reviews

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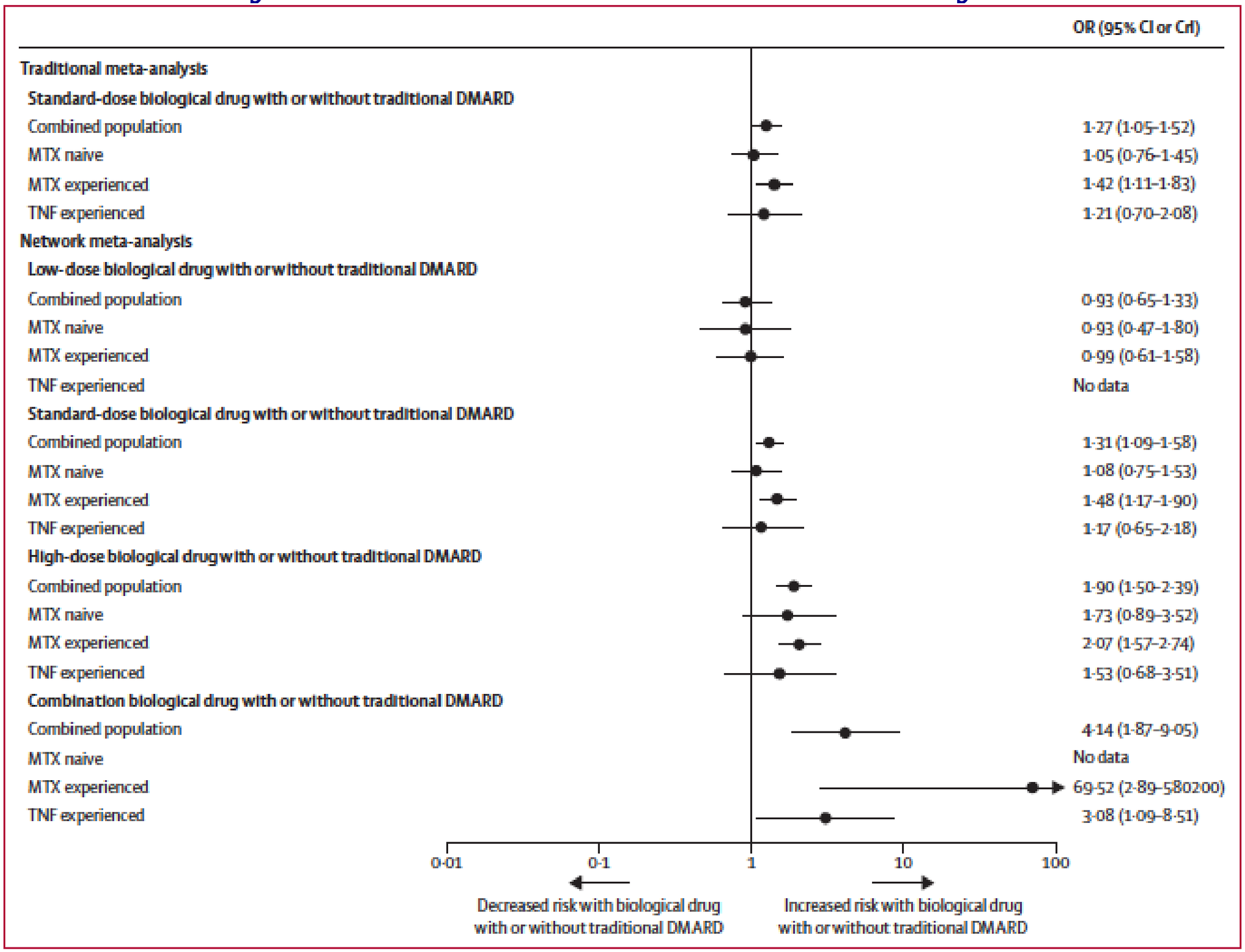
Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis

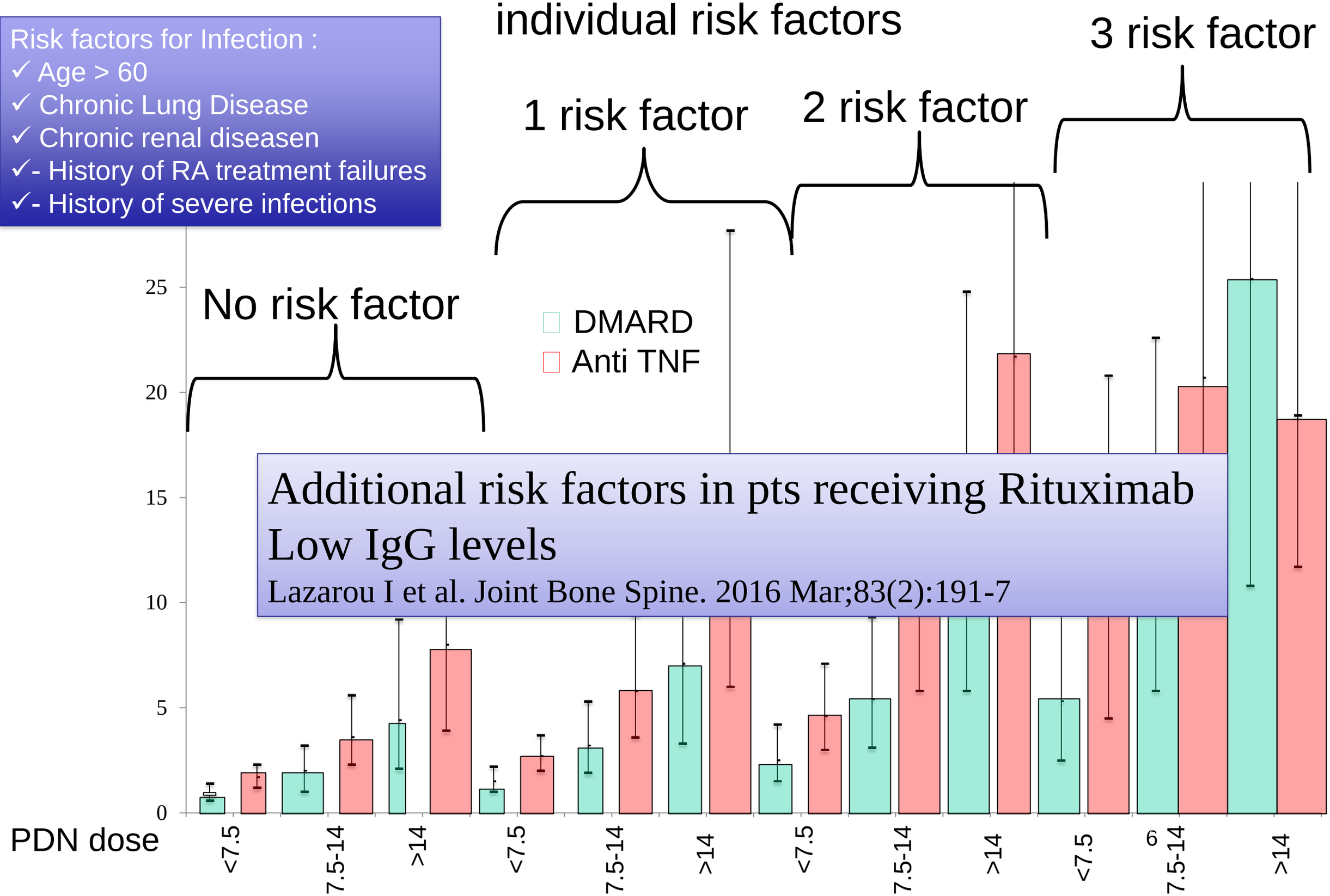


- 106 randomised trials published between1992 and Feb 11, 2014, which included 42 330 patients with rheumatoid arthritis 965 with serious infections

Singh JA et al The Lancet 2015; 386: 258-65

Estimates of incidence of serious infections per 100 pt/yr according to PDN dose , DMARD or anti TNF usage and individual risk factors

Risk factors for Infection :
- ✓ Age > 60
- ✓ Chronic Lung Disease
- ✓ Chronic renal diseasen
- ✓- History of RA treatment failures
- ✓- History of severe infections



Additional risk factors in pts receiving Rituximab
Low IgG levels
Lazarou I et al. Joint Bone Spine. 2016 Mar;83(2):191-7

Adapted from Strangfeld et al BMJ 2001

Management of Infections in Rheumatoid Arthritis

- Viral infections
  - Viral Hepatitis
  - Other viral infections
- Tuberculosis
- Opportunistic Infections
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  - Urinary tract infections
  - Skin & Soft tissue infections
  - Pneumonia

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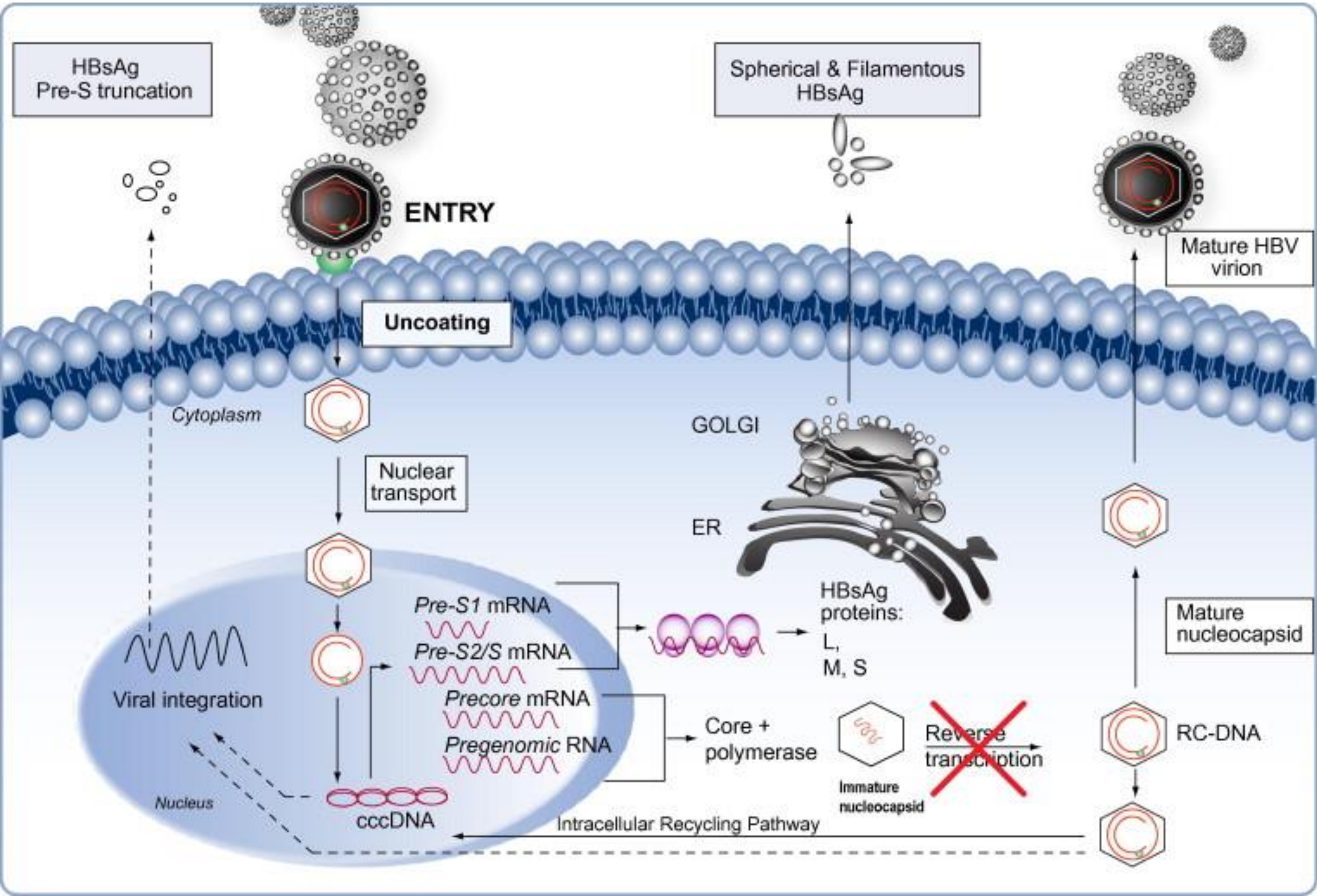
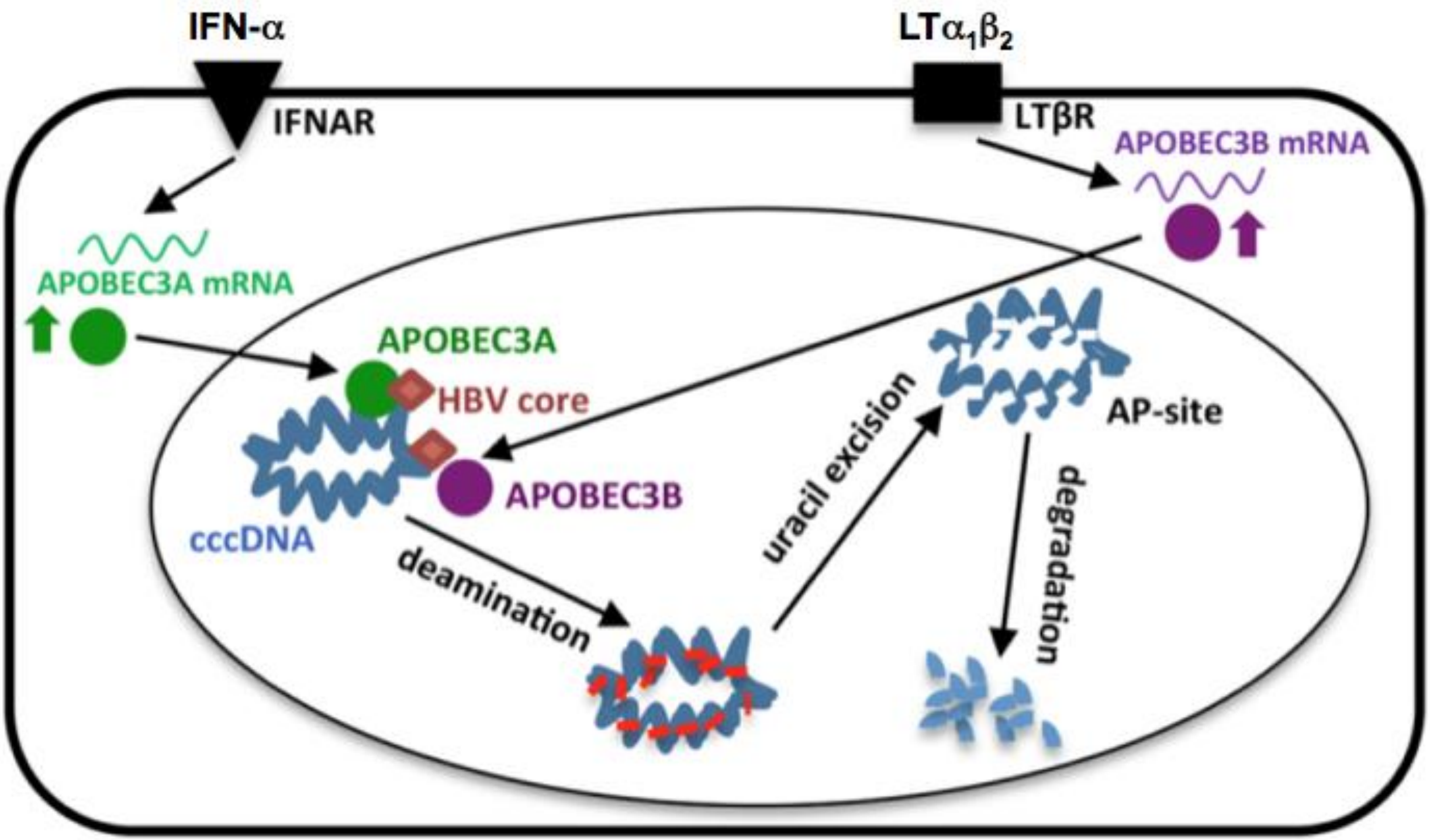
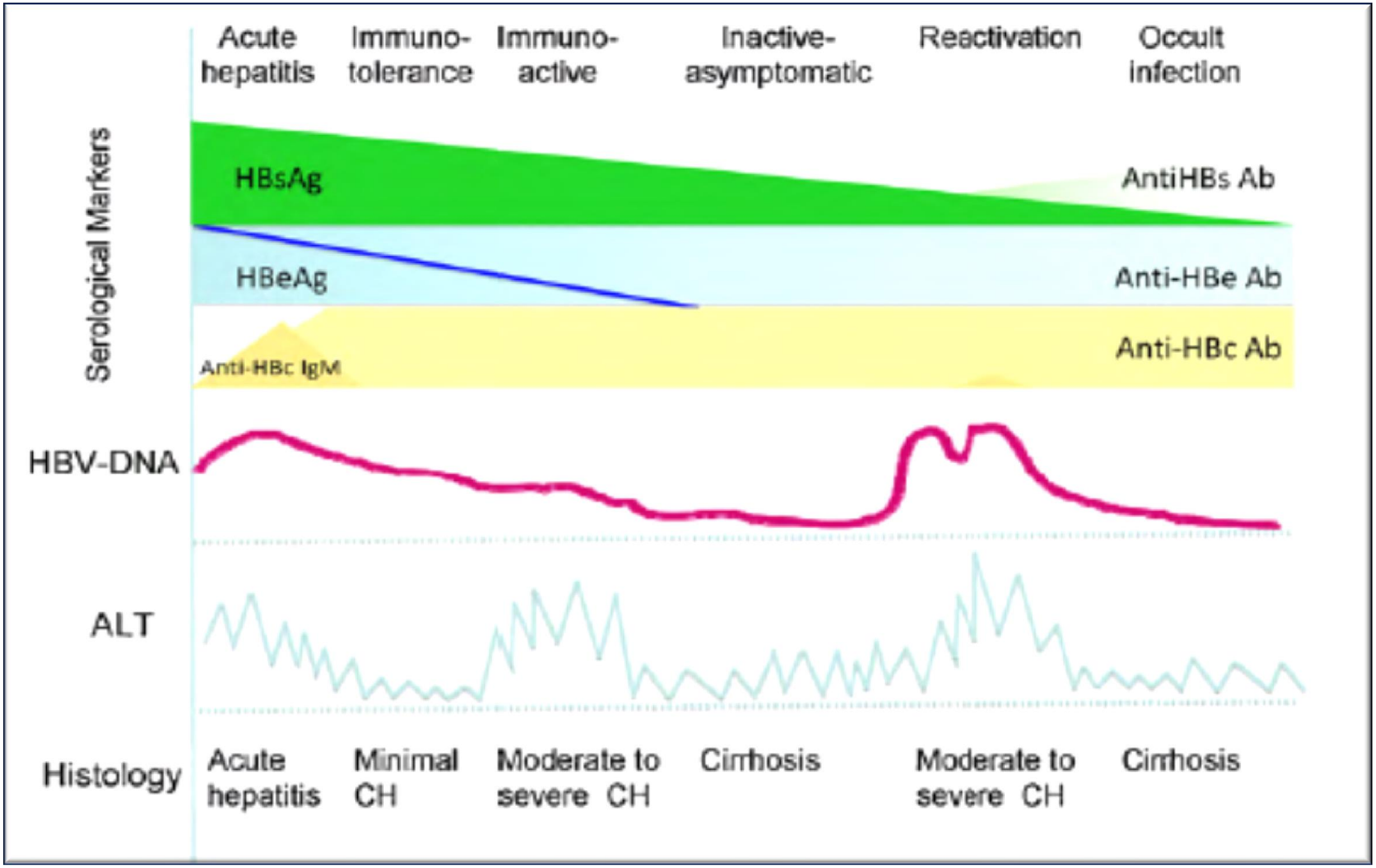
The lifecycle of HBV




IFN-α
IFNAR
LTα1β2
LTβR
APOBEC3B mRNA
APOBEC3A mRNA
APOBEC3A
HBV core
APOBEC3B
cccDNA
deamination
uracil excision
AP-site
degradation

HBV infection: natural history



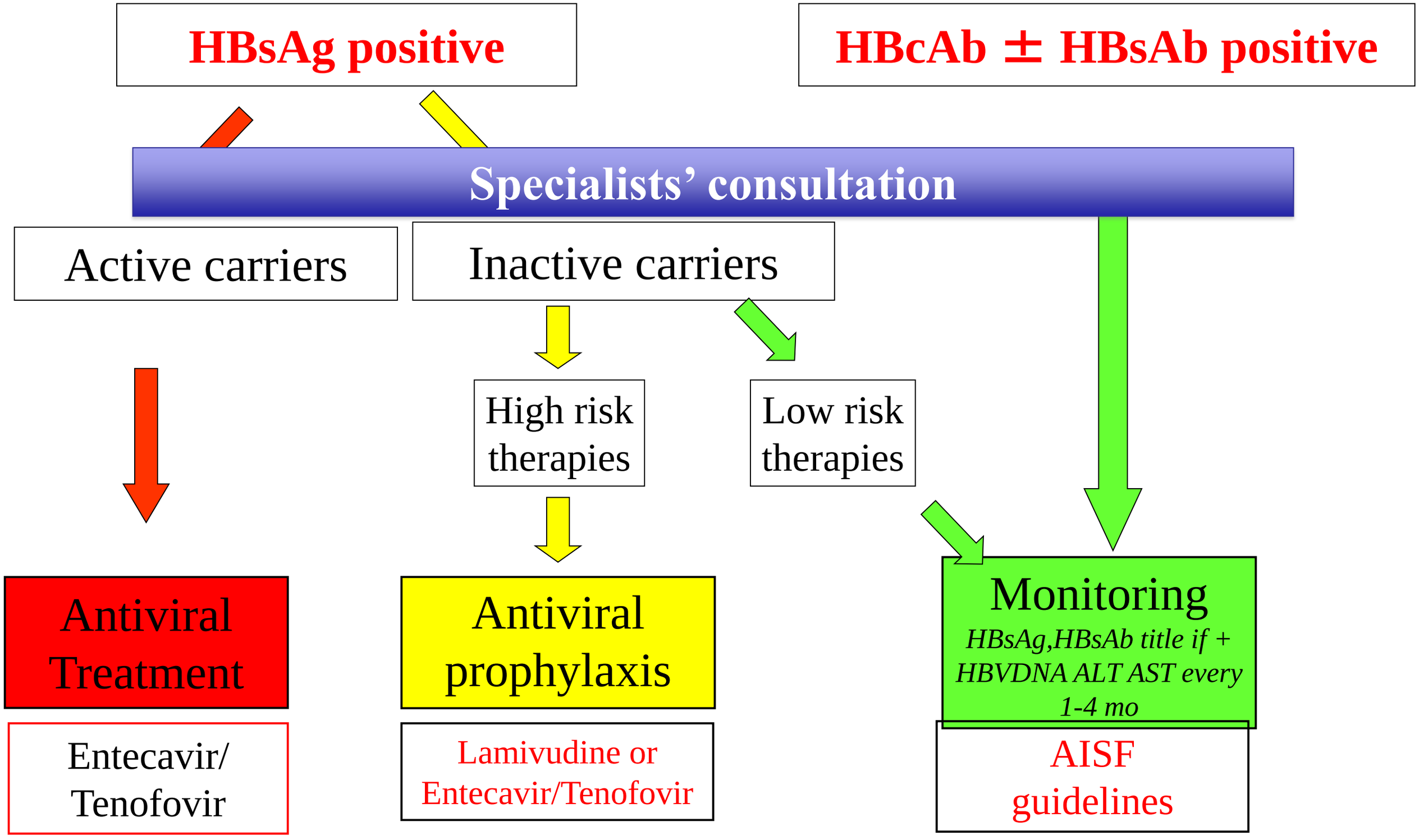
Chronic HBV infection: definition of the virological status

Overt Chronic infection	
HBsAg + &> 1000IU/ML	HBsAg +& < 1000 IU/mL*
Active carriers	**Inactive carriers**
Serum HBV DNA +	Serum HBV DNA +
≥ 2,000 IU/mL	< 2,000 IU/mL
Elevated ALT	Normal ALT
HBeAg + or antiHBe +	antiHBe +

Occult Chronic infection
HBsAg -
Anti- HBc + carriers
Serum HBV DNA -
Normal ALT
antiHBc + (± antiHBs)

* In HBV genotype D

HBV and Rheumatic Diseases
Statements 2011



Immunosuppressants and risk of HBV reactivation

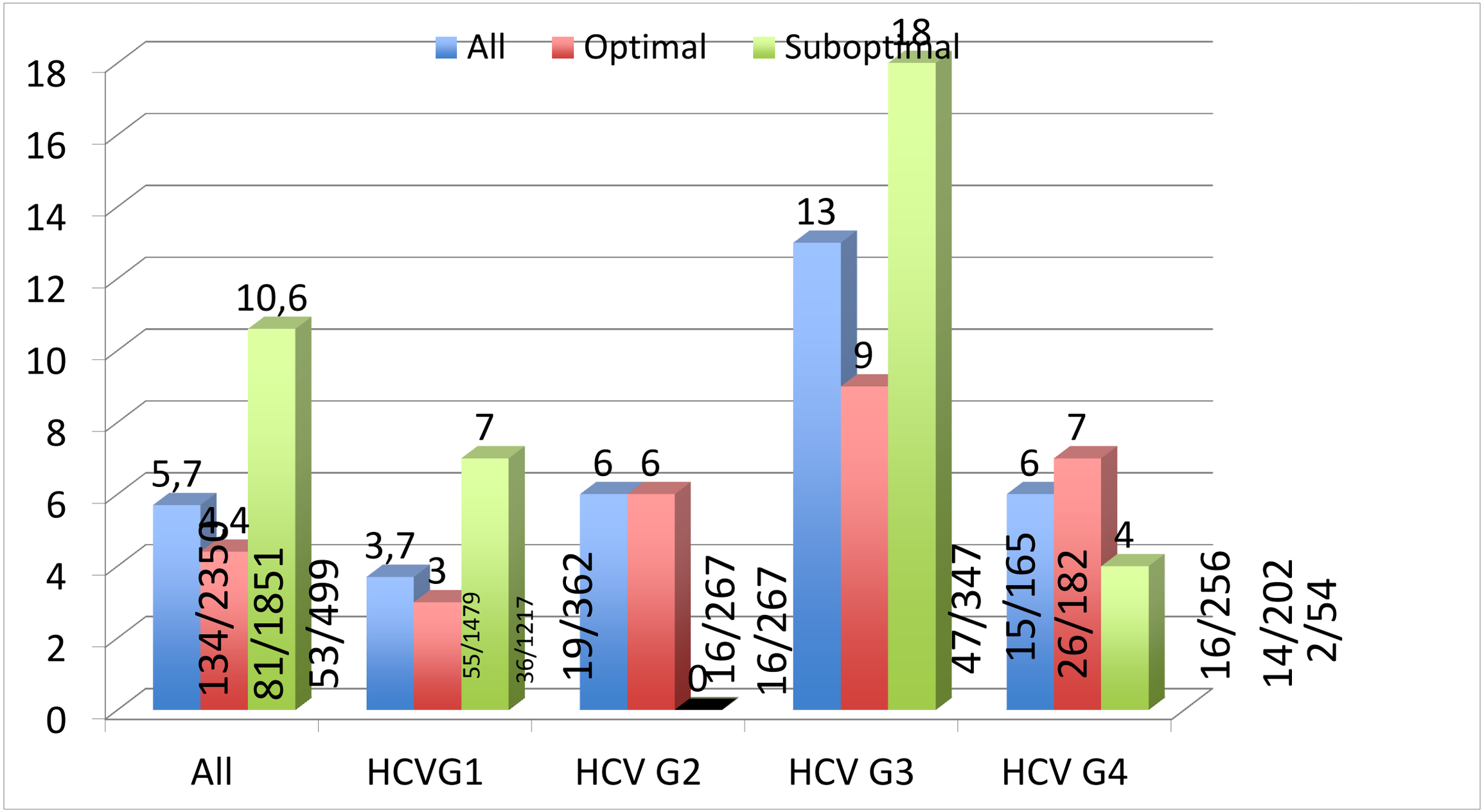
- No Risk
  - Sulfasalazine
  - Hydrocloroquine
- Low Risk
  - PDN < 7.5 mg/d
  - Calcineurin inhibitors
  - Azathioprine
- High risk
  - Bological DMARDS
  - PDN > 7.5 mg/d
  - Leflunomide
  - MTX
  - Ciclophosphamide
  - Rituximab

Hepatitis C

- Screening HCV Ab in all pts
- If positive
  - DD between HCV related arthritis, HCV related MC and RA + chronic HCV infection
  - HCVRNA & HCV genotype
  - Evaluation of liver disease etiology (NOSA, Iron, A1AT, ceruloplasmin, Cu++)
  - Evaluation of disease stage prognosis and priority for treatment :
    - Liver Biopsy in selected cases
    - Fibroscan
    - US
    - INR creatinine Bilirubin Albumin
    - Physical examination (Hepatic Hencephalopathy Ascites)
    - MELD CTP classification

NR rates in 2350 HCV pts with advanced liver disease treated in Lombardy according to adherence to EASL guidelines

Acknowledgment of all pts and investigators and Luisa Pasulo MD Gastroenterology Bergamo



In multivariate analysis after adjusting for HCV G3 infection non adherence to EASL recommendations remained significantly associated with lower SVR12 rate OR 1.76 95% CI 1.14-2.72 p=0.012

Concurrent Hepatitis C management in RA

Table 2 Anti-TNF-α agents administered to patients with rheumatoid arthritis (RA) with and without concomitant hepatitis C virus (HCV) infection

Author	Year	No. of patients (RA with HCV infection)	No. of controls (RA alone)	Regimen	Median duration of anti-TNF therapy, months	Outcome
Peterson et al. [22]	2003	24	None	Etanercept Infliximab	9	No difference in liver-related tests; decrease in viral load in 16 patients
Parke et al.[21]	2004	5	None	Etanercept Infliximab	41	No evidence of persistent elevation of transaminases
Roux et al.[23]	2006	3	None	Etanercept Adalimumab	21	No changes in transaminases or viral load
Vauloup et al.[24]	2006	6	None	Etanercept Infliximab	3.5	Viremia unchanged
Cansu et al.[17]	2008	3	None	Etanercept	22	No significant rise in liver transaminases
Ferri et al.[19]	2008	31	None	Etanercept Infliximab Adalimumab	3	No significant variations in transaminases or viral load; DAS28<2.6 in 15/31 (48 %) patients
Cavazzana et al.[18]	2008	4	None	Etanercept	14	No significant increase in viral load; significant reduction of DAS28
Li et al.[20]	2009	8	None	Etanercept Infliximab Adalimumab	20 ± 16	Transient transaminitis; no significant increase in viral load
Present study	2012	20	81	Etanercept Adalimumab	11	Elevated transaminase in 3 patients in both groups; similar effectiveness in both groups

All previous studies of anti-TNF therapy in more than two patients with RA and coexisting HCV infection are included here

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Screening for viral infections

- Mandatory:
  - VVZ IgG: Herpes zoster
  - HIVAb
- Optional
  - HSV type 1 and type 2 IgG
  - EBV IgG
  - CMV IgG
  - Other HHV6 IgG; HHV8 IgG

Viral infections: Agenda

- VVZ IgG
  - negative : immunization before immune suppression at diagnosis of RA
  - positive: consider immunization before immune suppression for prevention of HZ
  - Higher risk with Tofacitinib
  - prompt (< 72hrs) antiviral therapy (Valacyclovir and Famciclovir simpler schedules and better adherence) in case of symptoms of HZ (typical pain or zona) no reduction of Post Herpes Zoster Neuropathy
- CMV IgG
  - Negative: surveillance for acute infection
  - Positive: consider CMVDNA in case of symptoms of reactivation (interstitial pneumonia &/or Hepatitis &/or Retinitis &/or Pancytopenia)
- EBV IgG
  - Negative: surveillance for acute infection
  - Positive: consider EBVDNA in case of Mononuclosis or other uncommon syndromes related to EBV (Haemophagocytic syndrome and other cytokine disorders)

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LTBI: guide to guidelines

1. Spanish Society of Rheumatology. Update of the clinical practise guideline for the management of rheumatoid arthritis in Spain. Madrid: Sociedad Espanola de Reumatologia; 2007. Available from: http://www.ser.es/practicaClinica/Guias_Practica_Clinica.php
2. Australian Rheumatology Association. Updated recommendations for the use of biological agents for the treatment of rheumatic diseases. Sydney: Australian Rheumatology Association; 2010. [Internet. Accessed April 2, 2012.] Available from: http://www. rheumatology.org.au/downloads/
3. FINAL-biological-recommendations 060111.pdfDevlin J, Ramakrishnan SA, Fitzgerald O, for the Irish Society for Rheumatology (ISR). Guidelines for prescribing TNF alpha blockers in adults with rheumatoid arthritis. 2005.
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10. Furst DE, Keystone EC, Fleischmann R, Mease P, Breedveld FC, 2010;69 Suppl 1:i2-29.
11. Guidelines and Protocols Advisory Committee. Rheumatoid arthritis: diagnosis and management; 2006. Victoria, BC: British Columbia Ministry of Health; 2006. [Internet. Accessed April 2, 2012.] Available from: http://www.bcguidelines.ca/guideline_ra.html

LTBI: guide to guidelines

1. Massardo L, Suarez-Almazor ME, Cardiel MH, Nava A, Levy RA, Laurindo I, et al. Management of patients with rheumatoid arthritis in Latin America: A consensus position paper from Pan-American League of Associations of Rheumatology and Grupo Latino Americano De Estudio De Artritis Reumatoide. J Clin Rheumatol 2009;15:203-10.
2. Misra R, Sharma BL, Gupta R, Pandya S, Agarwal S, Agarwal P, et al. Indian Rheumatology Association consensus statement on the management of adults with rheumatoid arthritis. IndianJ Rheumatol 2008;3 Suppl:S1-S16.
3. Natonal Institute for Clinical Excellence (NICE). Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis: NICE technology appraisal guidance 130 (includes a review of technology appraisal guidance 36); 2007. London: National Institute for Health and Clinical Excellence. [Internet. Accessed April 2, 2012.] Available from http://www.nice.org.uk/nicemedia/live/11867/37914/37914.pdf 1600 The Journal of Japan College of Rheumatology
4. 2009 guidelines for the use of tocilizumab, a humanized anti-interleukin-6 receptor monoclonal antibody, in rheumatoid arthritis. Mod Rheumatol 2009;19:351-7.
5. Pham T, Claudepierre P, Constantin A, de Bandt M, Fautrel B, Gossec L, et al. Tocilizumab: Therapy and safety management. Joint Bone Spine 2010;77 Suppl 1:S3-100.
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7. Pham T, Fautrel B, Gottenberg JE, Goupille P, Hachulla E, Masson C, et al. Rituximab (MabThera) therapy and safety management. Clinical tool guide. Joint Bone Spine 2008;75 Suppl 1:S1-99.
8. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis [review]. Arthritis Care Res 2008;59:762-84.
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11. Canadian Rheumatology Association Recommendations for the Pharmacological Management of Rheumatoid Arthritis with Traditional and Biologic Disease-modifying Antirheumatic Drugs: Part II SafetyThe Journal of Rheumatology 2012; 39:8;

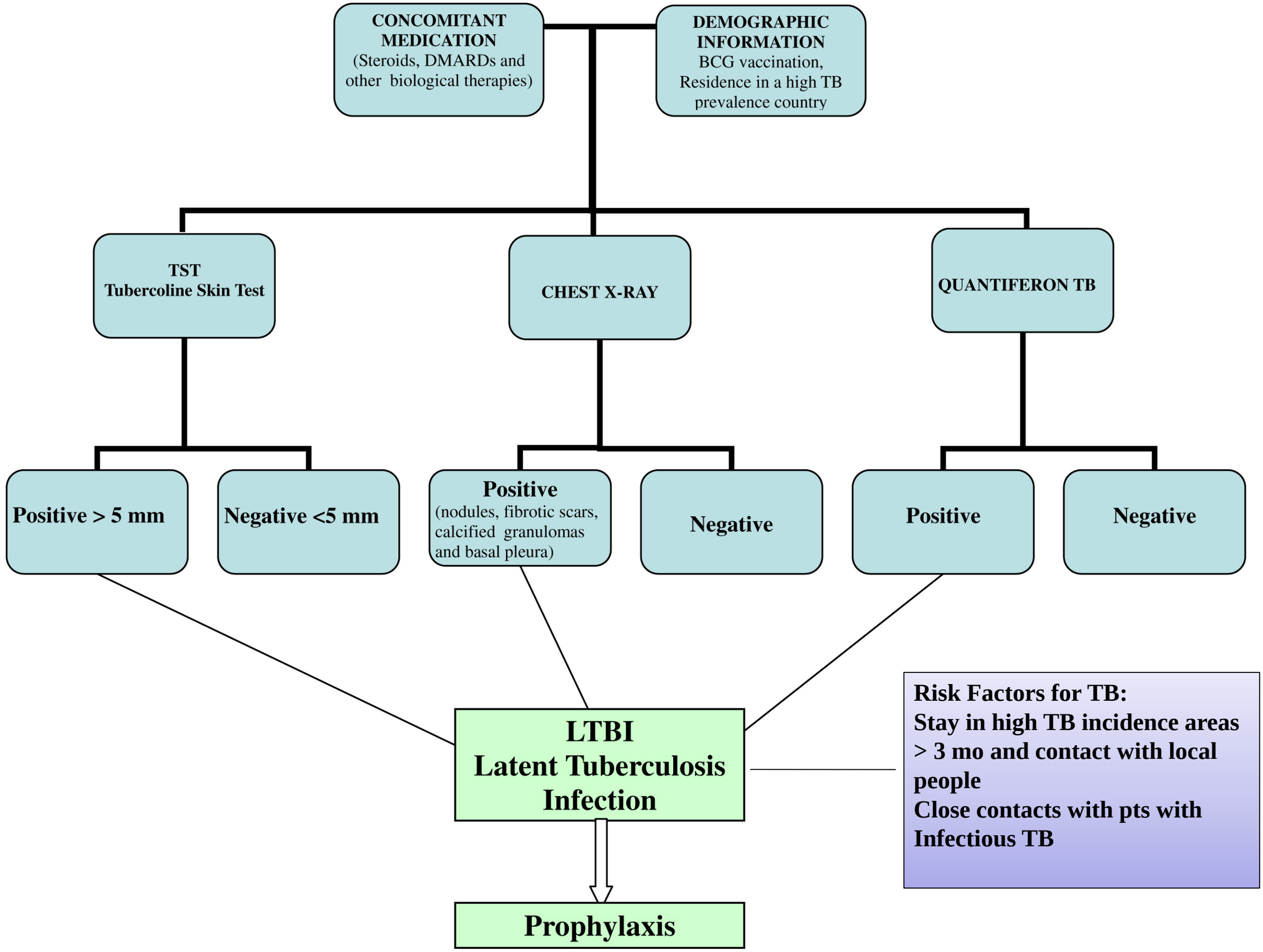
Screening for LTBI before biologic DMARD: guide to guidelines

Statement	Recommended	Recommended with provisos	Not recommended
LTBI screening before biologic DMARD	2	19	2
Anti-TNF therapy	15	0	0
ABAT	8	0	0
TCZ	8	0	0
RTX	4	2 not necessary but already screened	3 not necessary

LTBI Screening and prophylaxis: guide to guidelines

	Recommended	Recommended with provisos	Not recommended
How to screen: TBST	22		
How to screen: Chest X ray	21	1	

- LTBI prophylaxis:
  - 3 recommended without specification ;
  - 16 any with risk factors or TBST or chest X ray
  - 1 TBST or chest X ray
  - 2 balance with side effects of prophylaxis with the risk of LTBI rectivation
- When to start biologic DMARD:
  - 4/11 → 3 mo;
  - 4 + 2/11 → 1 mo;
  - 1 concurrently (1/11 anti TNF 1 ABAT 2 TCZ)


CONCOMITANT MEDICATION
(Steroids, DMARDs and other biological therapies)
DEMOGRAPHIC INFORMATION
BCG vaccination, Residence in a high TB prevalence country
TST
Tubercoline Skin Test
CHEST X-RAY
QUANTIFERON TB
Positive > 5 mm
Negative <5 mm
Positive
(nodules, fibrotic scars, calcified granulomas and basal pleura)
Negative
Positive
Negative
LTBI
Latent Tuberculosis Infection
Risk Factors for TB:
Stay in high TB incidence areas > 3 mo and contact with local people
Close contacts with pts with Infectious TB
Prophylaxis

Trattamento delle Infezioni Tubercolari attive

(Schema terapeutico) Grado di Raccomandazione[a] HIV+	HIV-	FASE INIZIALE/INTENSIVA		FASE DI CONTINUAZIONE		Dosi totali
		FARMACI	Frequenza e durata	Farmaci	Frequenza e durata[b]	
(1) A II	A I	Isoniazide Rifampicina Pirazinamide Etambutolo	Giornaliera per 8 settimane	Isoniazide Rifampicina	Giornaliera per 18 settimane	182
(2) B II	B I [c]	Isoniazide Rifampicina Pirazinamide Etambutolo	Giornaliera per 8 settimane	Isoniazide Rifampicina	Trisettimanale [d] per 18 settimane	110

Localizzazione	Durata complessiva della terapia in mesi	Grado di raccomandazione durata terapia[a]	Osservazioni	Grado di raccomandazione uso corticosteroidi[a, b]
Linfonodale	6	AI	Possibile beneficio dal drenaggio linfonodale (BIII); preferire la biopsia vs agoaspirato per la diagnosi colturale.	DIII
Osteoarticolare	9 (12 mesi HIV+)[c]	AI	Indicazioni alla chirurgia nella forma vertebrale: riduzione compressione midollare nei pz con deficit neurologici, instabilità della colonna vertebrale, sospetto fallimento terapeutico.	DIII
Pleurica	6	AII	Empiema tubercolare richiede drenaggio pleurico (spesso con approccio chirurgico tradizionale o videoassistito) ed una durata maggiore della terapia	DI [b]
Pericardica	6	AII	Dosaggio prednisone: 60 mg/die (adulti) per 4 settimane, poi 30 mg/die per 4 settimane, poi 15 mg/die per 2 settimane, ed infine 5 mg/die nell'ultima (11ª) settimana	AI [b]
Meningea/SNC (vedi Tab. 12)	12	BII	vedi [d]	AI [b]
Malattia disseminata (compresa forma miliare)	9 (12 mesi HIV+)[c]	AII	Eseguire emocoltura. Considerare biopsia epatica e agoaspirato midollare. Escludere localizzazione SNC[e]. Nella localizzazione epatica sono frequenti le alterazioni degli esami di funzionalità epatica. Alcuni esperti suggeriscono l'uso di corticosteroidi nelle forme con insufficienza respiratoria	DIII
Genitourinaria	6	AII	Se ostruzione ureterale/idronefrosi procedure chirurgiche; nefrectomia in casi particolari.	DIII
Peritoneale/intestinale	6	AII	Dati non conclusivi sull'efficacia dei coricosteroidi nella riduzione delle complicazioni fibrotiche	DIII
Altre localizzazioni (p.e. cutanea, ecc.)	6	-		-

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Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases:

Table 2 Pathogens and/or presentations of specific pathogens to be considered as opportunistic (or 'indicator') infections in the setting of biologic therapy (level of evidence I–V)

Definite*†	Probable‡
Pneumocystis jirovecii (II)	Paracoccidioides infections (V)
BK virus disease including PVAN (V)	*Penicillium marneffei* (V)
Cytomegalovirus disease (V)	*Sporothrix schenckii* (V)
Post-transplant lymphoproliferative disorder (EBV) (V)	Cryptosporidium species (chronic disease only) (IV)
Progressive multifocal leucoencephalopathy (IV)	Microsporidiosis (IV)
Bartonellosis (disseminated disease only) (V)	Leishmaniasis (Visceral only) (IV)
Blastomycosis (IV)	Trypanosoma cruzi infection (Chagas' disease) (disseminated disease only) (V)
Toxoplasmosis (IV)	Campylobacteriosis (invasive disease only) (V)
Coccidioidomycosis. (II)	Shigellosis (invasive disease only) (V)
Histoplasmosis (II)	Vibriosis (invasive disease due to *Vibrio vulnificus*) (V)
Aspergillosis (invasive disease only) (II)	HCV progression (V)
Candidiasis (invasive disease or pharyngeal) (II)	
Cryptococcosis (II)	
Other invasive fungi: Mucormycosis (zygomycosis) (Rhizopus, Mucor and Lichtheimia), *Scedosporium/Pseudallescheria boydii*, *Fusarium* (II)	
Legionellosis (II)	
Listeria monocytogenes (invasive disease only) (II)	
Tuberculosis (I)	
Nocardiosis (II)	
Non-tuberculous mycobacterium disease (II)	
Salmonellosis (invasive disease only) (II)	
HBV reactivation (IV)	
Herpes simplex (invasive disease only) (IV)	
Herpes zoster (any form) (II)	
Strongyloides (hyperinfection syndrome and disseminated forms only) (IV)	

*Generally does not occur in the absence of immunosuppression and whose presence suggests a severe alteration in host immunity.
†Can occur in patients without recognised forms of immunosuppression, but whose presence indicates a potential or likely alteration in host immunity.
‡Published data is currently lacking, but expert opinion believes that risk is likely elevated in the setting of biologic therapy.
EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; PVAN, polyomavirus-associated nephropathy.

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The JAMA Network

From: **The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)**

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	0	1	2	3	4
Respiration					
PaO_2/FIO_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: FIO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

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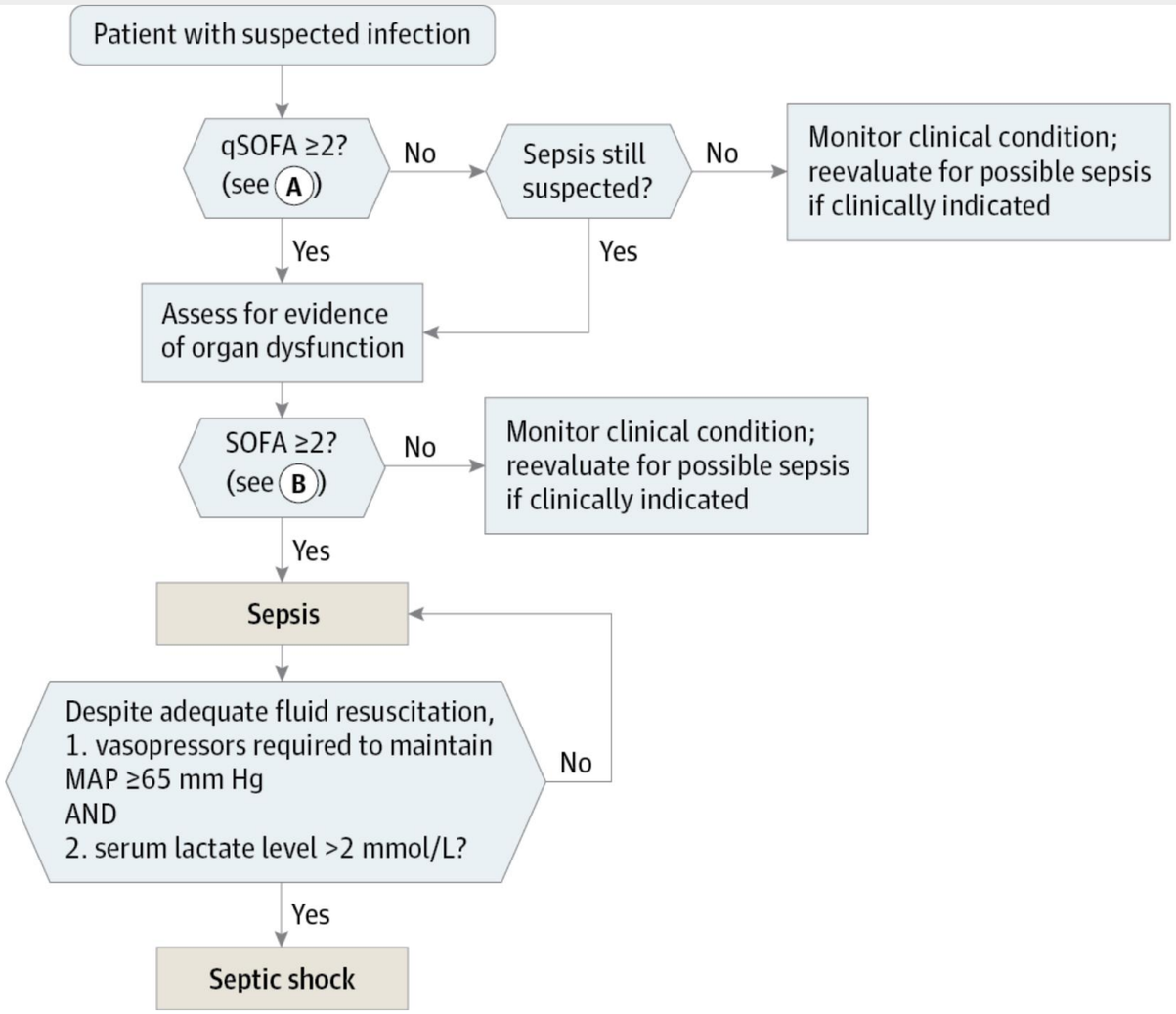
From: **The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)**

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287



qSOFA (Quick SOFA) Criteria
Respiratory rate ≥22/min
Altered mentation
Systolic blood pressure ≤100 mm Hg

A qSOFA Variables
Respiratory rate
Mental status
Systolic blood pressure

B SOFA Variables
PaO_2/FiO_2 ratio
Glasgow Coma Scale score
Mean arterial pressure
Administration of vasopressors with type and dose rate of infusion
Serum creatinine or urine output
Bilirubin
Platelet count

Figure Legend:

Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic ShockThe baseline Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicates quick SOFA; MAP, mean arterial pressure.

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Impact of treatment with biologic DMARDs on the risk of sepsis or mortality after serious infection in patients with rheumatoid arthritis

Table 4 ORs of multiple logistic regression for mortality after sepsis (85 deaths in 135 patients, approach B) and of a GEE-type regression model for all-cause mortality (138 deaths in 859 patients, approach C)

	Death from sepsis		All-cause mortality after SI	
	OR	CI	OR	CI
Age (by 10 years)	1.53	1.04 to 2.26	1.85	1.43 to 2.40
Sex (male vs female)	1.56	0.65 to 3.72	1.40	0.89 to 2.19
FFbH (by 10% improvement)			0.86	0.79 to 0.94
GC (<5 mg/d=reference)			.	.
GC (5– <10 mg/d vs ref.)			1.08	0.69 to 1.70
GC (≥10 mg/d vs ref.)			1.67	0.95 to 2.96
csDMARDs	Ref.		.	.
TNFα	0.28	0.12 to 0.63	0.34	0.21 to 0.55
Other bDMARD	0.76	0.22 to 2.67	0.27	0.14 to 0.51
Heart failure (yes vs no)	3.25	0.95 to 11.13	2.13	1.19 to 3.81
Chronic renal disease (yes vs no)			1.65	1.00 to 2.73

csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; GC, glucocorticoids; GEE, generalised estimating equations; SI, serious infection; TNFi, tumor necrosis factor-α inhibitor (adalimumab, etanercept, infliximab, golimumab, certolizumab), other bDMARD (tocilizumab, rituximab, abatacept). Physical function (FFbH) and doses of GC refer to measurements of most recent study visit, DMARD exposure is the current exposure at SI. The median time between the last study visit and the SI was 3.7 months (first quartile: 1.9 months, third quartile: 6.2 months).

Richter A Ann Rheum Dis 2015

The “golden hours” of sepsis

- Early recognition and intervention of patients with severe sepsis leads to improved outcomes
- Similar concept to:
  - Acute coronary syndrome
  - Stroke
  - Trauma

Serum Procalcitonin in Systemic Autoimmune Diseases—Where Are We Now?

Irina Buhaescu, MD,* Robert A. Yood, MD,† and
Hassan Izzedine, MD, PhD‡

Table 1 Summary of Studies That Compared PCT Level in Active Autoimmune Diseases Versus Systemic Bacterial Infections

Author	Autoimmune Disease Activity		Infection	
	Number of Patients	PCT Level	Number of Patients	PCT Level
Eberhard et al. (30)	N = 42 (18 with SLE and 35 with AAV)	PCT < 0.5 ng/mL in 39 of the 42 patients with various degrees of disease activity	N = 16 infections in 11 patients (all with AAV)	Mean (SD) = 1.93 (1.19) ng/mL in all 16 samples from 11 patients
Shin et al. (33)	N = 7 patients with SLE	Mean (SD) = 0.24 (0.18) ng/mL	N = 9 bacterial infections	Mean (SD) = 0.98 (0.12) ng/mL
Tamaki et al. (32)	N = 70	Mean 0.116 ± 0.127	N = 29 bacterial infections	Mean 4.539 ± 9.677
Delèvaux et al. (40)	N = 113	PCT level < 0.5 ng/mL in 108/113 patients	N = 60 bacterial or fungal infections	PCT levels > 0.5 ng/mL in 39/60 (65%) patients

PCT, procalcitonin; SLE, systemic lupus erythematosus; AAV, antineutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis; SD, standard deviation.

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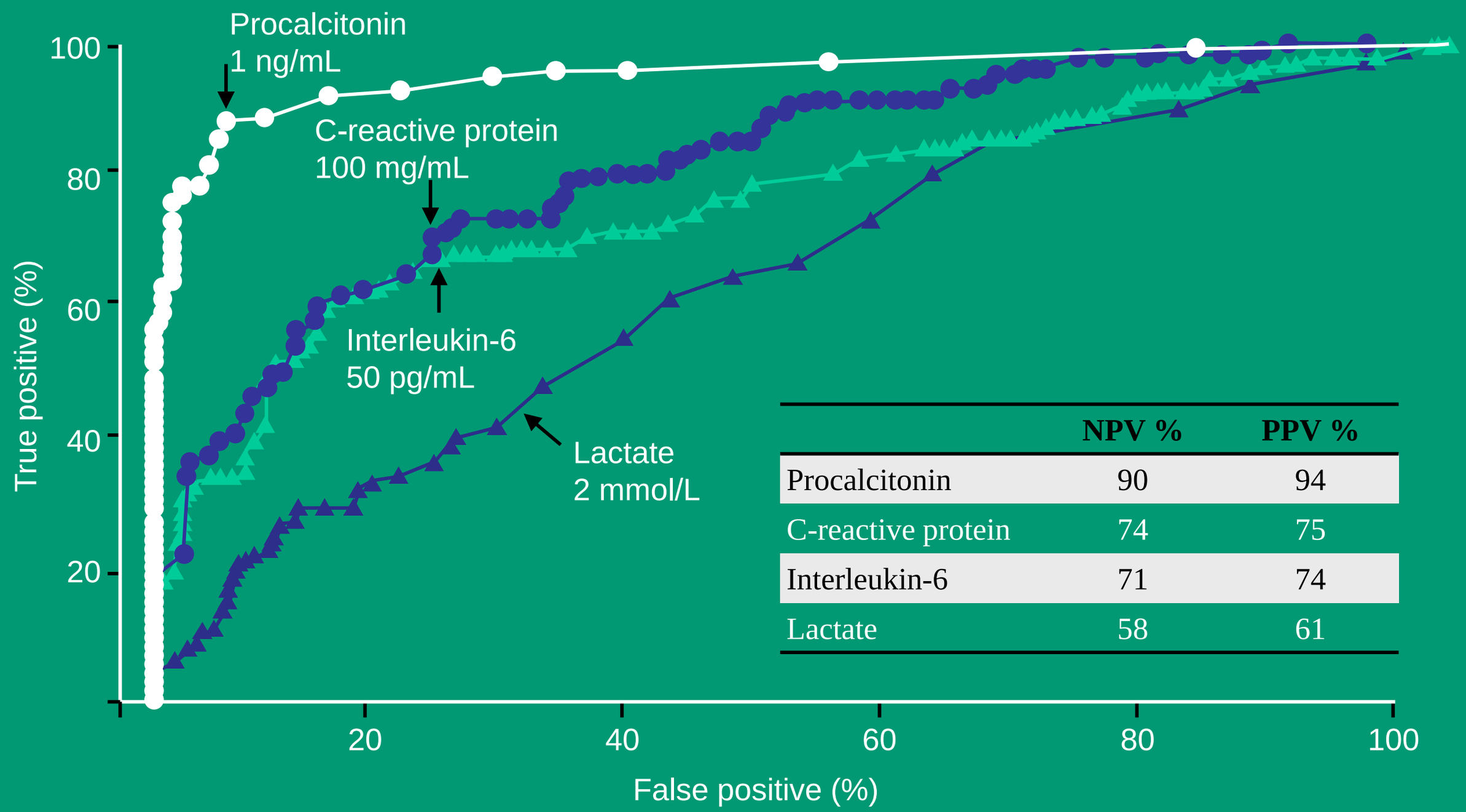
Markers for the diagnosis of sepsis



	NPV %	PPV %
Procalcitonin	90	94
C-reactive protein	74	75
Interleukin-6	71	74
Lactate	58	61

NPV: negative predictive value; PPV: positive predictive value

Muller B, et al. Crit Care Med 2000;28:977–83

Presepsin and procalcitonin as biomarkers of systemic bacterial infection in patients with rheumatoid arthritis

26 patients in the infection group, 45 patients in the CRP-positive non-infection group (CRP > 0.3 mg/dL), and 55 patients in the CRP-negative non-infection group (CRP < 0.3 mg/dL)

Condition	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value
Plasma presepsin				
221.5 pg/mL	92.31%	77.78%	0.706	0.946
300 pg/mL	73.08%	88.89%	0.760	0.848
400 pg/mL	46.15%	97.78%	0.923	0.759
500 pg/mL	34.62%	100%	1	0.738
Serum procalcitonin				
0.5 ng/mL	97.67%	53.85%	0.933	0.786

Tsujimoto T et al. International Journal of Rheumatic Diseases 2016

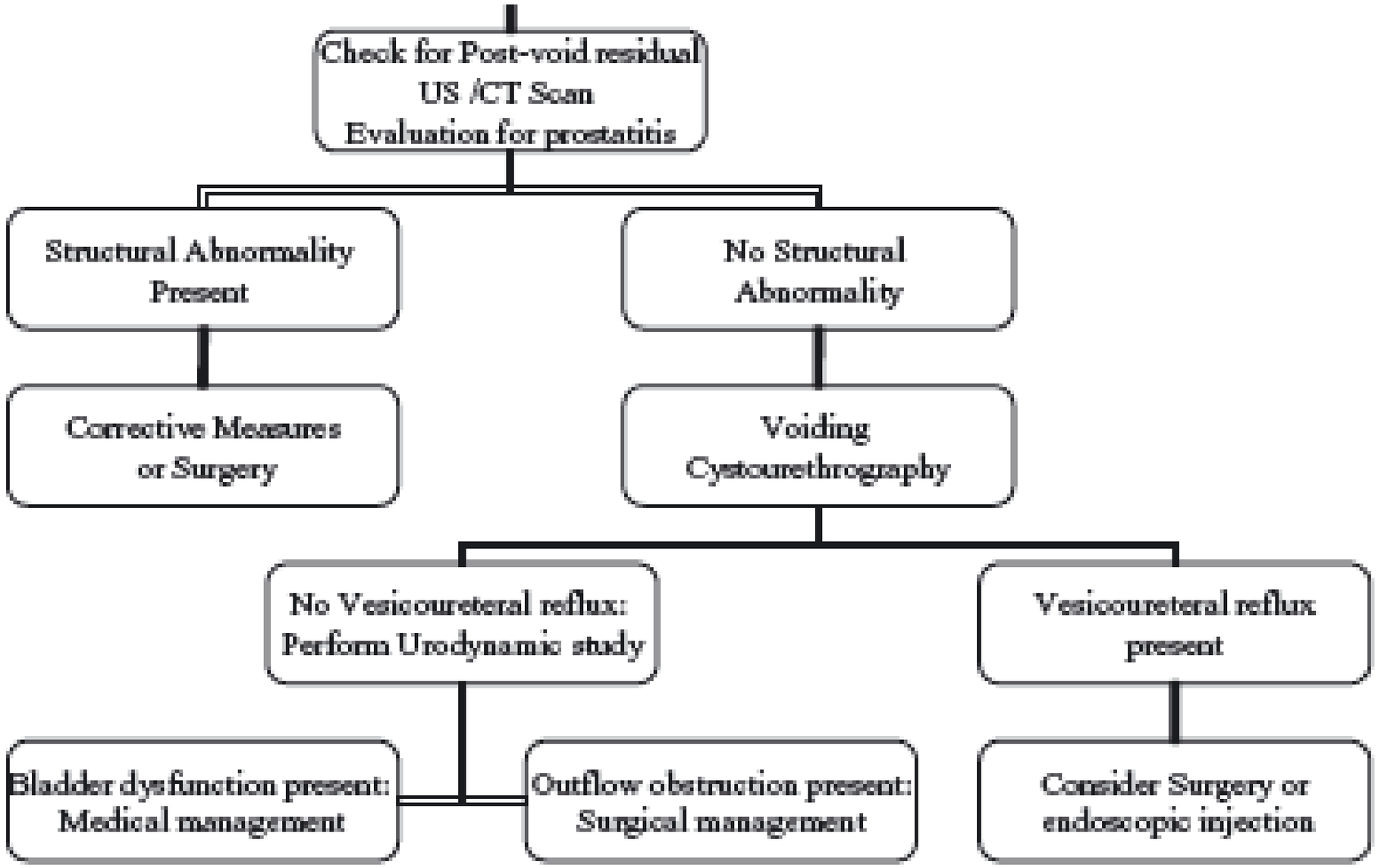
Management of Infections in Rheumatoid Arthritis

- Viral infections
  - Viral Hepatitis
  - Other viral infections
- Tuberculosis
- Opportunistic Infections
- Bacterial infections
  - Urinary tract infections
  - Skin & Soft tissue infections
  - Pneumonia

UTI in immunosuppressed patients

- Asymptomatic bacteriuria more common
- MDR ad fungi more common
- Diabetes and indwelling catethers : risk factors for fungal infections
- Consider screening for schistosomiasis in patients from endemic areas
- Consider BK virus in case of nephropathy

Suggested schema of evaluation for recurrent UTI



Management of Infections in Rheumatoid Arthritis

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  - Viral Hepatitis
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- Tuberculosis
- Opportunistic Infections
- Bacterial infections
  - Urinary tract infections
  - Skin & Soft tissue infections
  - Pneumonia

Risk of skin and soft tissue infections (including shingles) in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register

James B Galloway,[1] Louise K Mercer,[1] Alison Moseley,[1,2] William G Dixon,[1] Andrew P Ustianowski,[3] Matthew Helbert,[4] Kath D Watson,[1] Mark Lunt,[1] Kimme L Hyrich,[1] Deborah PM Symmons[1]

Three hundred and nine SSSI were reported to the registry (269 anti-TNF; 39 nbDMARD). The majority of these were cellulitis (227/309; 73%) with the remainder being coded as abscesses or infected ulcers. Four cases of SSSI were necrotising fasciitis (all in the anti-TNF cohort). The incidence rate for SSSI was 1.6/100 patient-years in the anti-TNF cohort, compared with 0.7/100 patient-years in the nbDMARD cohort (table 3). The unadjusted HR for SSSI for anti-TNF was 2.2 (95% CI 1.5 to 3.0).

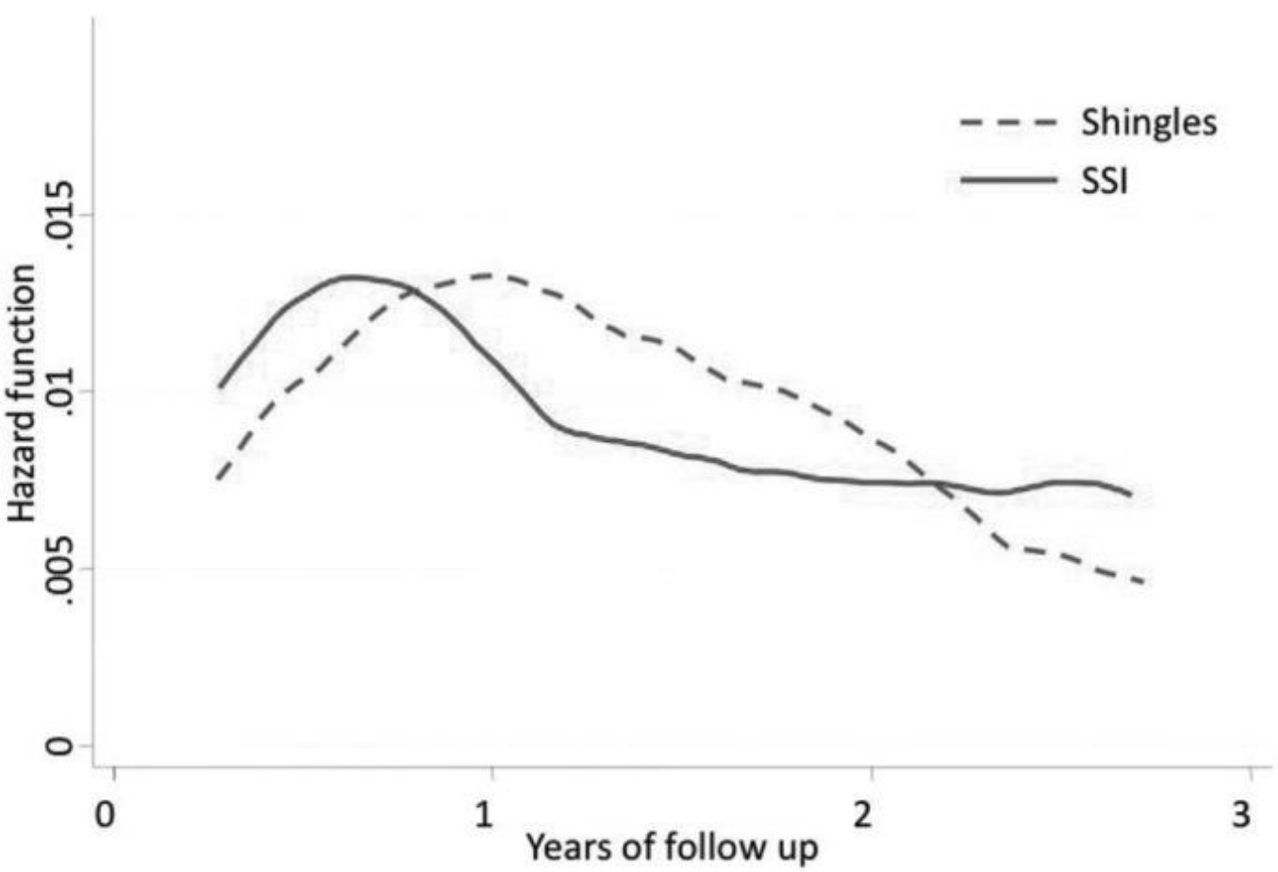

Table 2 Organisms responsible for skin and soft tissue infections

Organism	Anti-TNF, n	DMARD, n
Gram-positive species		
*Staphylococcus aureus**	84	11
Coagulase negative staphylococci	8	1
Streptococcus spp.†	11	1
Gram-negative species		
Pseudomonas aeruginosa	20	1
Proteus mirabilis	2	1
Stenotrophomonas maltophilia	1	0
Escherichia coli	1	0
Klebsiella spp.†	1	0
Morganella morganii	1	0
Enterobacter spp.	1	0
No culture information available	140	24

*Staphylococci were reported to be methicillin-resistant species in 24 (29%) of the anti-TNF episodes and four (36%) of the DMARD cases.
†Reports in which subspecies information was not provided are listed by generic 'spp.' The species breakdown for soft tissue infections shows that staphylococcus was the most prevalent organism in both groups. Pseudomonas was observed more frequently in the anti-TNF cohort.
DMARD, disease-modifying antirheumatic drug; TNF, tumour necrosis factor.

SSI in RA

- Consider unusual pathogens (fungi, nocardia, actynomices, mycobacteria) microscopic examination of samples for Gram, Acid fast, silver staining for fungi culture extended to fungi, slow growing bacteria, mycobacteria, fungi
- Assess systemic symptoms and look for signs of systemic toxicity, fascial and muscular involvement (CPK, CT scan, lactic acid)

Pneumonia

- **Assessment of LRTI risk**
  - Screening with clinical evaluation and chest X-ray.
  - General risk factors [old age (>65), smoking, comorbidity (e.g. diabetes, CKD, chronic lung disease, CVD)],
  - Intrinsic factors : glucocorticoid > 5 mg/d , methotrexate or leflunomide use.
  - Modifiable risk factors should be corrected and treatment of comorbidities optimized
- **Active surveillance for LRTI**
  - monitoring for the occurrence or worsening of respiratory symptoms (cough, dyspnea) or fever,

Diagnostic workup in Pneumonia in RA patients

- First level examination
  - Objective examination and blood tests (see CURB and PORT)
  - Chest X Ray
  - Blood gases
  - Sputum or Aspirates for: bacteria, fungi, MT- DNA (PCR), leukocytes (?)
  - Beta D glucan and Aspergillus Ag on serum
  - Mycoplasma & Chlamydia serology, CMVDNA
  - Legionella and Pneumococcus Ag, swab for influenza viruses
  - Procalcitonin
- Second Level
  - HR CT
  - BAL for fungi, slow growing bacteria, fungal antigens, Pj, bacteria, BAAR, (direct and culture) MT-DNA, Viruses (PCR)
- Third Level
  - Biopsy

Prevention of Exposure to pathogens

Pathogens	
Enteric pathogens	Cook meat thoroughly, wash fresh fruits and vegetables, wash hands after cooking, avoid certain soft cheese (brie , feta, gorgonzola) Avoid : -Drinking waters from lakes, streams and untested wells -Contact with human and animal faeces -Unpasteurized milk, raw eggs and products made with raw eggs
Respiratory viruses	Avoid childrens and crowded public places and wash hands after contact Immunize patient and family members against influenza yearly Immunize health care workers
Varicella	Vaccines VVZ negative patients Avoid contact with patients who have shingles or chickenpox
Zoonoses	Avoid changing litter boxes,cleaning birds, cages and acquaria Wear gloves if such cleaning is unavoidable Avoid jobs that involve frequent contact with animals
Airborne molds	Advise patient to avoid closed spaces with high risk of fungal exposure (barns, silos, chicken coops, attics, caves) or high risk activities (e.g. archeological excavation)
Legionella infection	Advise patient to avoid water areosols (whirlpools and commercial displays), and hospital or other institutional tap water that is not tested or treated
STD	Safe sexual practices
Exotic and tropical infections	Infectious Diseases Specialist consultation: Before international travel outside of Europe and North America Patients with history of stay in exotic areas > 3 mo

Mandell, Douglas and Bennett's Principles and practice of Infectious Diseases Churchill Livingstone 2010

Vaccines: recommendations

	Inactivated/Killed Vaccines			Live Attenuated Vaccines	
	Influenza (annual)	Pneumococcal (booster after 3-5 yrs)	Hepatitis B	Herpes Zoster	Other
Methotrexate*	✓	✓	✓†	✓††	Caution
Leflunomide	✓	✓	✓†	✓††	Caution
Sulfasalazine	✓	✓	✓†	✓††	Caution
All biologics	✓	✓	✓†	Avoid	Avoid

✓ Recommended; ideally administer prior to initiating therapy. † Recommended in high-risk groups including residents, travelers or close contact with individuals from hepatitis B endemic areas, illicit drug users, persons engaging in risky sexual behaviors/history of sexually transmitted infection, men who have sex with men, chronic liver disease, occupational exposures, frequent blood transfusions. †† Recommended in RA patients > 60 years old. * Methotrexate ≤ 25 mg per week.

Adherence to vaccination

UK : 15,724 80% patients received at least one influenza vaccination, and 50% patients received a pneumococcal vaccination, during follow-up (mean 5.3 years). Higher vaccination rate in age > 65

Vaccination in patients with RA

- Vaccination for influenza and pneumococcus is recommended for patients with RA before or during treatment with traditional and biologic DMARD
- Hepatitis B vaccine should be considered in high-risk groups.
- Zoster vaccine should be considered in high-risk groups and in RA patients age 60 years or older
- Inactivated vaccines should ideally be administered prior to starting treatment with methotrexate and/or biologic DMARD
- Live vaccines should be administered at least 2 weeks and ideally 4 weeks prior to starting treatment with biologic DMARD.
- In patients currently receiving biologic therapy, treatment with the biologic should be suspended and the vaccine administered after an appropriate interval based on the pharmacokinetic properties of the agent
- Herpes zoster vaccine may be given to patients receiving methotrexate (≤ 25 mg/week) and/or low-dose corticosteroids (< 20 mg per day).

Bombardier C et al. J Rheumatol 2012;39:1583–602

Infections in Rheumatoid Arthritis

- HBV screening and specialist consultation
- Viral infection mandatory screening only for VZV & HIV Useful informations from EBV & CMV screening
- TB screening with History, TST and Quantiferon → specialist consultation for prophylaxis
- Sepsis consider clinical signs and PCT for diagnosis
- UTI SSTI & pneumonia → consider opportunistic infections in the work up
- Vaccination → specific plan in RA
- CONSULTATION WITH A DEDICATED ID SPECIALIST COULD BE THE KEY OF SUCCESS IN REDUCING COMPLICATIONS DUE TO INFECTIONS