PANDORA ID-24: LE INFEZIONI E LE VACCINAZIONI NELL'OSPITE IMMUNOCOMPROMESSO, 7/10/24

Le infezioni nel paziente reumatologico trattato con farmaci biologici

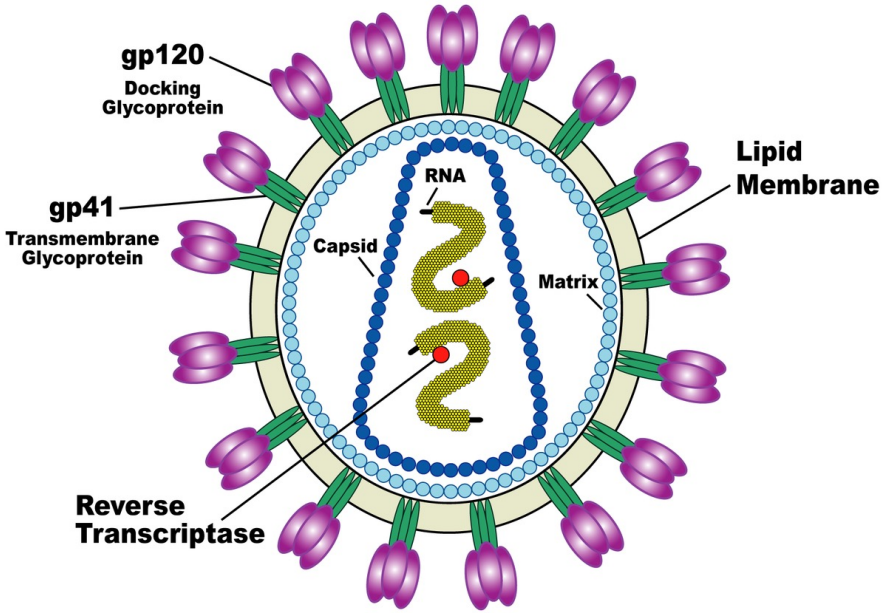
Dott. G. Pagani
UOC Malattie Infettive
Ospedale Nuovo di Legnano

Immunodeficienze

- Primarie
  - Rare, approccio *tailored* specialistico
- Secondarie
  - **HIV/AIDS**
  - **Patologie autoimmuni**
  - **Trapianti di organo solido**
  - **Patologie oncoematologiche**

  } **ID iatrogena**

  - Patologie croniche (DM, cardiopatia, pneumopatia, epatopatia, nefropatia)



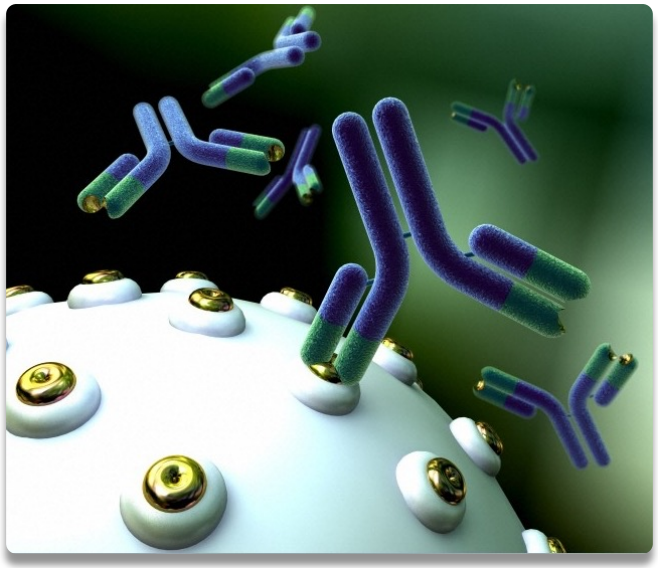
ID iatrogena: farmaci «classici»

- Si considera immunodepresso un paziente che assume:
  - Terapia steroidea: ≥ 20mg die prednisone (o equivalente) per almeno 14gg
  - Metotrexate ≥ 0.4 mg/kg/settimana
  - Azatioprina >3 mg/kg/di
  - 6-mercaptopurina >1.5 mg/kg/di
  - Antirigetto: ciclosporina, micofenolato, ecc.



ID iatrogena: farmaci biologici

- Si considera immunodepresso un paziente che assume:
  - Anti-TNF: infliximab, etanercept, adalimumab (reuma, neuro, IBD)
  - Anti-CD20: rituximab, ocrelizumab (reuma, neuro, IBD, CT emato)
  - Anti-IL6: tocilizumab (reuma)
  - Anti-JAK: baricitinib (reuma)
  - Anti-CD52 (anti linfociti): alemtuzumab (CT emato)
  - Anti-SP1: fingolimod (SM)
  - (Anti complemento: eculizumab (reuma))
  - CTLA-4-Ig (anti Linfociti T): abatacept
  - Anti-BLYS (anti Linfociti B): belimumab
  - Anti-IL12/IL23: ustekinumab (reuma, IBD)
  - Anti-IL1: anakinra
  - Anti-IL17: secukinumab (reuma, IBD)

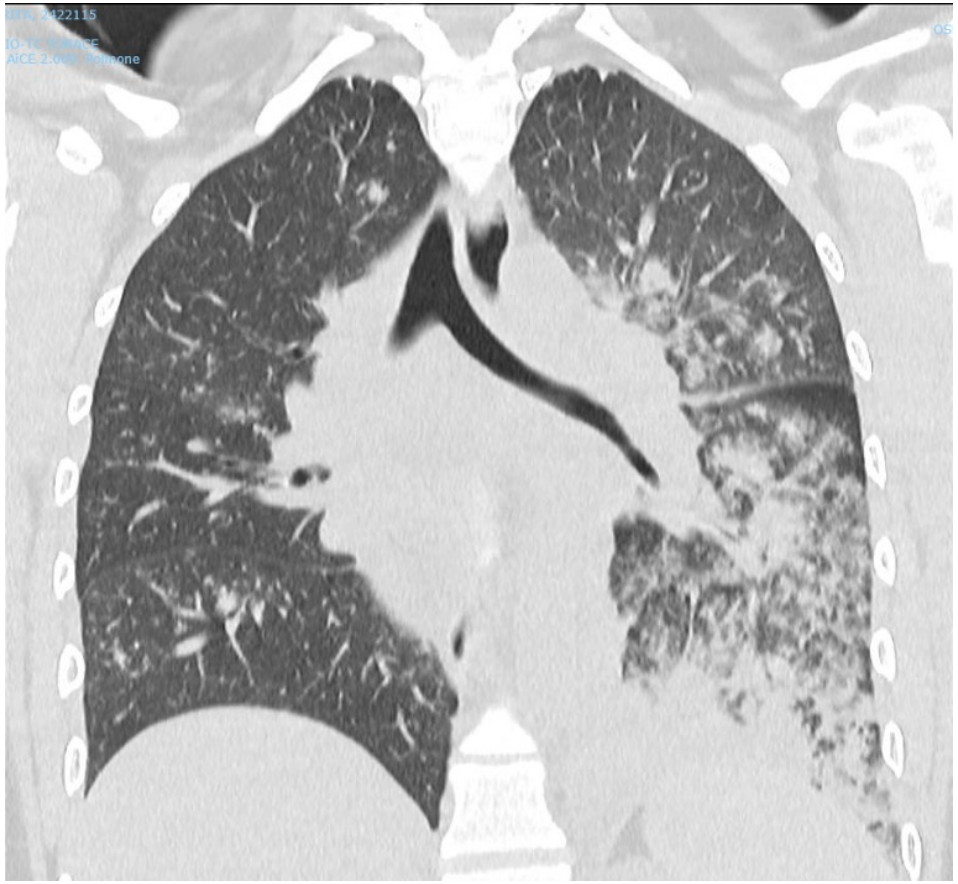


ID iatrogena: non ID

- NON immunodeprimono:
  - HCQ
  - Steroide/MTX/6-MP/AZT a basse dosi
    - Steroide: <20mg die prednisone
    - MTX: <0.4mg/kg/sett
    - 6-MP: <1.5mg/kg die
    - AZT: <3mg/kg die
  - Steroidi topici (cutanei, intra-articolari)
  - Leflunomide/talidomide (MM)
  - Check-point Inhibitors (es. nivolumab/pembrolizumab)
  - Azacitadina/decitabina
- Ancora dubbio approccio a steroide basse dosi + metotrexate/6-MP basse dosi

Caso clinico: parte 1

- MM, 27aa, in terapia con ADALIMUMAB (anti-TNFalfa) per M. di Crohn in remissione
- Nel 2017 screening con IGRA: neg
- Vaccinata per HBV, HPV, Men ACWY, Men B, Pneumo, influenza.
- Dal 27/12/23 febbre, tosse, addensamento: CRO i.m. + azitro
- Si presenta in PS il 17/01: polmonite bilaterale (angioTC) + pleuropericardite
- Ricoverata inizialmente in UTIC, quindi RIA per supporto ventilatorio (HFNC), quindi medicina (25/1)
- In data 17/2 su indicazione infettivologica FBS+BAL: MSSA e BAAR pos (PCR pos per MTb) -> trasferita in Mal Infettive



Infezione/malattia tubercolare in ID

- Malattia tubercolare in ID più spesso:
  - Extrapolmonare
  - BAAR negativa
  - Disseminata/miliare
- Rischio di ritardo diagnostico e quadri gravi
- Meno evidente «epidemiologicamente»



Infezione tubercolare: screening



Idealmente screening alla diagnosi (anche se non necessità di biologici)



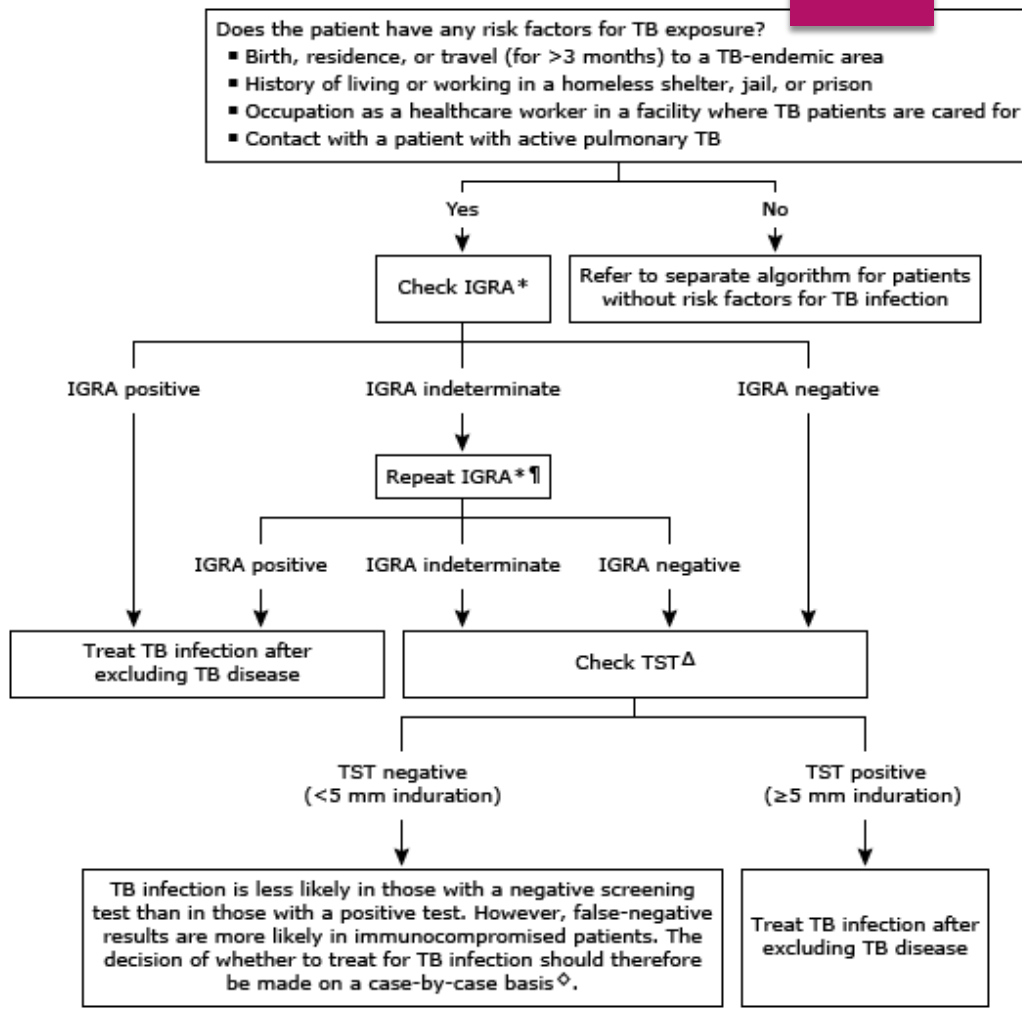
Screening con TUTTE le terapie biologiche, a prescindere dal rischio



Se rischio continuato nel tempo screening seriati annuali

Screening: alto vs. basso rischio

- Se paziente con fattori di rischio per esposizione a TB utile approccio two-step se IGRA neg
- FDR:
  - Nascita, residenza o viaggio prolungato in zona ad alta incidenza
  - Lavoro a contatto con carcerati, senzatetto
  - Lavoro in struttura sanitaria a possibile contatto con TB pos
  - Contatto noto con TB attiva



Infezione tubercolare: alto rischio

- Si considerano ad alto rischio di riattivazione:
  - Anti TNF: infliximab, adalimumab, etanercept, ecc
  - Anti JAK: baricitinib, tofacitinib
- Rischio medio/alto (consigliato screening e terapia, pochi casi negli studi):
  - Anti IL-6: tocilizumab, sarilimumab
- Rischio medio/basso (pochi/zero casi ma comunque consigliata tp):
  - Anti IL 12/23: Ustekinumab
  - Anti IL 1: anakinra
  - Anti integrine: vedolizumab

Target	Generic name	Trade name	Indication	tb risk	preventive therapy
TNF	Infliximab	Remicade biosimilars	RA, PsoA, SpA, Pso, CD, UC	high	yes
	Adalimumab	Humira+biosimilars	RA, PsoA, SpA, Pso, CD, UC, JIA, uveitis	high	yes
	Etanercept	Enbrel+biosimilars	RA, PsoA, SpA, Pso, JIA	medium	yes
	Golimumab	Simponi	RA, PsoA, SpA, UC	high	yes
	Certolizumab Pegol	Cimzia	RA, PsoA, SpA, Pso	high	yes
IL6R	Tocilizumab	RoActemra	RA, JIA	medium/high	yes
	Sarilumab	Kevzara	RA	medium/high	yes
JAKs	Tofacitinib	Xeljanz	RA, PsoA, UC	high	yes
	Baricitinib	Olumiant	RA	high	yes
	Upadacitinib	Rinvoq	RA	high	yes
	Filgotinib	Jyseleca	RA	high	yes
CD80/86	Abatacept	Orencia	RA, PsoA, JIA	low	yes[a,b]
IL 12/23	Ustekinumab	Stelara	PsoA, Pso, MC, UC	low	yes[a,b]
IL23	Guselkumab	Tremfya	PsoA, Pso	low	yes[a,b]
	Risankizumab	Skyrizi	Pso	low	yes[a,b]
	Tildrakizumab	Ilumatri	Pso	low	yes[a,b]
IL 1	Anakinra	Kineret	RA, FMF, Still, FS	low	yes[a,b]
	Canakinumab	Ilaris	FMF, Still, gout, FS	low	yes[a,b]
IFNAR 1	Anifrolumab	Saphnelo	SLE	low	yes[a,b,c]
Integrin	Vedolizumab	Entyvio	CD, UC	low	yes[a,b]

Infezione tubercolare: basso rischio

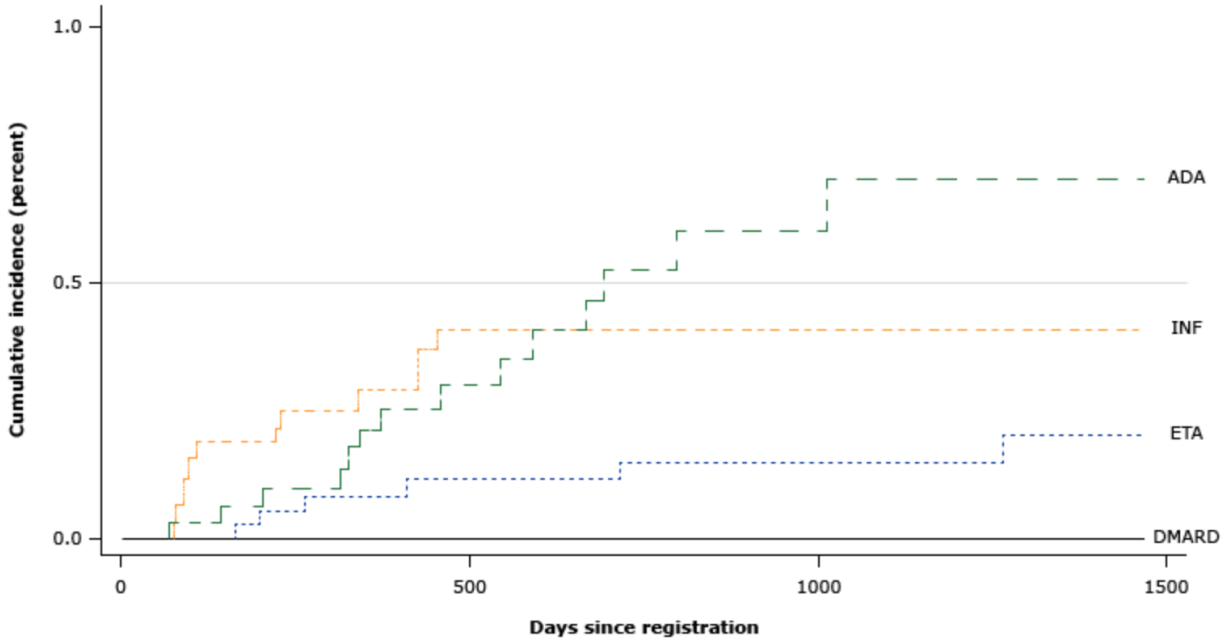
- Basso rischio di attivazione, ma che potrebbe comunque valere la pena trattare (casi sporadici):
  - AntiCD20: rituximab
  - Anti IL 17: secukinumab
- Non controindicano assolutamente tp biologica
- Non necessitano per forza trattamento LTBI prima di iniziare

IL 17	Secukinumab	Cosentyx	PsoA, SpA, Pso	low	no[a,b,c]
	Ixekizumab	Taltz	PsoA, SpA, Pso	low	no[a,b,c]
	Brodalumab	Kyntheum	Pso	low	no[a,b,c]
CD20	Rituximab	MabThera+biosimilars	RA, GPA, MPA	no	no[c]
BLyS	Belimumab	Benlysta	SLE	no	no
PDE4	Apremilast	Otezla	PsoA, Pso, Behcet	no	no
RANKL	Denosumab	Prolia, XGEVA	osteoporosis	no	no
Sklerostin	Romosozumab	Evenity	osteoporosis	no	no
IgE	Omalizumab	Xolair	asthma, chron. spontaneous urtikaria	no	no
C5	Eculizumab	Soliris	PNH, aHUS, Myast., NMOSD	no	no
	Ravulizumab	Ultomiris	PNH, aHUS	no	no
C5aR	Avacopan	Tavneos	MPA, GPA	no	no
IL 5	Mepolizumab	Nucala	eosinoph. asthma	no	no
	Restizumab	Cinqaero	eosinoph. asthma	no	no
IL 5R	Benralizumab	Fasenra	eosinoph. asthma	no	no
IL 4R/IL 13R	Dupilumab	Dupixent	asthma, atop, dermatits	no	no

Fig. 2 Heat map of bDMARDs and tsDMARDS regarding the risk of tuberculosis and need for preventive treatment; *red*: high risk, preventive treatment necessary, *orange*: low risk, preventive treatment necessary, *yellow*: low risk, preventive treatment not necessary, *green*: no risk, preventive not necessary. *TNF* tumor necrosis factor, *IL* interleukin, *IFNAR1* type I interferon receptor, *JAKs* Janus kinase inhibitor, *BlyS* B-lymphocyte stimulator, *PDE4* phosphodiesterase 4 inhibitor, *RANKL* receptor activator of NF-κB ligand, *IgE* immunoglobulin E, *RA* rheumatoid arthritis, *PsoA* psoriatic arthritis, *SpA* spondylarthritis, *Pso* psoriasis, *CD* Crohn's disease, *UC* ulcerative colitis, *JIA* juvenile idiopathic arthritis, *FMF* familial Mediterranean fever, *Still* systemic juvenile idiopathic arthritis, adult onset Still's disease, *FS* fever syndromes, *SLE* systemic lupus erythematosus, *PNH* paroxysmal nocturnal hemoglobinuria, *aHUS* atypical hemolytic uremic syndrome, *Myast.* myasthenia gravis, *NMOSD* neuromyelitis optica spectrum disorder, *MPA* microscopic polyangiitis, *GPA* granulomatosis with polyangiitis. [a]Low incidence, due to routinely screening in studies. [b]Theoretical risk low. [c]According to the summary of product characteristics, this does not require screening

Timing riattivazione anti TNFalfa

- Studio su BMJ (Dixon et al.) su 13000 pz che assumevano anti-TNFalfa
- Studio su CID (Wallis et al.) 233000 infliximab vs. 113000 etanercept
- In entrambi tempo molto minore infliximab vs. etanercept (adalimumab più lungo ma incidenza maggiore)



Drug	Registration (entry to study)	1 year (365 days)	2 years (730 days)	3 years (1095 days)	4 years (1460 days)
DMARD	3232	2652	1839	742	213
ETA	3913	3474	3051	2363	1020
INF	3295	2694	1918	1392	918
ADA	3504	2457	1531	729	247

Trattamento

- Occhio alle interazioni!
- Se possibile sempre meglio RIF/INH
- Monoterapia con INH **per 9 mesi**
- Rifapentina non disponibile in Italia

Regimen	Dosing	Clinical considerations
Rifamycin-based regimens[¶] (preferred)		
Rifampin (daily for 4 months; 4R)	▪ Rifampin 10 mg/kg (600 mg maximum) orally daily for 4 months	Better completion rates and less toxicity (relative to isoniazid monotherapy)
Isoniazid[Δ] and rifampin (daily for 3 months; 3HR)	▪ Isoniazid 5 mg/kg (300 mg maximum) orally daily for 3 months ▪ Rifampin 10 mg/kg (600 mg maximum) orally daily for 3 months	Better completion rates and less toxicity (relative to isoniazid monotherapy)
Isoniazid[Δ] and rifapentine (weekly for 3 months; 3HP)	▪ Isoniazid (orally once weekly for 3 months; direct observation is preferred): • 15 mg/kg, rounded up to the nearest 50 or 100 mg; 900 mg maximum ▪ Rifapentine (orally once weekly for 3 months; direct observation is preferred): • 10 to 14 kg: 300 mg • 14.1 to 25.0 kg: 450 mg • 25.1 to 32.0 kg: 600 mg • 32.1 to 49.9 kg: 750 mg • ≥50 kg: 900 mg maximum	Better completion rates (relative to isoniazid monotherapy) Important side effects of 3HP include hypersensitivity or flu-like symptoms (eg, light headedness, dizziness, headache, nausea or vomiting, syncope, rash, or angioedema). For this reason, 3HP usually is administered via directly observed therapy, to facilitate side effect review and treatment withholding if needed. Self-administration of 3HP may be acceptable for patients who can reliably take their medications on schedule and inform their providers promptly of side effects (while withholding the next dose pending provider review).
Isoniazid monotherapy regimens (alternative)		
Isoniazid[Δ]	▪ Isoniazid 5 mg/kg (300 mg maximum) orally daily for 9 months[◇] ▪ Isoniazid 5 mg/kg (300 mg maximum) orally daily for 6	Fewer drug interactions (relative to rifamycin-based regimens)

Caso clinico: parte 2

- MM inizia in data 28/2 terapia standard con HRZE
- (Sospeso adalimumab il 18/1)
- Dal 29/3 febbre serotina (fino a 39.5/40)
- Ricoverata in data 4/4: accertamenti microbiologici negative (Enterococco su urine)
- Alla **TC PEGGIORAMENTO DEL QUADRO**
- Cortisone, switch da rifampicina a rifabutina, defervescenza e dimissione con decalage steroide ambulatoriale
- Attualmente ancora in terapia con HRbZE, ben tollerata, netto miglioramento clinico



IRIS TB

- Sindrome da immunoricostituzione, comune in ID (AIDS, malnutriti, ecc)
- Comune anche in pz in terapia con biologici dopo sospensione immunosoppressore e inizio tp
- Particolarmente violenta dopo sospensione biologici, casi quasi letali (Wallis et al, CID, 2009)
- Case series su CID: 4 su 6 tb riattivate in corso di infliximab hanno avuto IRIS
- **Rivoisy et al: Mediana 45 gg dopo inizio HRZE; 110 gg dopo stop ID, 7% incidenza, più comune in disseminate**



Paradoxical response to antituberculous therapy in infliximab-treated patients with disseminated tuberculosis

Carolina Garcia Vidal [1], Serena Rodríguez Fernández, Javier Martínez Lacasa, Miquel Salavert, Rafael Vidal, Monica Rodríguez Carballeira, Javier Garau

Affiliations + expand

PMID: 15714425 DOI: 10.1086/427941

Paradoxical anti-TNF-associated TB worsening: Frequency and factors associated with IRIS

Claire Rivoisy [1], Florence Tubach [2], Carine Roy [2], Nathalie Nicolas [3], Xavier Mariette [4], Dominique Salmon [5], Olivier Lortholary [6], Anne Bourgarit [7]; RATIO Group

Collaborators, Affiliations + expand

PMID: 26677996 DOI: 10.1016/j.jbspin.2015.04.022

Case Reports > Open Forum Infect Dis. 2022 Jul 22;9(8):ofac367. doi: 10.1093/ofid/ofac367. eCollection 2022 Aug.

CNS TB-IRIS Following Cessation of Adalimumab in an Adolescent With Crohn's Disease

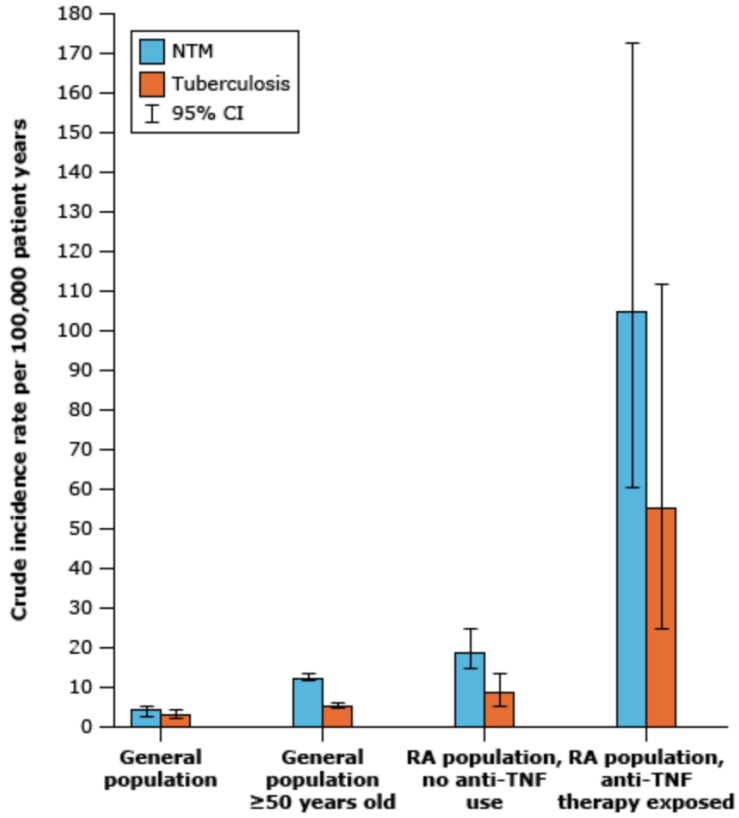
Elizabeth Christian [1], Alicia Johnston [1]

Affiliations + expand

PMID: 35949406 PMCID: PMC9356675 DOI: 10.1093/ofid/ofac367

E gli NTM?

- In paesi a bassa incidenza TB più frequenti in ID
- Di solito nel contesto di malattia polmonare cronica pre-esistente
- Mandateli da Codecasa

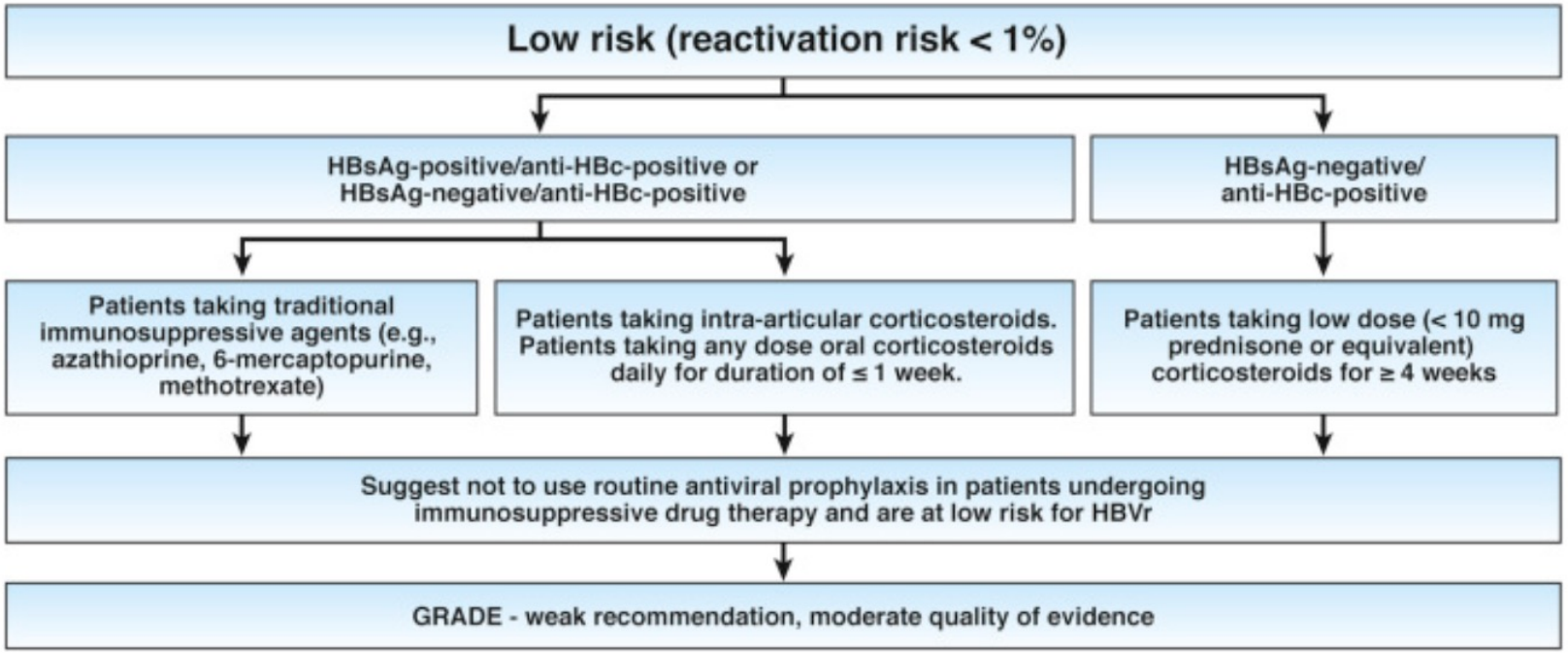


Epatiti virali

- Screening per HBV ed HCV alla diagnosi
- Epatite C si tratta salvo controindicazioni
- HBV dipende da stato clinic/sierologico e farmaco utilizzato
  - Screening: HBsAg/Ab, HBcAb
  - Se HBsAg+: HBeAg, HBV-DNA
- Indicazioni al trattamento "standard" valgono anche in ID

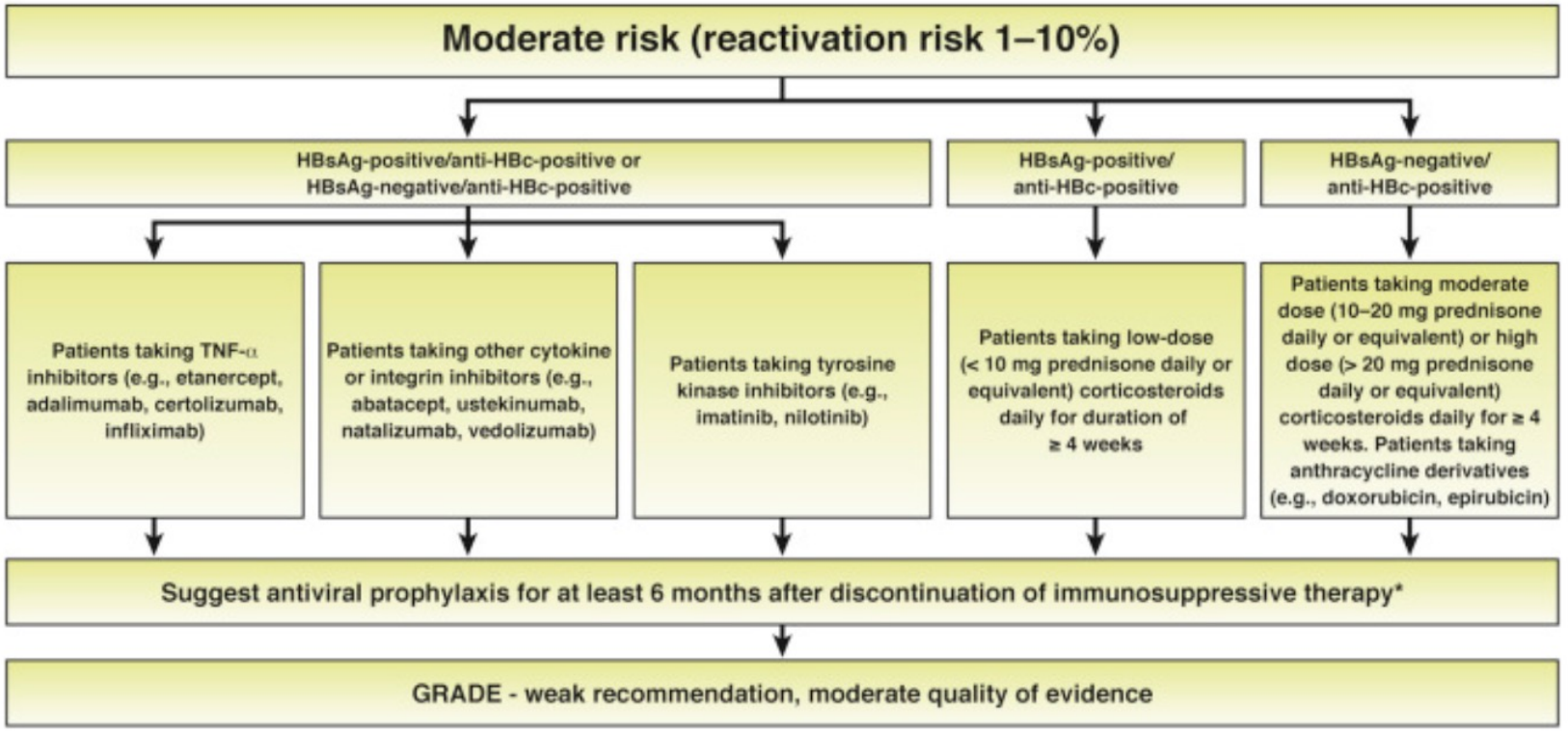
HBeAg	HBV DNA (PCR)	ALT	Treatment strategy
Patients without cirrhosis*			
+	>20,000 international units/mL	≤2 × ULN¶	Treatment is not recommended, because current treatment has low efficacy in inducing HBeAg seroconversion. Treatment may be considered in older patients (>40 years) and in those with family history of HCC. Patients should be monitored△ and treatment considered if ALT becomes elevated >2 × ULN, liver biopsy shows moderate/severe inflammation or fibrosis◇ (eg, METAVIR score ≥F2), and/or noninvasive testing suggests moderate/severe fibrosis.
+	>20,000 international units/mL	>2 × ULN¶	Observe for 3 to 6 months if compensated and treat if no spontaneous HBeAg loss. Immediate treatment if severe hepatitis flare (eg, icteric or clinical decompensation). ETV, TAF, TDF, or PegIFN alfa are preferred for initial therapy.§¥ End-point of treatment – Seroconversion from HBeAg to anti-HBe.‡ Duration of therapy: ▪ PegIFN alfa: 48 weeks. ▪ ETV, TAF, or TDF: Continue for at least 12 months after HBeAg seroconversion.
–	>2000 international units/mL	>2 × ULN¶ **or** 1 to 2 × ULN¶ if liver biopsy shows moderate/severe necroinflammation or significant fibrosis◇ (eg, METAVIR score ≥F2) or non-invasive testing shows significant fibrosis	ETV, TAF, TDF, or PegIFN alfa are preferred for initial therapy.§¥ End-point of treatment – HBsAg loss. Duration of therapy: ▪ PegIFN alfa: One year. ▪ ETV, TAF, or TDF: Several years or indefinite.†
–	≤2000 international units/mL	≤ULN¶	Monitor and treat if HBV DNA and ALT increase as described above.

HBV: farmaci basso rischio



AGA guidelines, 2014

HBV: farmaci medio rischio



*Patients who place a higher value on avoiding the long-term use of antiviral therapy and cost associated with its use and a lower value on avoiding the small risk of reactivation (particularly in those who are HBsAg-negative), may reasonably select no prophylaxis over antiviral prophylaxis

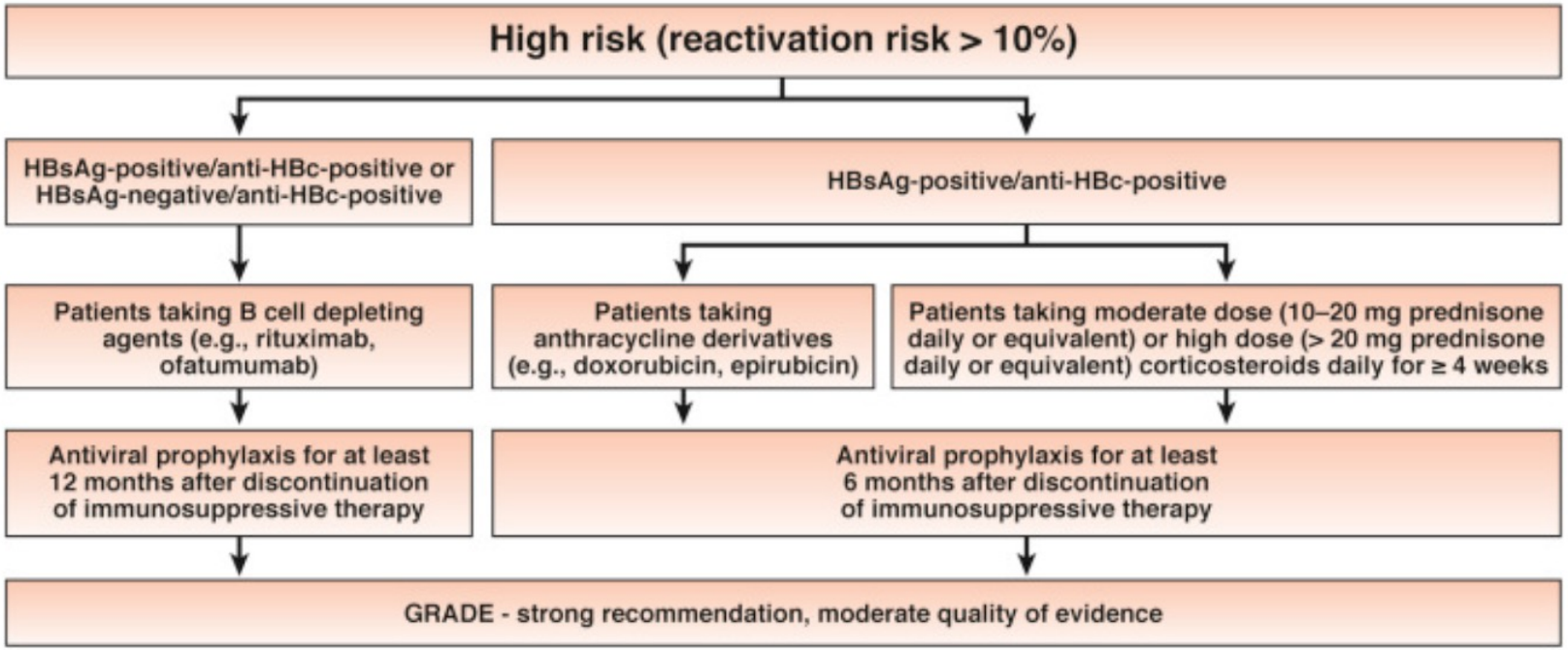
AGA guidelines, 2014

HBV: farmaci medio rischio

- Monitoring HBV DNA levels during immunosuppressive therapy may allow for early detection and treatment of HBVr and the latter may attenuate liver injury and improve patient outcomes, which differ little from those observed in patients given prophylactic antiviral therapy. **The best evidence that improved outcomes are achievable with prophylactic antiviral therapy as opposed to deferred treatment comes from randomized controlled trials that compared both means of drug administration**. When taken collectively, **data from the observational studies suggest that the overall rate of HBVr is considerably lower when prophylactic antiviral therapy is compared with on-demand treatment**. However, most of these studies are of poor quality, use differing definitions of HBVr, and inconsistently report outcomes other than the frequency of reactivation, severe elevation of ALT level, and reactivation-related death.

AGA guidelines, 2014

HBV: farmaci alto rischio



AGA guidelines, 2014

HBV: trattamento

- La maggior parte delle linee guida internazionali (compresa AGA) consiglia TAF/TDF o entecavir nel paziente immunodepresso
- Consigliato mantenere terapia soppressiva fino a:
  - Almeno 12 mesi dopo farmaci ad alto rischio (anche 18 con RTX)
  - Almeno 6 mesi dopo farmaci medio rischio
- Spesso terapia soppressiva impostata durante ID diventa vita natural durante



The AGA recommends antiviral drugs with a high barrier to resistance over lamivudine for established HBVr in patients undergoing immunosuppressive drug therapy. (*Strong recommendation; Moderate-quality evidence*)

AGA guidelines, 2014

Altre infezioni

TNF alfa:

- **Lysteria, Nocardia, Legionella**
- Micosi endemiche
- Funghi filamentosi e lieviti

JAK:

- HZ ed altri erpetici
- **PCP**
- **Micosi (endemiche, muffe, lieviti)**

Altre infezioni

CD20:

- **JCV**
- **PCP**
- HZ e altri erpetici
- Micosi endemiche e lieviti

IL-1:

- **Muffe e lieviti**

IL-6:

- **Lieviti**
- **PCP**

Altre infezioni

IL-17 e IL 12/23:

- Lieviti
- **Funghi dermatofiti**

IL-5 e IgE:

- **Parassiti**
- HZ?

C5:

- **Capsulati**

Altre infezioni: prevenzione e trattamento

- VACCINAZIONI!
- PCP: ancora dibattuto, alcuni autori suggeriscono profilassi se antiCD20 + altro (CT/altra ID)
- Se infezione attiva **STOP ID fino a risoluzione**
- Con antiC5 (eculizumab) come asplenia funzionale (valutare profilassi capsulati o trattamento precoce)

Grazie per l'attenzione