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Infezioni Opportunistiche, Latenzti & Riattivazioni

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Conflitti di Interesse

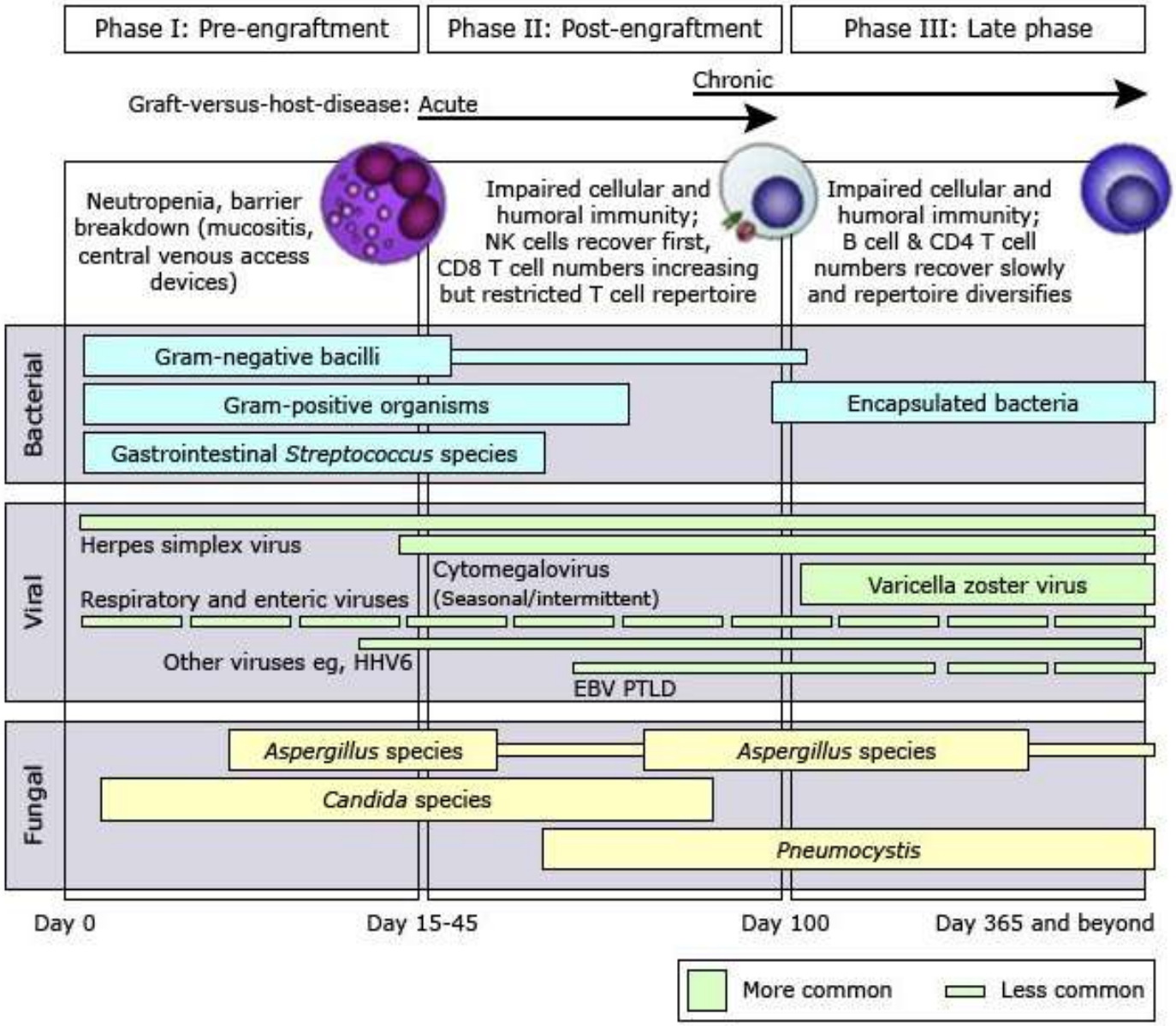
Consultant/Advisory Board/Speaker fee

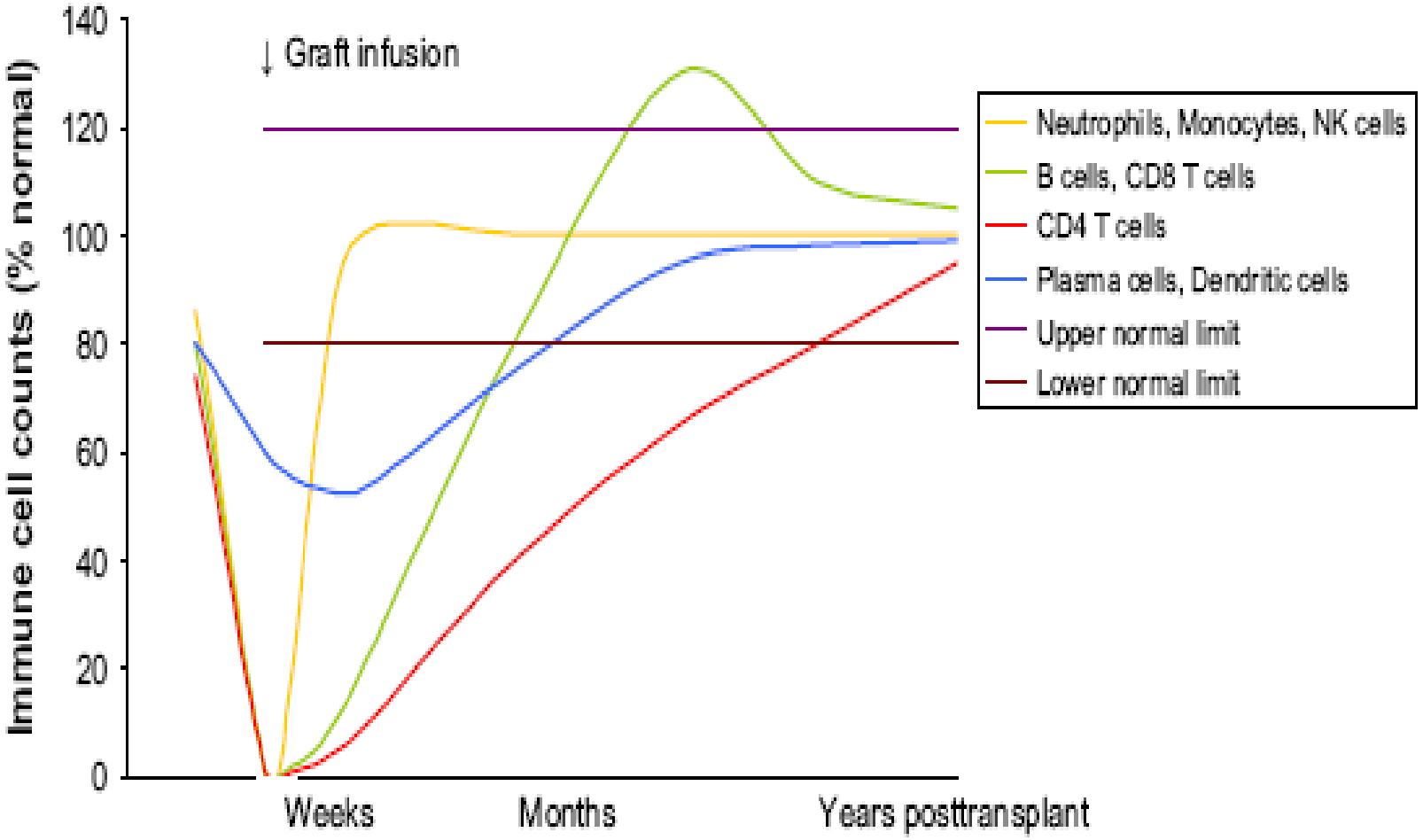
- Pfizer, MSD
- AstraZeneca, Angelini
- Basilea, Astellas Pharma
- Sanofi Aventis, Thermofisher

Herpesviruses Infections in Immunocompromised Patients

- Old pathogen, old disease:
  - CMV
  - HSV
    EBV
- Old pathogens, previously unrecognized:
  - HHV-6 , HHV-7
- New pathogen, old disease :
  - HHV-8

Phases of opportunistic infections among allogeneic hematopoietic cell transplant recipients




Immune cell counts (% normal)
140
120
100
80
60
40
20
0
↓ Graft infusion
Weeks
Months
Years posttransplant
Neutrophils, Monocytes, NK cells
B cells, CD8 T cells
CD4 T cells
Plasma cells, Dendritic cells
Upper normal limit
Lower normal limit

Farmaci “Biologici”

- **Anticorpi monoclonali, proteine di fusione, citochine**
- **Molecole derivate da organismi viventi prodotte mediante tecnologia del DNA ricombinante**
- **Meccanismo d’azione:**
  - **Meccanismi di blocco o stimolo**
  - **Effetto antagonista**
- **Effetto citotossico**

Biologic Compounds:

Antibodies & Other Peptides

- **Mechanisms**:
  - Inhibiting inflammatory cytokine signaling (typically tumor necrosis factor or TNF)
  - Inhibiting T-cell activation
  - Depleting B-cells
  - **After market…….**
  - Knowledge of the infectious complications
  - Risk for developing atypical and opportunistic infections:
    - Tuberculosis
    - Herpes zoster
    - *Legionella pneumophila …..*
    - *Listeria monocytogenes*

TABLE 1. CUMULATIVE NUMBERS OF PATIENTS TREATED WITH INFLIXIMAB OR ETANERCEPT, ACCORDING TO LOCATION AND INDICATION.*

DRUG	UNITED STATES	OTHER COUNTRIES
	no. of patients	
Infliximab	121,000	26,000
Crohn's disease	76,000	NA
Rheumatoid arthritis	45,000	NA
Etanercept	95,493	6,638

*Data, provided by the manufacturers, are for all patients who had received infliximab as of March 30, 2001, and for all those who had received etanercept as of January 31, 2001. NA denotes not available.

Characteristics (1)

- Median age 57 yy (18-83)
- CD 18
- RA 47
- Others 5
- Interval 1st dose and diagnosis 1-52 (12)
- Median n of doses 3 (1-9)

The NEW ENGLAND JOURNAL of MEDICINE

To the Editor: Keane et al. report that tuberculosis developed in some patients with Crohn's disease or rheumatoid arthritis after treatment with infliximab. We believe that these patients need to be described separately, especially with respect to their clinical characteristics and the interval between infliximab treatment and the appearance of tuberculosis. There is a possibility that some patients who have been given a diagnosis of Crohn's disease actually have abdominal tuberculosis. Both conditions can present with transmural spread and penetration through the muscle coat, although this presentation is relatively less common in Crohn's disease. These conditions have a similar microscopic appearance that includes granulomas, and the caseation that is characteristic of tuberculosis is often difficult to identify.[1] In areas where abdominal tuberculosis is more frequent, some criteria must be fulfilled to differentiate intestinal tuberculosis from Crohn's disease: there must be histologic evidence of tubercles with caseation necrosis; there must be a good typical gross description of operative findings, with biopsy of mesenteric nodes showing histologic evidence of tuberculosis; inoculation into animals or culture of the suspected tissue must result in the growth of tubercle bacilli; and histologic examination must show *Mycobacterium tuberculosis* in a lesion.[2] In an urban British population with a large number of Asian immigrants, abdominal tuberculosis was not infrequent, whereas Crohn's disease occurred rarely in Asian immigrants.[3] A clear distinction in describing the general characteristics of patients with Crohn's disease and rheumatoid arthritis in whom tuberculosis developed will be useful, given that when we diagnose Crohn's disease we are at risk of underdiagnosing abdominal tuberculosis.

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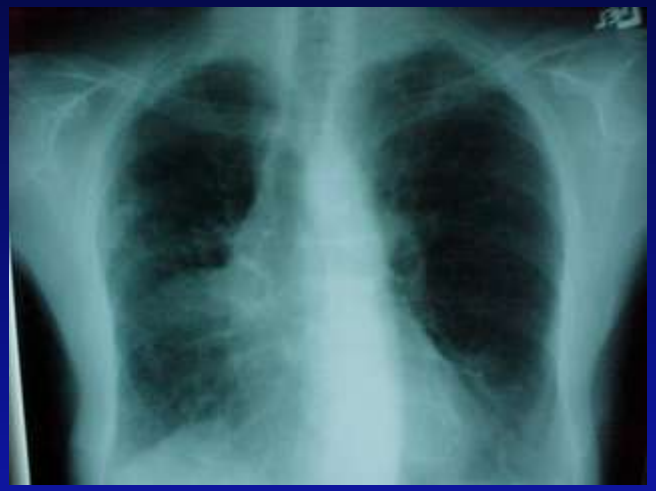
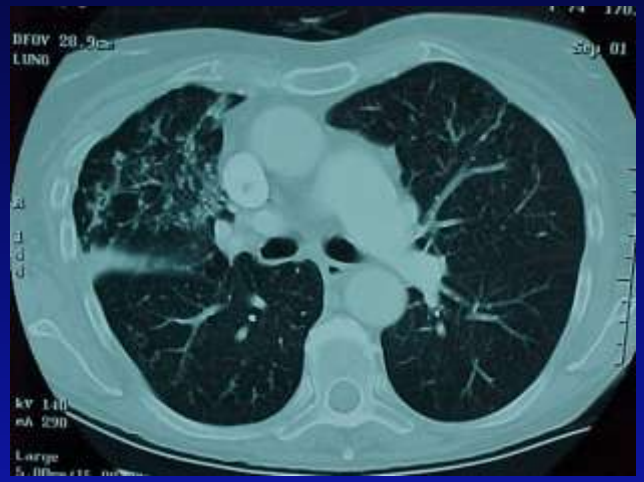
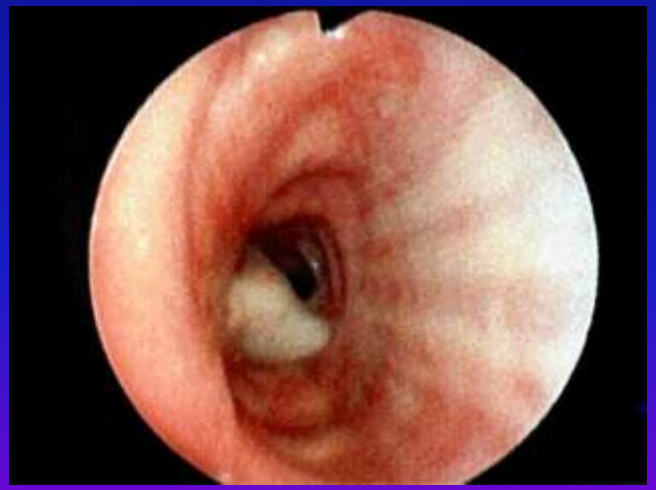
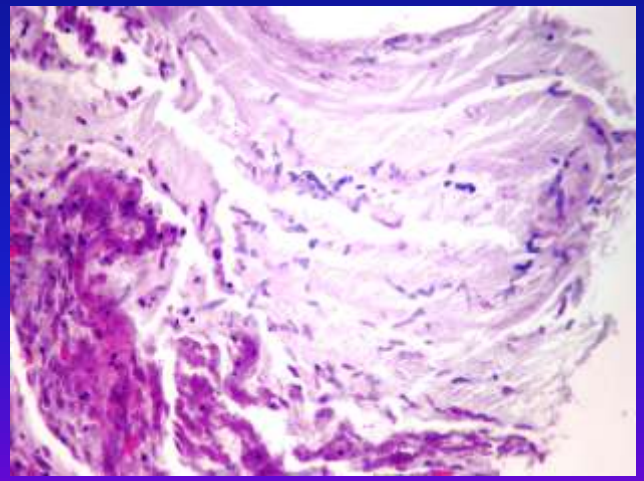
Pseudomembranous Aspergillus Tracheobronchitis after anti-TNF- Treatment: A Possible Health-Care Associated Case?

De Rosa FG et al, ICHE 2002









Pathogen	Pathogen burden	Survival
Coxiella burnetii	Increased	No difference
Helicobacter pylori	Increased	NA
Helicobacter felis	No difference	NA
Listeria monocytogenes	Increased	Reduced
Mycobacterium tuberculosis	Increased	Reduced
Mycobacterium bovis BCG	Increased	Reduced
Mycobacterium avium	Increased	Reduced
Mycobacterium smegmatis	Delay in bacterial clearance	No difference
Pseudomonas aeruginosa	Increased	NA
Rhodococcus aurantiacus	Increased	Reduced
Salmonella typhimurium	Increased	Reduced
Staphylococcus aureus	Increased	Reduced
Streptococcus pneumoniae	No difference[a], increased[b]	No difference[a], reduced[b]
Cryptosporidium parvum	No difference	NA
Leishmania donovani	Increased	Reduced
Leishmania major	Increased	Reduced
Plasmodium berghei	No difference	NA (moribund)
Plasmodium chabaudi chabaudi	No difference	NA
Plasmodium chabaudi adami	Increased	Reduced
Toxoplasma gondii	Increased	Reduced
Trypanosoma brucei	Increased	No difference
Trypanosoma congolese	Increased	Reduced
Blastomyces dermatitidis	Increased (in young, not old)	Reduced (in young, not old)
Candida albicans	Increased	NA
Adenovirus, replication deficient	Delay in virus clearance	NA
Bovine leukemia virus	Increased	NA
Coxsackie virus	No difference	Improved
Murine leukemia retrovirus	NA	NA (no difference in pathology)
Herpes simplex virus	Increased	Reduced
Theiler's murine encephalomyelitis	No difference	No difference

Susceptibility to bacterial, parasitic, fungal, and viral infections in tumor necrosis factor knockout mice in comparison to wild type mice

Curr Opin Rheumatol
19:626–635; 2007

Tuberculosis & Infliximab

Gordon R et al 2012

- **Cochrane review:**
  - Increased risk of reactivation with all TNF-α inhibitors, anakinra, tocilizumab, abatacept, and rituximab for any indication:
    - OR: 4.68, 95% CI: 1.18-18.60 in comparison with the control group
      - Singh JA et al. *Cochrane Database Syst Rev*. 2011(2):CD008794
- **Risk with TNF-α inhibitors in psoriasis patients:**
  - Lifetime risk of TB:
    - 0-17.1% in comparison to 0.3% without TNF-α inhibitors
  - Risk of tuberculosis is still far lower than the lifetime risk of America's more common afflictions: cancer (40.4%), heart disease (36.2%), and stroke (18.4%)
    - Kaminska E et al. J Dermatolog Treat 2011

Infliximab:
Most Heavy Association with Risk of TB

- A study of the FDA Adverse Event Reporting System (AERS) between 1998-2002 → Increased risk of developing TB for infliximab and etanercept users:
  - 144 per 100,000 infliximab-treated patients compared
  - 35 per 100,000 etanercept-treated patients, p<0.001) with a rate ratio of 4.17
    - Wallis RS et al. Clin Infect Dis 2004; 38(9) :1261-5
- In France, a case-control analysis of newly diagnosed TB associated with anti-TNF agents found that exposure to infliximab or adalimumab versus etanercept was an independent risk factor for TB
  - OR: 13.3 (95% CI: 2.6-69.0) and OR: 17.1 (95% CI: 3.6-80.6), respectively
    - Tubach F et al. Arthritis Rheum. 2009; 60(7): 1884-94

Listeria in TNF Inhibitors

Pena-Sagredo JL et al. Clin Exp Rheumatol 2008; 26(5): 854-9
Schett G et al. J Clin Microbiol 2005; 43(5): 2537-41

- **Sepsis, endocarditis, meningitis**
- An **assessment** of the incidence with TNF inhibitors:
  - Spanish Registry of Adverse Events of Biological Therapies in Rheumatic Diseases (BIOBADASER) with the Spanish Rheumatoid Arthritis Registry Cohort Study (EMECAR)
  - → RA patients treated with TNF-α antagonists had an increased rate compared to RA patients treated with conventional therapy, as well as the general population
- **Infective endocarditis:**
  - 92 cases related to infliximab treatment in the FDA AERS database.
- **Meningitis**
  - The most common type of infection reported (69 cases, 75%)
  - More frequently in patient treated with infliximab versus etanercept

Legionella spp. & TNF-Inhibitors

- Clear association in the literature
  - Empiric coverage
  - Urinary Antigen
- In France
  - RATIO, over a 1-year period: 10 cases
  - Median duration of therapy = 38.5 weeks
  - The relative risk in people receiving anti-TNF therapy was reported as 16.7-21.0 in comparison with the general population
    - Tubach F et al. Clin Infect Dis 2006; 43(10): e95-100
- Case review of the incidence of legionellosis:
  - 10 cases
    - Hofmann A et al. Can J Gastroenterol 2009; 23(12): 829-33

Fungal Infections & Anti-TNF

- **Black Box warning by the FDA in 2008**
  - 240 cases of histoplasmosis after infliximab, etanercept, or adalimumab
  - Infections unrecognized and treatment delayed 21 patients, the signs of infection was unrecognized and antifungal therapy was delayed
  - 12 deaths
    - http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm107878.htm
- **A recent review**
  - Atypical presentation and symptoms of infection mimicking the underlying disease
  - ……

Fungal Infections & Anti-TNF

- Wide geographic area of *H. capsulatum* compared to Blastomyces dermatididis or *Coccidiodes spp.*
- Infection with *H. capsulatum* is contained almost exclusively by cellmediated immunity
  - Smith JA et al. Drugs 2009; 69(11): 1403-15
- Multiple cases of aspergillosis have also been associated with TNF-α antagonists
  - Nedel WL et al. Rev Iberoam Micol 2009; 26(3): 175-83

Herpes Zoster

- **Significantly higher risk of HZ in RA**
  - **T**reated with etanercept, infliximab, or adalimumab compared with DMARDs
    - Strangfeld A et al. JAMA. 2009; 301(7): 737-44
- **Ustekinumab**
  - Two patients developing severe, multidermatomal HZ 1 & 9 months after initiating therapy

→ Vaccination against HZ is strongly encouraged before ustekinumab

→ Failla V et al. Dermatology 2011; 222(2): 119-22

Rituximab & Infezioni Virali

- Epatite fulminante da HBV
  - Anche in soggetti anti-HBs e anti-HBc positivi
  - Necessità di profilassi con lamivudina
- Interstiziopatia polmonare
- Aplasia eritroide acuta da Parvovirus B19
- Infezioni fatali da VZV
- PML
- Infezione da Listeria & riattivazione di HBV

Perceau G et al. Br J Dermatol 2006; 155: 1053-6
Tsutsumi Y et al. Expert Opin Drug Saf 2005; 4: 599-608
Hamaki T et al. Am J Med 2001; 68: 292-4