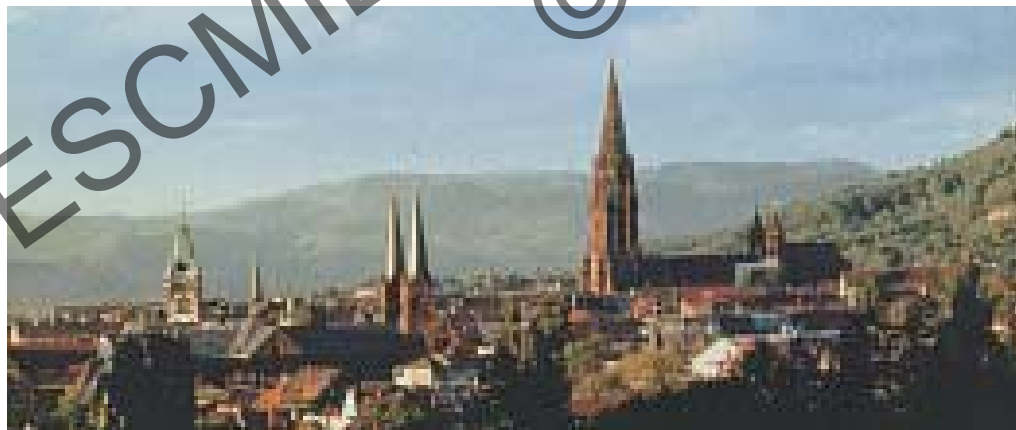


# Targeted immune suppressive therapies and emerging fungal infections

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# Targeted immune suppressive therapy

- B cell antibodies
- T cell antibodies
- anti-cytokine antibodies
  - TNF $\alpha$  „blockers“
  - anti-IL6 antibodies
  - anti-IL2 antibodies

# Targeted immune suppressive therapy

- indications
  - transplantation
  - rheumatoid arthritis etc.
  - Crohn's disease
  - ...

# Targeted immune suppressive therapy

- B cell antibodies
- T cell antibodies
- anti-cytokine antibodies
  - TNF $\alpha$  „blockers“
  - anti-IL6 antibodies
  - anti-IL2 antibodies

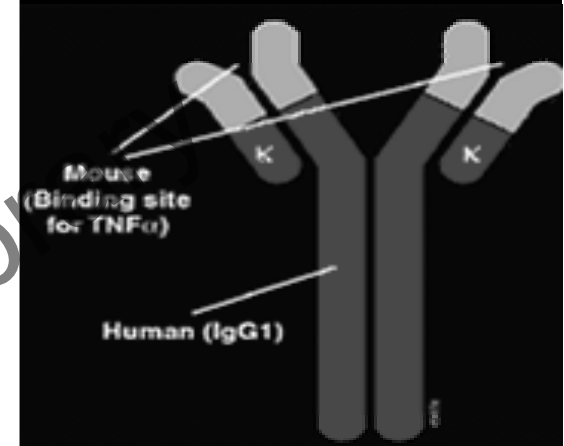
# Anti-TNF

- 1998 infliximab  
& etanercept

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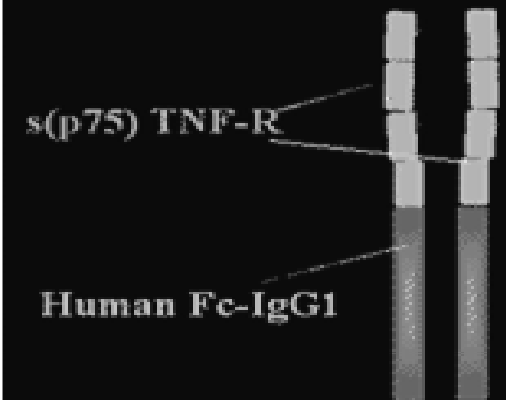
## ■ Infliximab (Remicade®)

chimeric (murine variable and human IgG1 constant region) antibody binding diverse TNF moieties incl. monomeric and trimeric soluble and transmembrane TNF



## ■ Etanercept (Enbrel®)

dimeric fusion protein of TNFRp75 linked to the Fc domains of human IgG1



# Anti-TNF species & tuberculosis

- **Wallis et al. 2005 (US)**

- ... ~54/100.000 (Infliximab)

- ... ~28/100.000 (Etanercept)

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# Anti-TNF species

- infliximab (*Remicade*<sup>®</sup>)
- etanercept (*Enbrel*<sup>®</sup>)
- adalimumab (*Humira*<sup>®</sup>)
- certolizumab pegol (*Cimzia*<sup>®</sup>)
- golimumab (*Simponi*<sup>®</sup>)



# Anti-TNF species & tuberculosis

- **Wallis et al. 2005 (US)**

  - ... ~54/100.000 (Infliximab)

  - ... ~28/100.000 (Etanercept)

- **Dixon et al. 2008 (UK)**

  - ... >100/100,000 (Infliximab, Adalimumab)

  - ... ~40-50/100,000 (Etanercept)

- **Salmon et al. 2008 (Ratio, France)**

  - ... ~200/100.000 (Infliximab, Adalimumab)

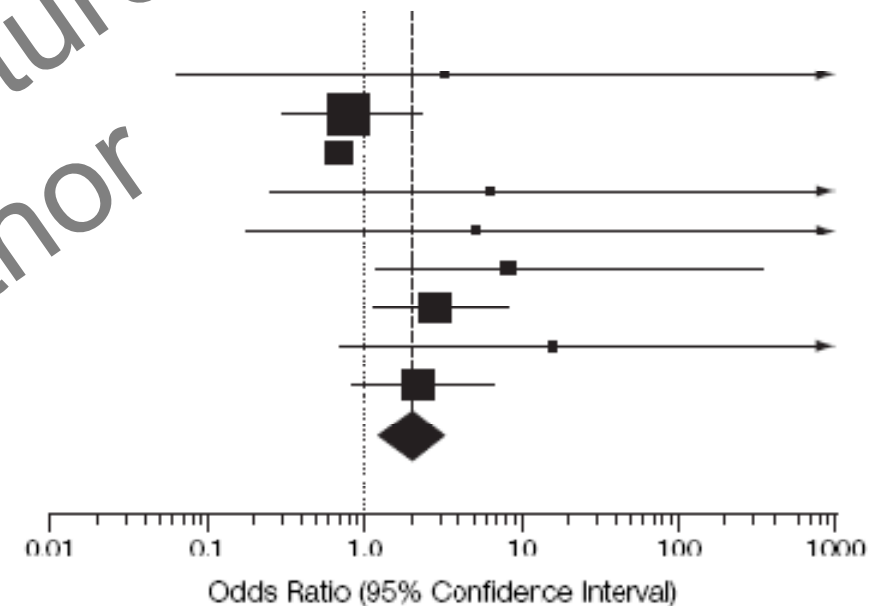
  - ... ~10/100.000 (Etanercept)

Wallis et al *CID* 2005 Suppl 3  
abstract *EULAR* 2008  
abstract K-1416 *ICAAC* 2008

# Anti-TNF & serious infections

Source	Serious Infections, No./Total		Odds Ratio (95% Confidence Interval)
	Anti-TNF	Placebo	
Maini et al, <sup>32</sup> 1990	2/07	0/14	3.13 (0.06-Infinity)
Lipsky et al, <sup>9</sup> 2000	21/342	7/66	0.76 (0.30-2.18)
Furet et al, <sup>8</sup> 2003	4/318	6/318	0.66 (0.14 2.88)
Van de Putte et al, <sup>10</sup> 2003	4/214	0/70	6.33 (0.30-Infinity)
Weinblatt et al, <sup>11</sup> 2003	3/200	0/62	4.08 (0.10-Infinity)
Keystone et al, <sup>6</sup> 2004	16/419	1/200	7.90 (1.21-332.96)
St Clair et al, <sup>7</sup> 2004	40/749	6/991	2.68 (1.11-7.61)
Van de Putte et al, <sup>33</sup> 2004	11/434	0/110	15.34 (0.71-Infinity)
Westhovens et al, <sup>34</sup> 2004	25/721	6/361	2.13 (0.84-6.39)
<b>Total</b>	<b>126/3493</b>	<b>26/1512</b>	<b>2.01 (1.31-3.09)</b>

Test for overall effect:  
Mantel-Haenszel  $\chi^2 = 9.1$ ;  $P = .002$



# Anti-TNF & serious infections

- **Askling et al. 2007**

.... in the first year ↑ (RR 1.4 [95%CI 1.2-1.7])

- **Bernatsky et al. 2007**

.... ↑ ~2-fold (similar to other immunosuppressive therapies)

# Anti-TNF & serious infections

- **Curtis et al. 2007 (bacterial only)**
  - .... 2.9/100 patient years (first 6 months) versus 1.4/100 subsequently (1.9-fold higher than with MTX alone)
- **Schneeweiss et al. 2007 (bacterial only)**
  - .... 2.2/100 patients years (>60 yrs of age, similar to MTX alone)

# Anti-TNF & serious infections

- **Salliot et al. 2007**

..... ~3 → ~10/100 patient years

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# Rituximab & serious infections

	Overall (N = 2578)	Patients receiving any biological agent after rituximab treatment (n = 185)		Patients receiving TNF inhibitor after rituximab treatment (n = 153)	
		Before other biological agent	After other biological agent	Before other TNF inhibitor	After other TNF inhibitor
Total exposure, patient-years	5013	186.05	182.31	150.87	162.41
Serious infections, n	216	13	10	10	8
Serious infections/100 patient-years	4.31	6.99	5.49	6.63	4.93
95% CI	3.77 to 4.92	4.06 to 12.03	2.95 to 10.19	3.57 to 12.32	2.46 to 9.85

# Anti-TNF & **fungal** infections

- **Salliot et al. 2007**

..... ~3 → ~10/100 patient years

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# Anti-TNF & **fungal** infections

All treatment courses  $n = 913$

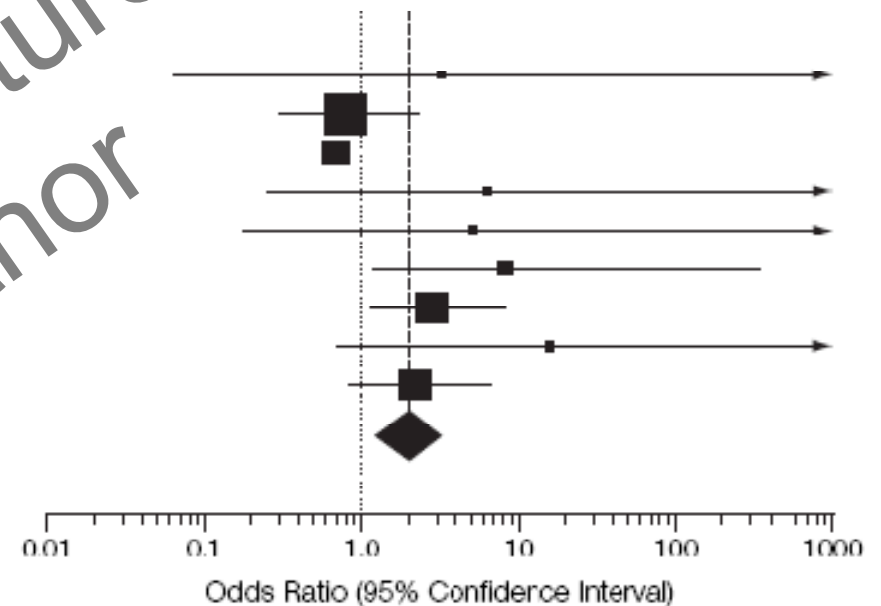
Any infections $n$ (% <sup>a</sup> )	275
Sites of infection $n$ (% <sup>b</sup> ):	
Upper respiratory tract	98 (10.7)
Lung	59 (6.4)
Skin	58 (6.3)
Urinary tract	22 (2.4)
Gastrointestinal tract	16 (1.7)
Genital tract	5 (0.5)
Osteoarticular	3 (0.3)
Neurological	0 (0)
Other	14 (1.5)
Micro-organisms $n$ (% <sup>b</sup> ):	
Bacterial	148 (16.2)
Viral	84 (9.2)
Mycobacterial	2 (0.2)
Fungal	18 (1.9)
Parasitic	1 (0.1)
Not defined	22 (2.4)
Outcome $n$ (% <sup>c</sup> ):	
Death	1 (0.3)
Cured	272 (98.9)
Sequelae	2 (0.7)



# Anti-TNF & serious infections

Source	Serious Infections, No./Total		Odds Ratio (95% Confidence Interval)
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Test for overall effect:  
Mantel-Haenszel  $\chi^2 = 9.1$ ;  $P = .002$



~4%

# Anti-TNF & **fungal** infections

- **Bongartz et al. 2006**

.... only 12 of the 126 serious infections reported in the included randomized controlled trials could be identified as granulomatous (10 cases of tuberculosis, 1 case of histoplasmosis, and 1 case of coccidioidomycosis) ...

= **1/3493 (~ 0.3/1000 or ~29/100.000) each**

# Anti-TNF & **funga**l infections

- Systematic review of the literature
  - e.g. Bongartz et al
- National registries, other studies
- Adverse Event Reporting System (AERS)
  - voluntary reporting system established by the FDA
  - analysis of events 1998-2002 reported in Wallis et al *CID* 2004 (summarized in Wallis et al *CID* 2005 Suppl 3)

# Anti-TNF & **fungal** infections

(incidence per 100.000 pts treated, FDA AERS data, 1998-2002)

Infection	Infliximab (n = 197,000)	Etanercept (n = 113,000)	RR	P
Aspergillosis	17 (8.63)	7 (6.19)	1.39	.243
Candidiasis	20 (10.15)	6 (5.31)	1.91	.061
Bartonellosis	1 (0.51)	0 (0)	...	.563
Coccidioidomycosis	11 (5.58)	1 (0.88)	6.31	.013
Cryptococcosis	10 (5.08)	8 (7.08)	0.72	.179
Histoplasmosis	37 (18.78)	3 (2.65)	7.07	<.0001
Legionellosis	1 (0.51)	0 (0)	...	.563
Leprosy	1 (0.51)	0 (0)	...	.563
Listeriosis	17 (8.63)	1 (0.88)	9.75	.0006
Nontuberculous mycobacterioses	22 (11.17)	7 (6.19)	1.80	.066
Nocardiosis	7 (3.55)	1 (0.88)	4.02	.090
Pneumocystosis	1 (0.51)	0 (0)	...	.563
Salmonellosis	0 (0)	2 (1.77)	0.00	.031
Toxoplasmosis	4 (2.03)	0 (0)	...	.101
Tuberculosis	106 (53.81)	32 (28.32)	1.90	<.0001
Total	255 (129.44)	68 (60.18)	2.15	<.0001

**NOTE.** Data are no. of infections (no. of infections/100,000 treated patients), except where noted. *P* values were determined by use of Poisson analysis. RR, risk ratio (infliximab:etanercept).

# Anti-TNF & **fungal** infections

(incidence per 100.000 pts treated, FDA AERS data, 1998-2002)

	<i>Infliximab</i>	<i>Etanercept</i>	<i>P value</i>
<i>Pneumocystis</i>	0.5	<0.5	
Cryptococcosis	~5	~7	
Coccidioidomycosis	~6	~1	0.013
Aspergillosis	~9	~6	
Candidiasis	~10	~5	
Histoplasmosis	~19	~3	<0.01

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	<i>Infliximab</i>	<i>Etanercept</i>	<i>P value</i>
<i>Pneumocystis</i>	0.5	~	
Cryptococcosis			
Coccidioidomycosis			
Aspergillosis			
Candidiasis		~5	
Histoplasmosis	~19	~3	<0.01

**incidence of post-transplant histoplasmosis (Cleveland, Ohio) ~1/1000**  
(Cuellar-Rodriguez et al *CID* 2010)



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## Information for Healthcare Professionals Cimzia (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab), and Remicade (infliximab)

**FDA ALERT [9/4/2008]:** FDA is notifying healthcare professionals that histoplasmosis and other invasive fungal infections are not consistently recognized in patients taking tumor necrosis factor- $\alpha$  blockers (TNF blockers), Cimzia (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab), and Remicade (infliximab). This has resulted in delays in appropriate treatment, sometimes resulting in death.

FDA has received reports of patients developing pulmonary and disseminated histoplasmosis, coccidioidomycosis, blastomycosis and other opportunistic infections while taking TNF blockers. In some patients, the diagnosis of histoplasmosis was initially unrecognized and antifungal treatment was delayed. Some of these patients died from histoplasmosis. There were also deaths in patients with coccidioidomycosis and blastomycosis.

For patients taking TNF blockers who present with signs and symptoms of possible systemic fungal infection, such as fever, malaise, weight loss, sweats, cough, dyspnea, and/or pulmonary infiltrates, or other serious systemic illness with or without concomitant shock, healthcare professionals should ascertain if patients live in or have traveled to areas of endemic mycoses. For patients at risk of histoplasmosis and other invasive fungal infections, clinicians should consider empiric antifungal treatment until the pathogen(s) are identified. Consultation with an infectious diseases specialist should be sought when feasible. As with any serious infection, consider stopping the TNF blocker until the infection has been diagnosed and adequately treated.

FDA will require the makers of the tumor necrosis factor- $\alpha$  blockers (TNF blockers) to further highlight the information about the risk of invasive fungal infections, such as histoplasmosis, in the *Boxed Warning* and *Warnings sections* of the drugs' prescribing information and the Medication Guide for patients. FDA will also require that the makers of the TNF blockers educate prescribers about this risk.

*This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this sheet when additional information or analyses become available.*

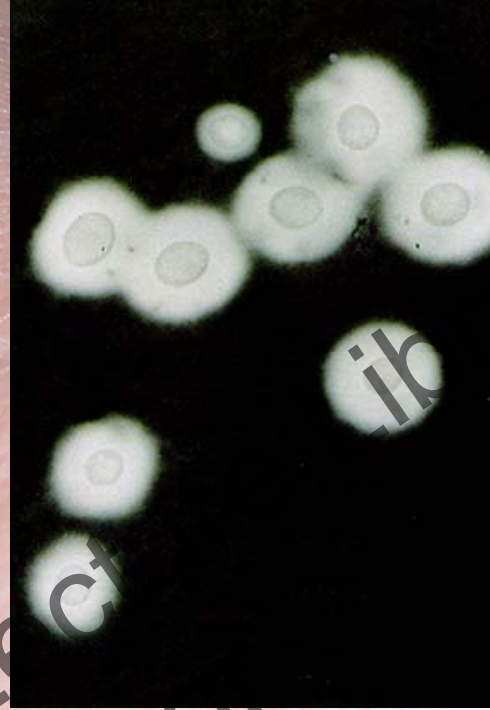
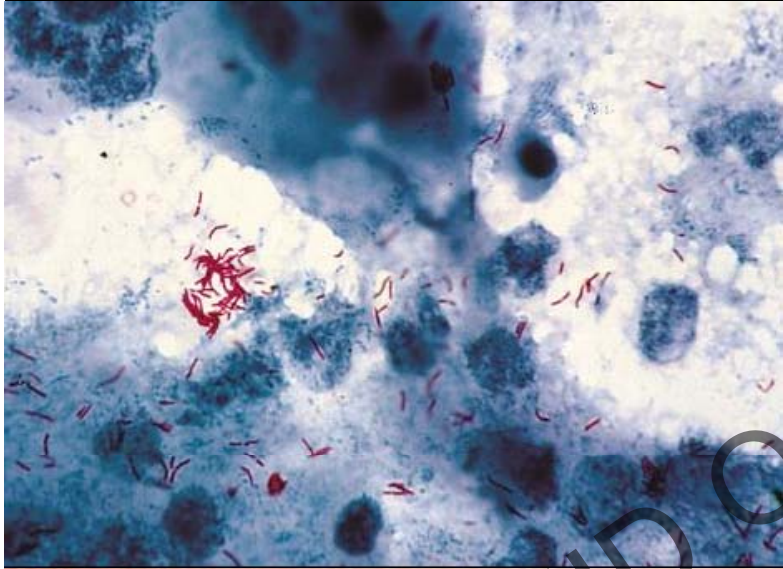
# Summary

- Relatively robust data for anti-TNF („serious“ infection incidence density ~2-10/100)
  - ~1/100 „opportunistic“ incl. granulomatous infection, depending on background endemicity (and many other variables)
  - ↑ aspergillosis and candidiasis
  - ↑ endemic mycoses (less with etanercept)
  - ↑ cryptococcosis
  - NOT or ?: *Pneumocystis jiroveci*
- Difficult-to-interpret data for other biologicals



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# **Fungal Infections Complicating Tumor Necrosis Factor $\alpha$ Blockade Therapy**

SOTIRIOS TSIODRAS, MD, MSc, ScD; GEORGE SAMONIS, MD; DIMITRIOS T. BOUMPAS, MD;  
AND DIMITRIOS P. KONTOYIANNIS, MD, MSc, ScD

***Mayo Clin Proc.* 2008;83(2):181-194**

## **New Immunosuppressive Agents and Risk for Invasive Fungal Infections**

*Georg Maschmeyer, MD, and Thomas F. Patterson, MD*

Current Infectious Disease Reports 2009, 11:435–438