Clinical Risk Factors for Invasive Aspergillosis

February 5, 2010

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Risk Factors for IA

Risk factor: variable associated with an chance of developing something

Types of risk factors for IA:

Clinical- host-related, co-morbidities, transplant variables

Biologic- iron overload, hyperglycemia

Environmental

Host/pathogen interaction

Identifying clinical risk factors for IA:

Clinical Trials

Cohort (usually retrospective)

Case-control studies

Case series

Risk of Invasive Aspergillosis*

Group	Risk (%)
Hematopoietic Stem Cell Transplants	5-10
Solid Organ Transplants	10-15
Hematologic malignancies	5-25
Chronic Obstructive Pulmonary Disease	1-9
HIV/AIDS	0-5
Other Causes (Trauma, ICU, steroids)	4-7
Other immunosuppression	0-??

* Risk defined as cumulative incidence per year

Adapted from Maschmeyer et al., Drugs 2007;67:1567-1601

HSCT Risk Factors

- Age
- Underlying disease
- Stem cell source
- T-cell depleted products
- Corticosteroids (dose, duration)
- Conditioning regimen
- GVHD presence and treatment
- Neutropenia (pre- and post-engraftment)
- Lymphopenia
- CMV disease
- Iron overload
- Elevated ferritin
- Previous IA
- Respiratory viruses
- Antifungal prophylaxis

Marr et al. Blood 2002;100:4358
Girmenia et al, Clin Infect Dis 2009:49;1226-36.
Maschmeyer et al., Drugs 2007;67:1567-1601.
Post MJ et al. Transplant Infect Dise 2007;9:189-195.
Garcia-Vidal et al., CID 2008;47:1041-50

Epidemiology of invasive mold infections in allogeneic stem cell transplant recipients: biological risk factors for infection according to time after transplantation.

Garcia-Vidal et al., Clin Infect Dis 2008:47:1041-50

- Objectives:
  1) Analyze risk factors for IMI after HSCT
  2) Differentiate risk factors for early vs. late IMI
  3) Evaluate biological risk factors
- 1248 HSCT patients evaluated (1998-2002)
- 163 IMI cases, 142 (87%) with IA

Garcia-Vidal et al., CID 2008;47:1041-50.

Garcia-Vidal et al.

Risk Factors (for IMI) per multivariable analysis:

- Older age
- CMV disease
- Respiratory virus infection (influenza, parainfluenza)
- Severe acute GVHD
- Cell-line cytopenias
- High frequency of blood transfusions

Garcia-Vidal et al., CID 2008;47:1041-50

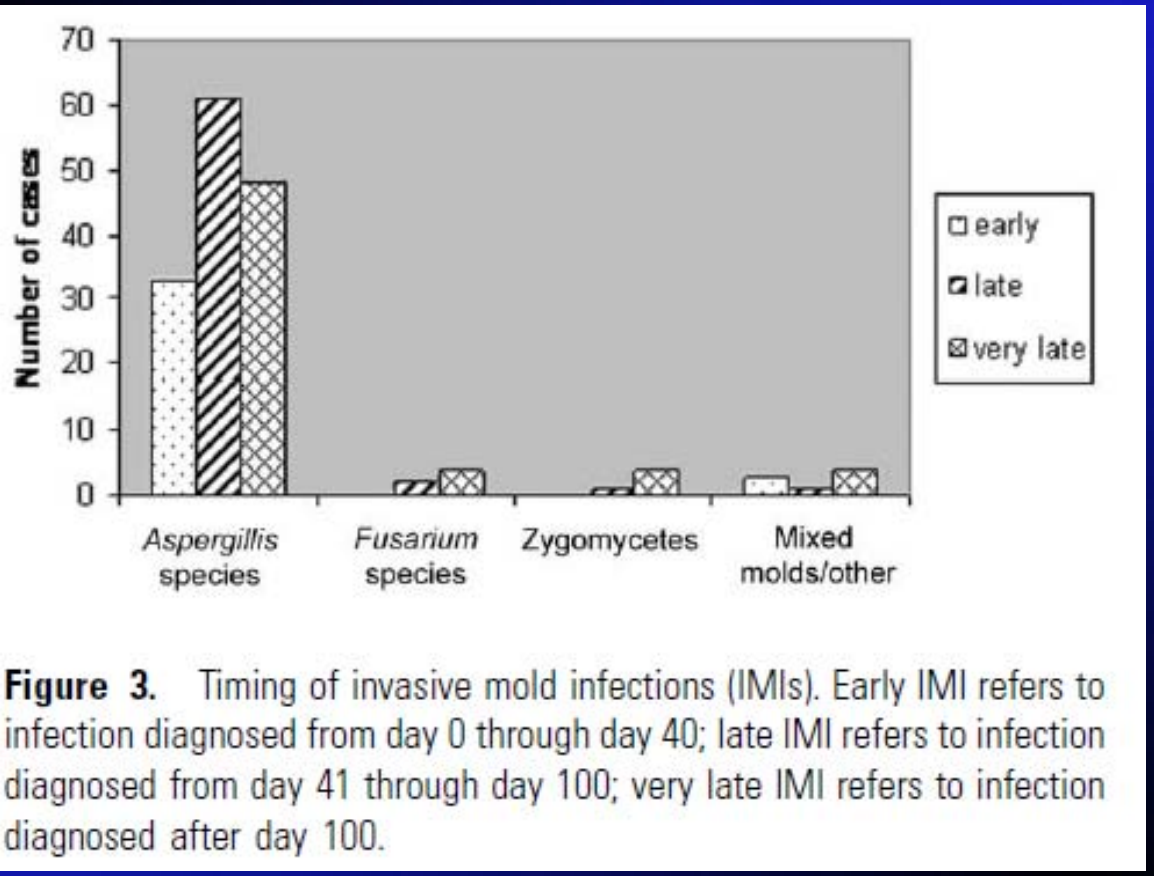


Figure 3. Timing of invasive mold infections (IMIs). Early IMI refers to infection diagnosed from day 0 through day 40; late IMI refers to infection diagnosed from day 41 through day 100; very late IMI refers to infection diagnosed after day 100.

Garcia-Vidal et al., CID 2008;47:1041-50.

Garcia-Vidal et al.

Early (1-39)

- Unrelated donor
- HLA mismatch
- ATG
- CMV disease
- Transfusion
- Corticoseroids
- Hyperglycemia
- Lymphopenia
- Ferritin level

Late (40-100)

- Sex (female)
- Age
- CMV disease
- Transfusion
- Acute GVHD
- Corticosteroids

Garcia-Vidal et al., CID 2008;47:1041-50.

WELCOME TO ROME!

Lower respiratory tract infections increase risk of aspergillosis after a reduced-intensity allogeneic hematopoietic SCT

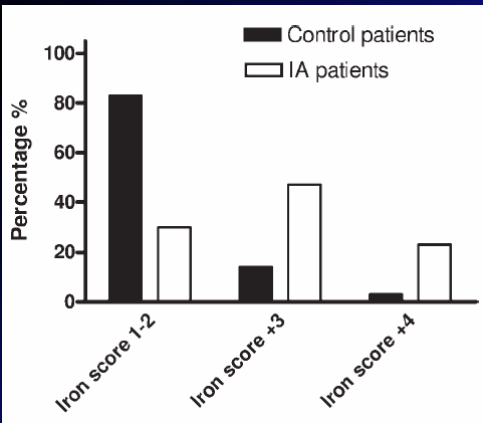
Martino et al, Bone Marrow Transplantation 2009 44;749

- Analyzed 219 patients with reduced intensity conditioning (fludarabine + BU or melphalan) transplanted between 1997-2007.
- Prospectively monitored patients for IA, viral infections
- 4-year cumulative incidence of IA was 15%
- 27 patients developed IA
- **Risk factors** (multivariable analysis):
  - -Steroid therapy for moderate-to-severe GVHD
  - -CMV disease
  - -**Viral lower respiratory tract infection**
    (HR 4.3, 95% CI 2-9.4)
- **Viruses:** influenza A/B, parainfluenza virus, RSV, metapneumovirus, adenovirus

Increased bone marrow iron stores is an independent risk factor for IA in patients with high-risk hematologic malignancies and recipients of allogeneic hematopoietic stem cell transplantation.

Kontoyiannis et al., Cancer 2007; 110:1303-6.

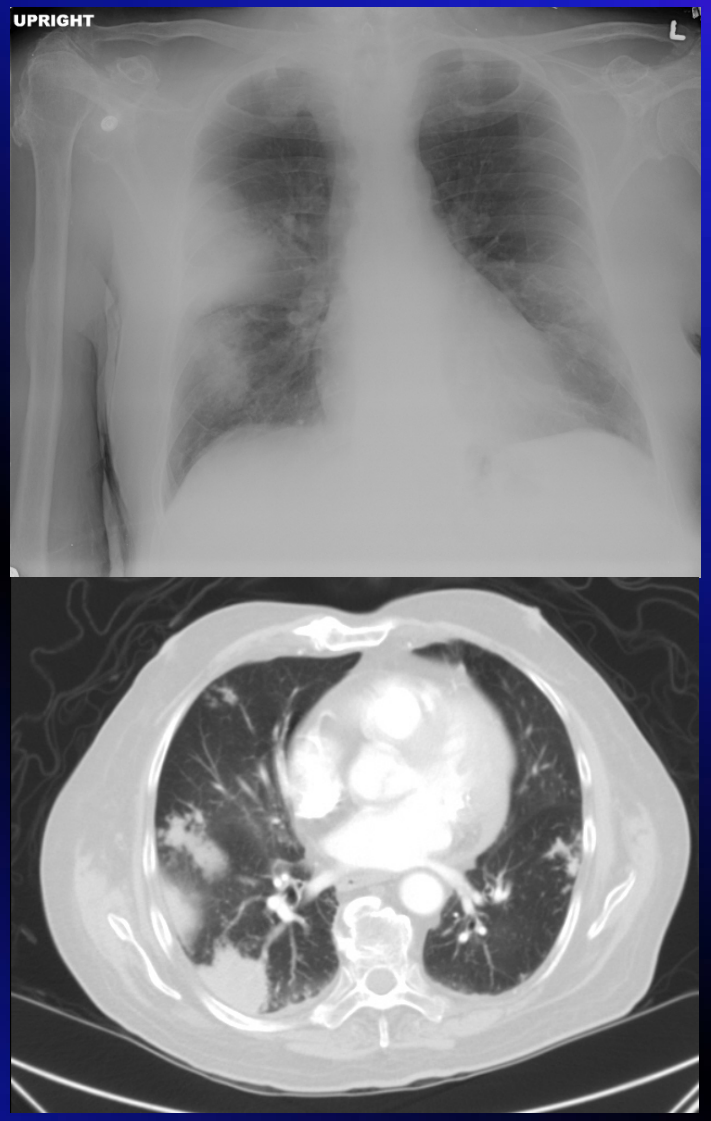
- Compared 33 patients with IA and 33 high-risk patients without IFI (9/2002-3/2003)
- Calculated and compared bone marrow iron stores and other characteristics
- Patients similar, except APACHE II greater in cases
- 23 (70%) cases, compared with 6 (18%) controls had elevated iron stores ($p<0.001$)
- Increased BMIS and APACHE II were independent predictors of IA (logistic regression)



Kontoyiannis et al, Cancer 2007;110:1303-6

Cancer Patients

- Neutropenia
- Type of cancer
- Corticosteroid use
- Chemotherapy



Maschmeyer et al., Drugs 2007;67:1567-1601
Rubio et al., J Pediatric Hematol Oncol 2009; 31:642-646.

Clinical characteristics of 45 patients with invasive aspergillosis. Restrospective analysis of 1711 lung cancer cases.

Yan et al., Cancer 2009;115:5018-25.

- All lung cancer patients with IPA seen during 2000-2007 were evaluated
- 45 (2.63%) cases of IPA in 1711 lung cancer patients
- **Risk Factors:**

  -Stage IV cancer

  -Chemotherapy (preceding month)

  -Corticosteroid therapy > 3 days

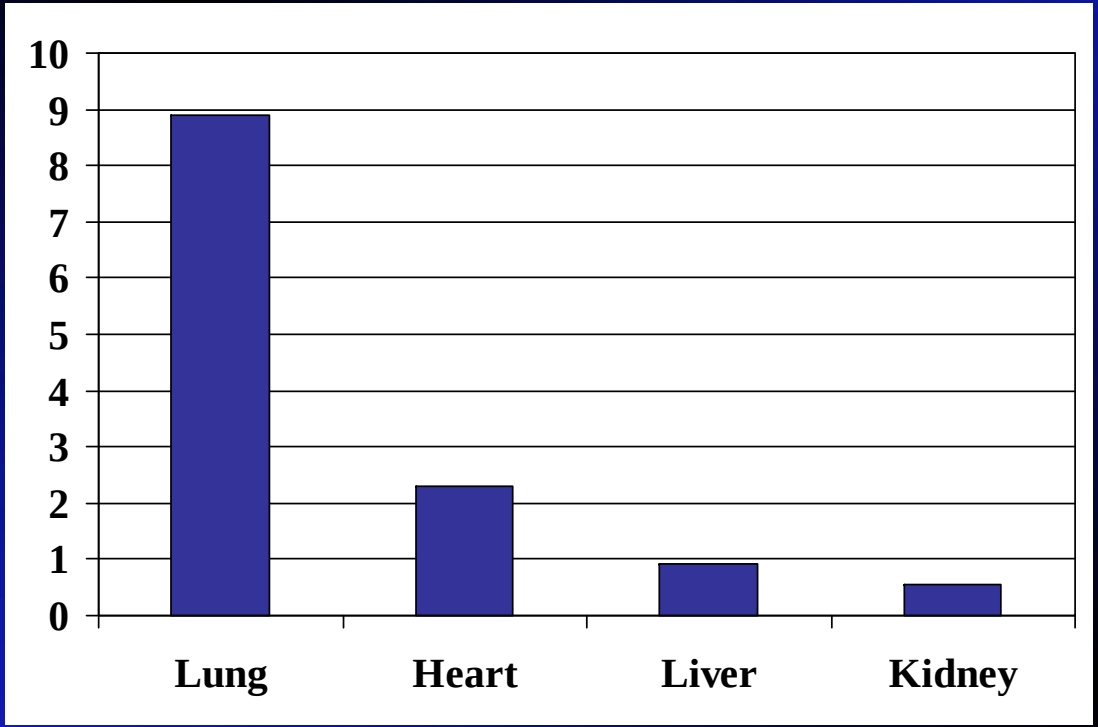
Solid Organ Transplants

- **Lung**: Single lung, rejection, reperfusion injury, *Aspergillus* colonization, anastamotic site ischemia, hypogammaglobulinemia, CMV, cystic fibrosis(?), antifungal prophylaxis(?)
- **Liver**: Poor allograft function, pre-transplant hepatic failure, Re-transplantation, renal insufficiency, dialysis, high transfusion requirement, iron overload, steroids, ICU stay
- **Heart**:?
- **Kidney or Kidney/Pancreas**: ?

Silveira and Husain, Medical Mycology 2007;45:305-20.
Paterson and Singh, Medicine 1999:78:123-38.

IA in SOTs

Expressed as IA cases per 100 patients transplanted



TRANSNET, unpublished data
Permission from Tom Chiller and Pete Pappas

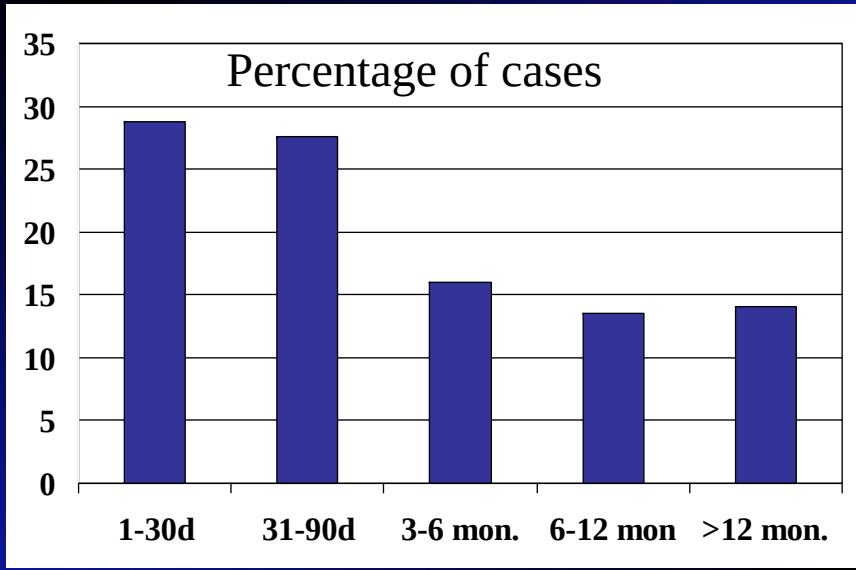
Risk factors for invasive aspergillosis in solid organ transplant recipients: a case-control study

Gavalda et al., Clinical Infectious Diseases 2005:41:52-9.

- Retrospective case-control study of 156 cases of proven/probable IA, matched to 312 controls
- 11 Spanish centers (REISTRA), total of 11,014 SOT patients
- Study period: transplant program start date to 2001

- **IA Cases:**

Liver	80 (51.3%)
Heart	47 (30.1%)
Lung	17 (10.9%)
Kidney	10 (6.4%)
Kidney/Pancreas	2 (1.3%)



Gavalda et al.

Early (<3 months)

- CMV mismatch
- ICU stay
- Renal failure
- Hepatic failure
- Hemodialysis
- >1 bacterial infection
- CMV disease

Late (>3 months)

- Age > 50 years
- Renal failure
- Immunosuppressive use
- > 1 bacterial infection
- Chronic-graft rejection
- Immunosuppression-related neoplasm

Gavalda et al., CID 2005;41:52-59

IA in the ICU

- Potentially emerging problem (247,000 Google hits 1/15; 248,000 hits 2/1)
- Incidence of up to 6% in Medical ICUs
- **Non-traditional groups at risk:**
  - Corticosteroid use
  - **COPD**
  - Cirrhosis
  - HIV
  - Malnutrition
  - Prolonged antibiotic use

Meerssemen et al., CID 2007:45:205-16

IA in COPD Patients

- Increasing reports of the importance of COPD as a risk factor or an underlying co-morbidity in patients with IA
- It is estimated that up to 10% of cases of IA occur in patients with COPD and up to 5% of patients with COPD have IA.
- Mortality in COPD patients with IA ranges from 30-100%
- Problem: certainty of diagnosis of IA
- **Risk factors- few data:**
  - -Corticosteroid treatment (daily oral doses of >20 mg of prednisone)
  - -Previous antibiotic use
  - -Late-stage COPD
  - -Viral infection
  - -Inhaled steroids

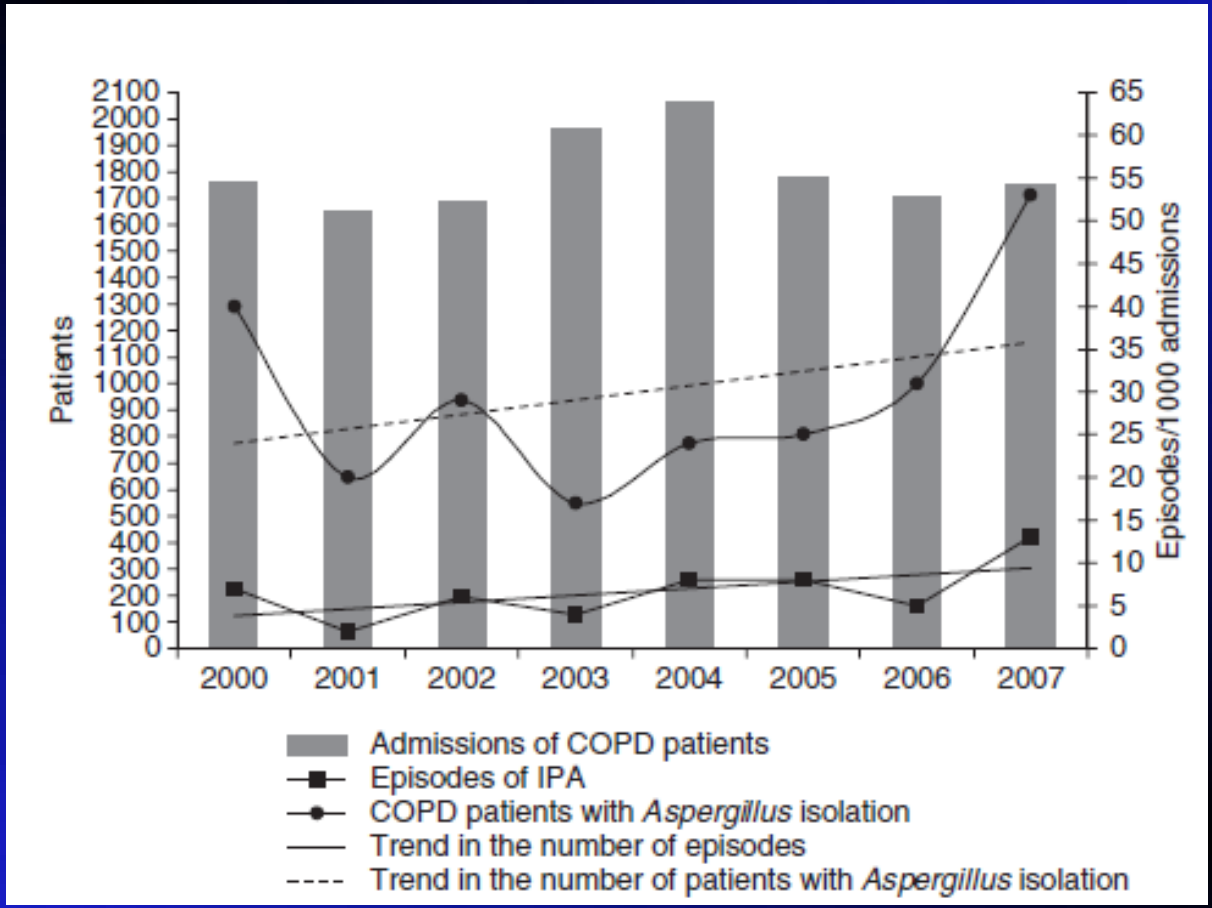
Rello et al. Clin Infect Dis 1998;26(6):1473-5.
Vandewoude et al. Acta clinica Belgica 2004;59(5):251-7.
Guinea et al. Clin Microbiol Infect 2009.
Denning DW. American J Resp Crit Care Med 2004;170(6):580-1.

Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome.

Guinea et al. Clinical Microbiology and Infection 2009

- Retrospective study of COPD admissions who had isolation of *Aspergillus* from a pulmonary sample (2000-2007)
- 14, 618 with COPD, 239 of whom had positive *Aspergillus* respiratory tract cultures
- 53 cases of probable IA identified (3.6 cases/1000 COPD admissions)
- IPA present in 22% of cases of COPD with positive *Aspergillus* cultures

IA in COPD Patients



Guinea et al, *Clin Microbiol* Infect 2009

Risk Factors for IA in COPD

Factor	OR	95% CI
ICU admission	2.4	1.09, 5.29
Steroids[1]	2.98	1.26, 7.0
Steroids[2]	4.67	2.02, 10.3
Antibiotic use	2.57	1.2, 5.4
Chronic HF	2.1	0.98, 4.5

[1] accumulated dose prior to admission

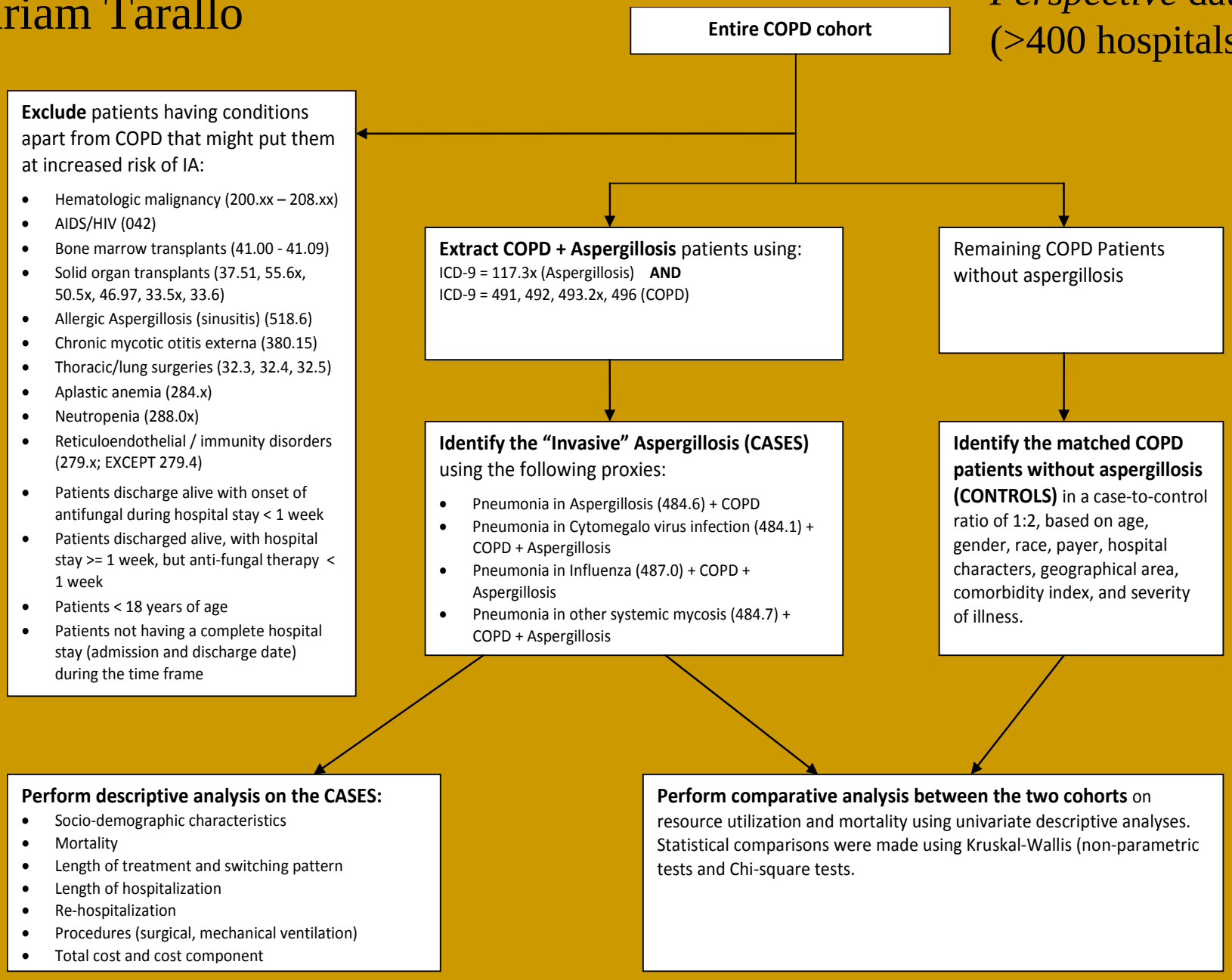
[2] accumulated dose during admission

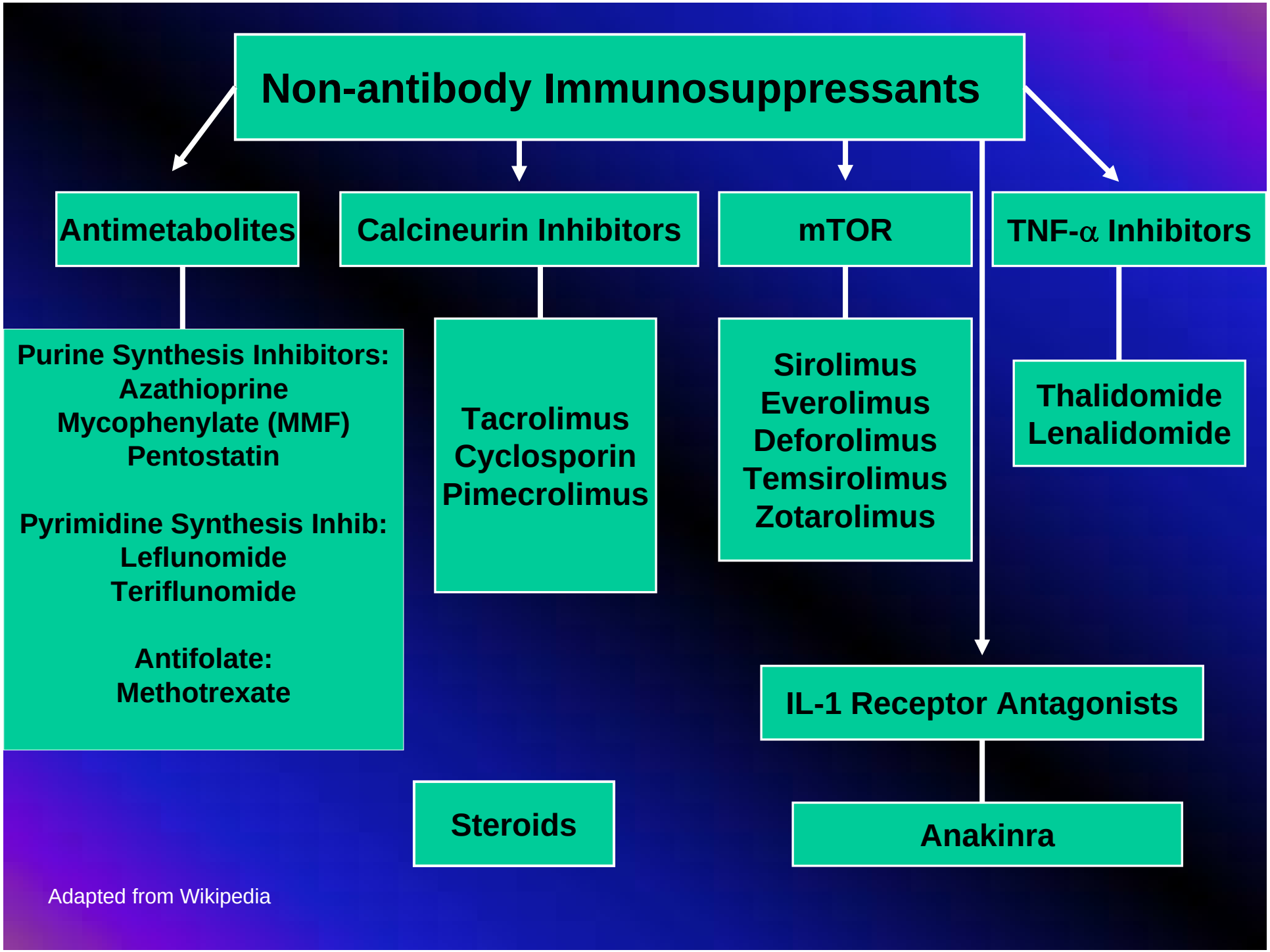
Guinea et al, *Clin Microbiol* Infect 2009

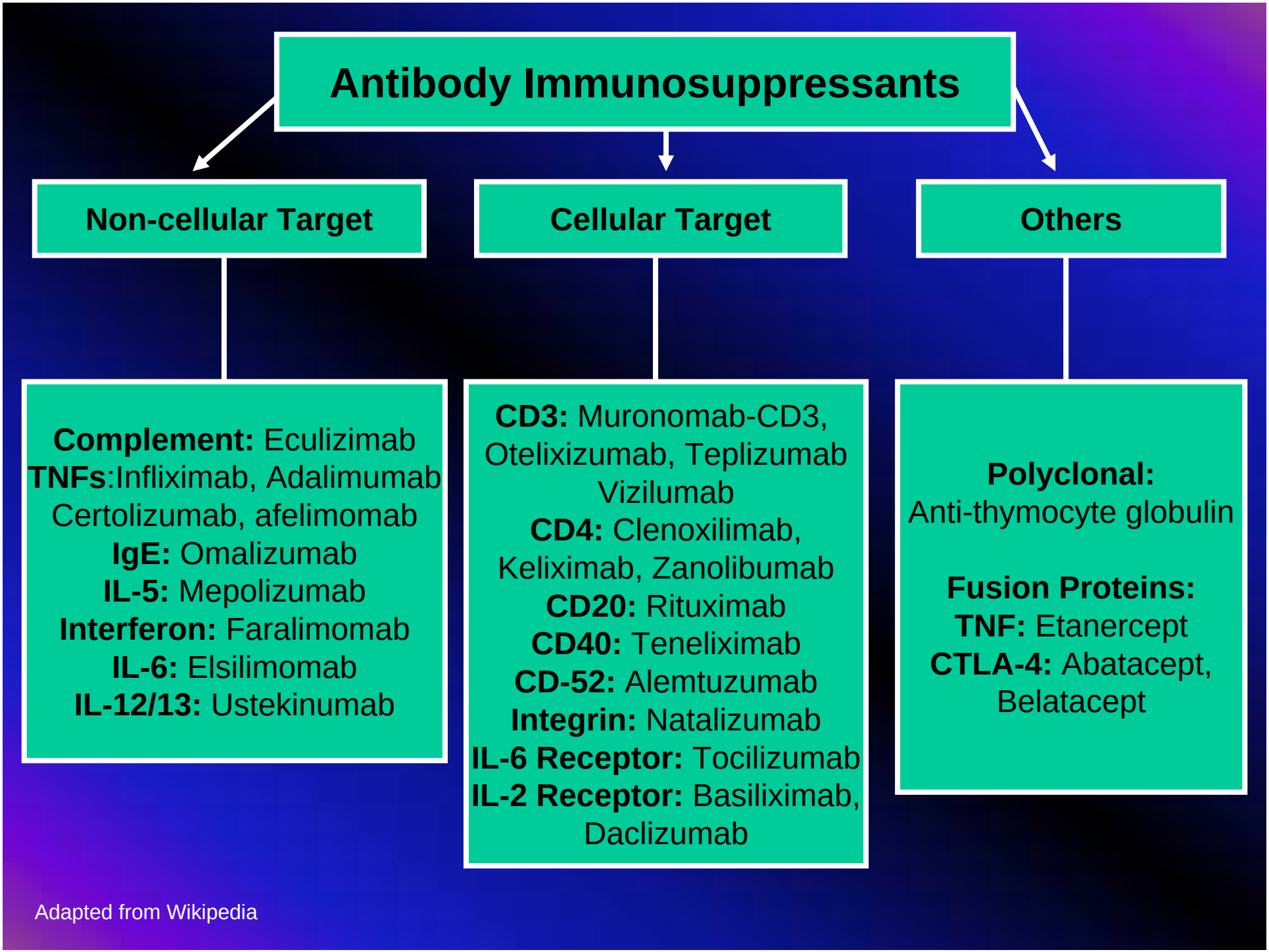
Thanks to
Miriam Tarallo

Study Design Schematic

Perspective database
(>400 hospitals)




Non-antibody Immunosuppressants
Antimetabolites
Calcineurin Inhibitors
mTOR
TNF-α Inhibitors
Purine Synthesis Inhibitors:
Azathioprine
Mycophenylate (MMF)
Pentostatin
Pyrimidine Synthesis Inhib:
Leflunomide
Teriflunomide
Antifolate:
Methotrexate
Tacrolimus
Cyclosporin
Pimecrolimus
Sirolimus
Everolimus
Deforolimus
Temsirolimus
Zotarolimus
Thalidomide
Lenalidomide
IL-1 Receptor Antagonists
Steroids
Anakinra
Adapted from Wikipedia


Antibody Immunosuppressants
Non-cellular Target
Cellular Target
Others
Complement: Eculizimab
TNFs:Infliximab, Adalimumab
Certolizumab, afelimomab
IgE: Omalizumab
IL-5: Mepolizumab
Interferon: Faralimomab
IL-6: Elsilimomab
IL-12/13: Ustekinumab
CD3: Muronomab-CD3,
Otelixizumab, Teplizumab
Vizilumab
CD4: Clenoxilimab,
Keliximab, Zanolibumab
CD20: Rituximab
CD40: Teneliximab
CD-52: Alemtuzumab
Integrin: Natalizumab
IL-6 Receptor: Tocilizumab
IL-2 Receptor: Basiliximab,
Daclizumab
Polyclonal:
Anti-thymocyte globulin
Fusion Proteins:
TNF: Etanercept
CTLA-4: Abatacept,
Belatacept
Adapted from Wikipedia

Background: Anti-TNF Therapy

- **Tumor Necrosis Factor:** expressed in many cells of the immune system and induces responses in both innate and adaptive immunity
- Transmembrane and soluble forms that differentially bind to two TNF receptors
- **Roles:**
    1) Recruitment of inflammatory cells
    2) Activates macrophages
    3) Regulates inflammation (induces apoptosis)

- TNF-RI (p55)- role in inflammation and granuloma formation
- TNF-RII (p75)- affects survival of macrophages

Ehlers, CID 2005
Rigby, Nature Rheum 2007

Anti-TNF and Aspergillosis

TABLE 2. **Fungal Infections Associated With Anti–Tumor Necrosis Factor α Therapy**[a]

Infectious agents	Infliximab	Etanercept	Adalimumab
Aspergillus species (n=64)	48	14	2
Zygomycetes (n=4)	3	NC	1
Candida species (n=64)	54	9	1
Cryptococcus species (n=28)	17	10	1
Blastomyces species (n=2)	ND	ND	ND
Coccidioides species (n=29)	27	2	NC
Histoplasma species (n=84)	72	8	4
Sporothrix species (n=1)	1[b]	NC	NC
Prototheca species (n=1)	1	NC	NC
Tinea or pityriasis versicolor (n=6)	3	1	2
Total	226	44	11

[a] ND = no data available; NC = no cases identified.
[b] In this case etanercept was used as well, but symptoms worsened while the patient received infliximab.

Tsiodras et al., Mayo Clin Proc. 2008;83:181-94

Differential Effects of TNF-α Inhibitors

Pathogen, type of infection	Infliximab group (n = 233,000)	Etanercept group (n = 113,000)	Rate ratio	P
Mycobacterium tuberculosis	335 (143.8)	39 (34.5)	4.17	<.001[a]
Histoplasma capsulatum	39 (16.7)	3 (2.7)	6.30	<.001[b]
Candida species				
Any	38 (16.3)	8 (7.1)	2.30	.006[b]
NS	26 (11.2)	7 (6.2)	1.80	.065[b]
Systemic	10 (4.3)	1 (0.9)	4.85	.046[b]
Listeria species	36 (15.5)	2 (1.8)	8.73	<.001[b]
Mycobacterium species (NS)	30 (12.9)	7 (6.2)	2.08	.023[b]
Aspergillus species	29 (12.4)	10 (8.8)	1.41	.17[b]
Cryptococcus species	11 (4.7)	8 (7.1)	0.67	.91[b]
Nocardia species	10 (4.3)	1 (0.9)	4.85	.046[b]
Salmonella species	7 (3.0)	4 (3.5)	0.85	.75[b]
Toxoplasma species	5 (2.1)	0 (0)	…	.088[b]
Brucella species	2 (0.9)	0 (0)	…	.38[b]
Bartonella species	1 (0.4)	0 (0)	…	.62[b]
Leishmania species	1 (0.4)	0 (0)	…	.62[b]
Mycobacterium leprae[c]	1 (0.4)	0 (0)	…	.62[b]
Overall	556 (238.6)	83 (73.5)	3.25	<.001[a]

NOTE. Data are no. of patients (no. per 100,000 patients who received the drug). NS, species was not specified.

[a] By χ^2 analysis.
[b] By Poisson analysis.
[c] Resulted in leprosy.

Wallis et al., CID 2004

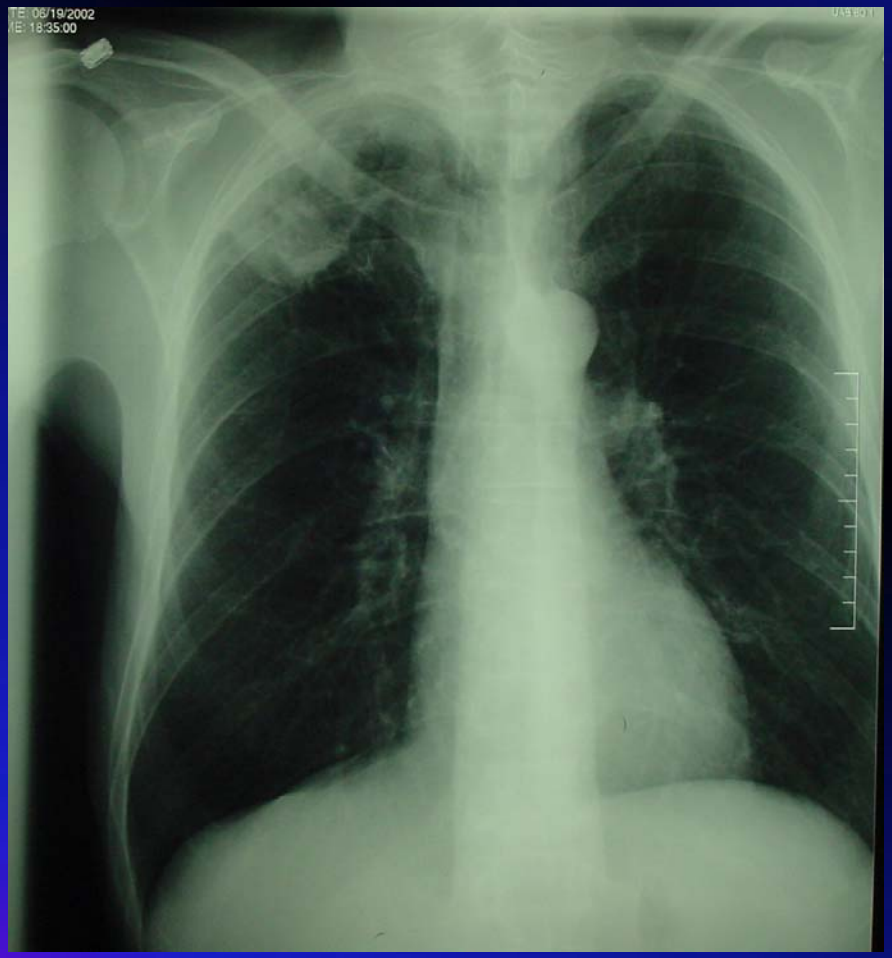
Anti-TNF and Aspergillosis

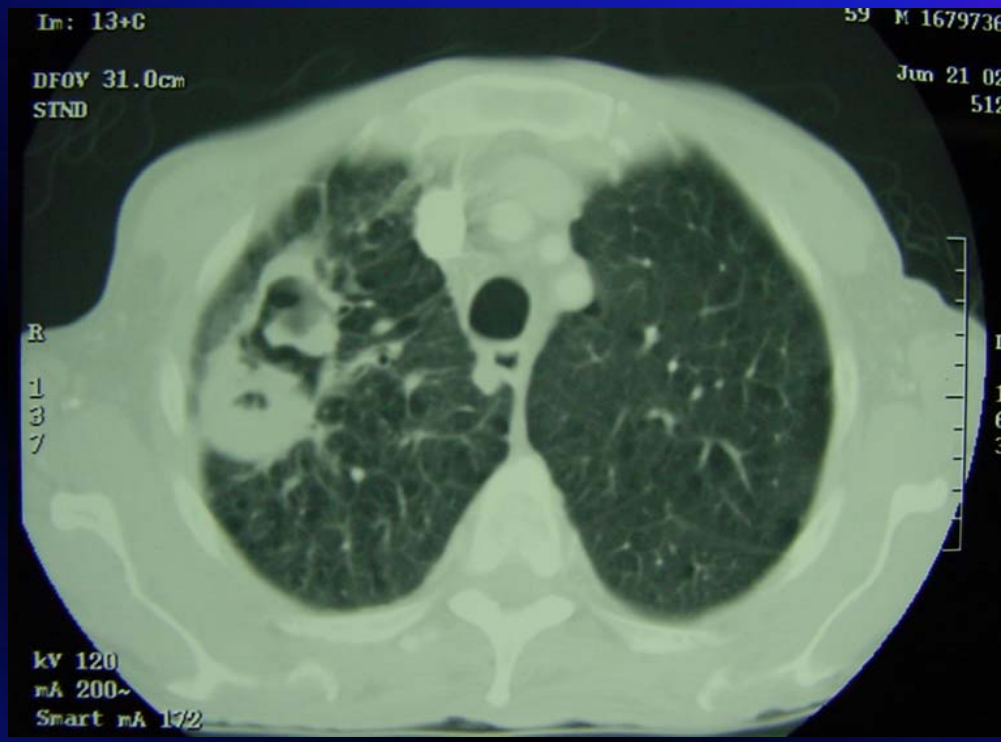
Multiple Studies/Registries In Progress:

1) Biologics Safety Project (SABER)
   -AHRQ/FDA-funded
   -Databases from CMS, TennCare, Kaiser Permanente

2) US Veteran's Health Administration database
   -330,000 unique RA/inflammatory arthritis patients

3) German biologics register (RABBITT) (2001-present)





AIDS and Aspergillosis

HIV and Aspergillosis

- Relatively uncommon infection, with an overall incidence of <1%. Is it increasing?
- 2003 NIS database of 10,400 aspergillosis cases, 3.7% in HIV-infected, incidence of 0.43%[1]
- **Risk Factors:**
  - -Advanced AIDS
  - -Neutropenia (zidovudine, sulfa)
  - -Steroids
  - -Antibiotics
  - -Marijuana or alcohol use
  - -Previous *Pneumocystis* infection
  - -Tuberculosis?

[1] Tong et al, Int J Infect Dis 2009;13;24-36

Conclusions

- Increasing groups at risk for IA
- Data on clinical risk factors are lacking for certain groups (TNF, SOTs)
- Timing is everything
- Interest in biologic factors
- Tailoring prevention strategies to risk factors is the goal