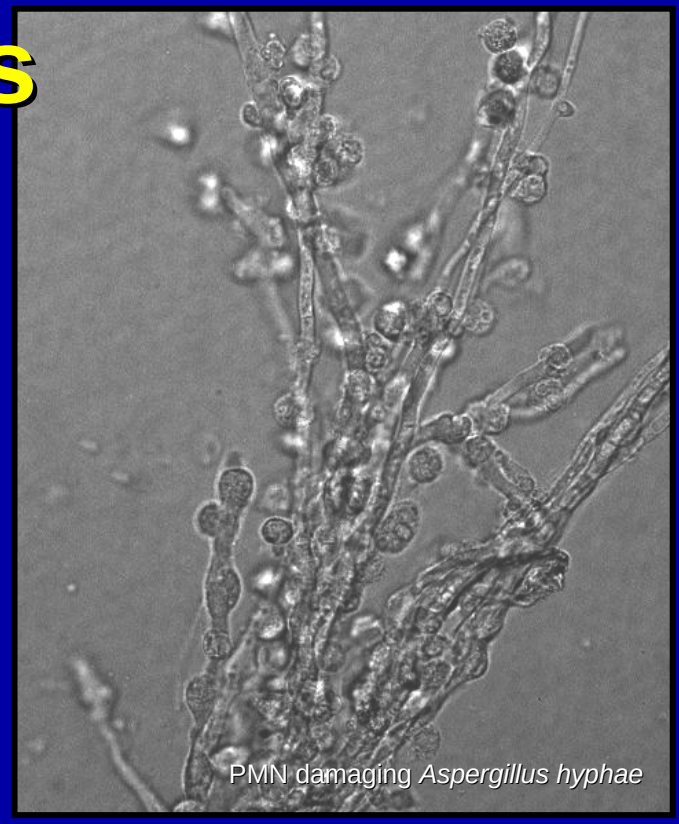
Invasive Aspergillosis in Steroid-Treated Patients


PMN damaging *Aspergillus hyphae*

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Outline

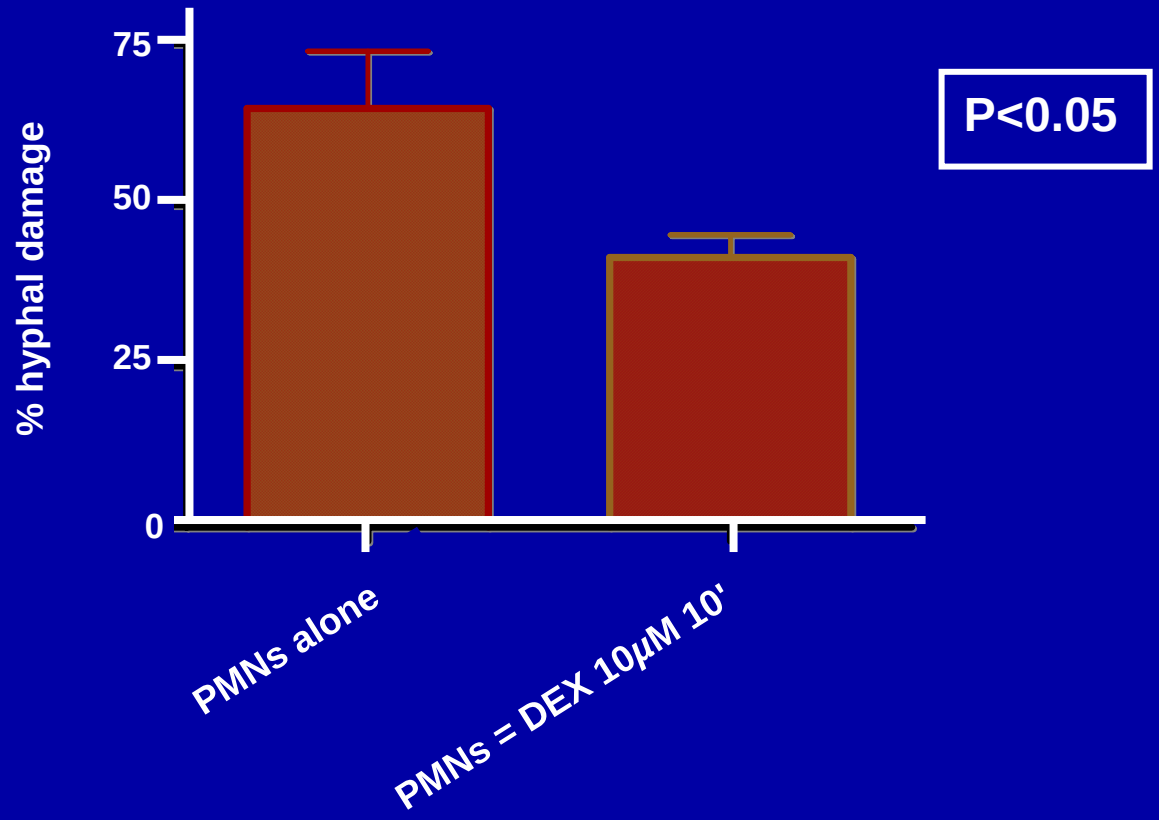
- Steroids as a risk factor of IA
- New insights into the immunobiology of steroid-associated IA
  - ・Implications for diagnosis
  - ・Implications for treatment
- Unanswered questions and future directions

Pleiotropic effects of steroids on host immunity against *Aspergillus*

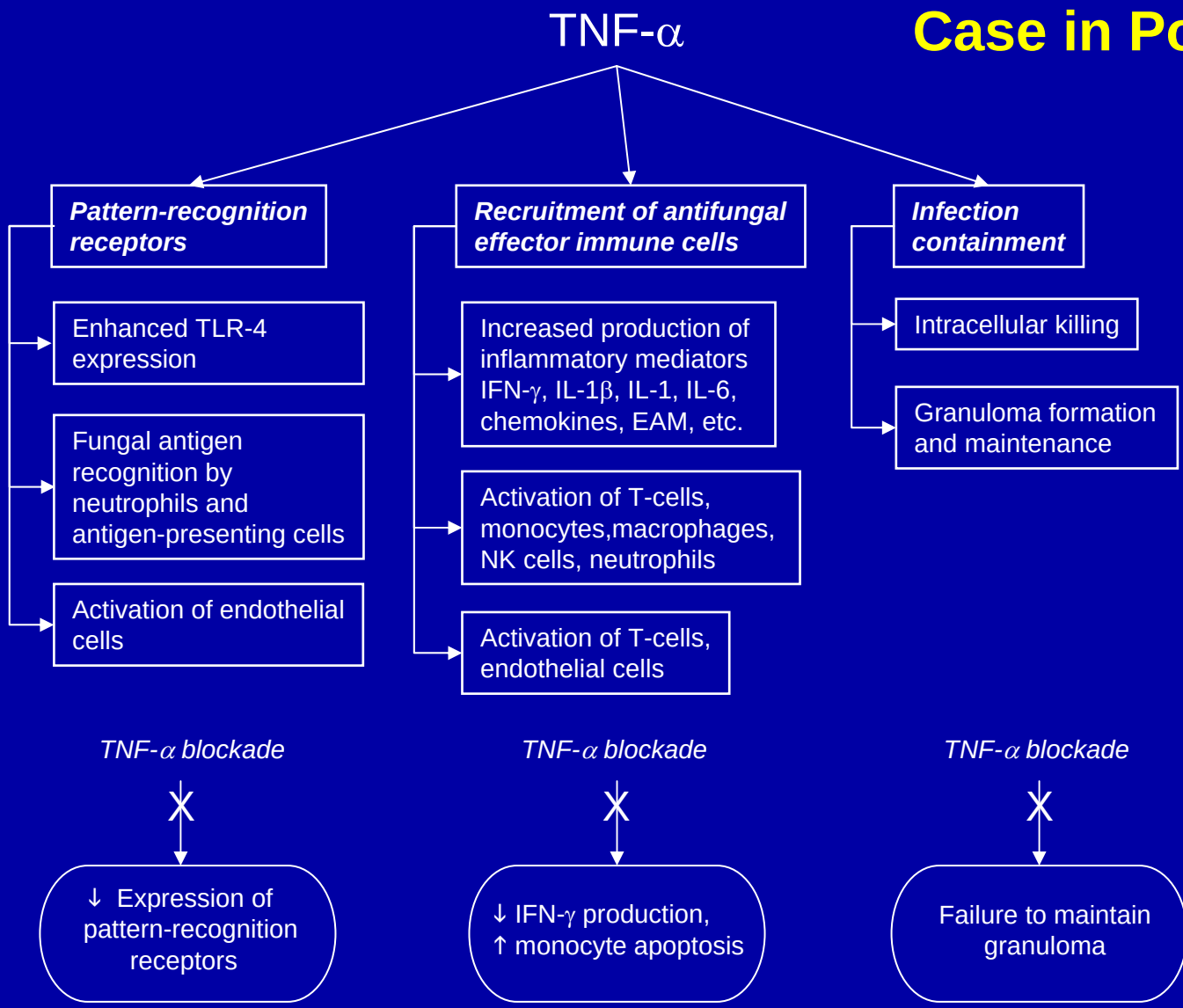
- Lymphocytes
  - Lymphopenia, decreased lymphokine production (e.g, TNF, g-INF), Th1/Th2 dysregulation
- Neutrophils
  - Defective chemotaxis, phagocytosis, degranulation, NO production, adherence
- Monocytes-Macrophages
  - Monocytopenia, inhibition of pro-inflammatory cytokine production, decreased chemotaxis, impaired phagocytosis, impaired antigen-presenting capacity by dendritic cells

Lionakis M & Kontoyiannis DP. Lancet 2003

Effect of dexamethasone exposure on the *Aspergillus* hyphae killing capacity of PMN

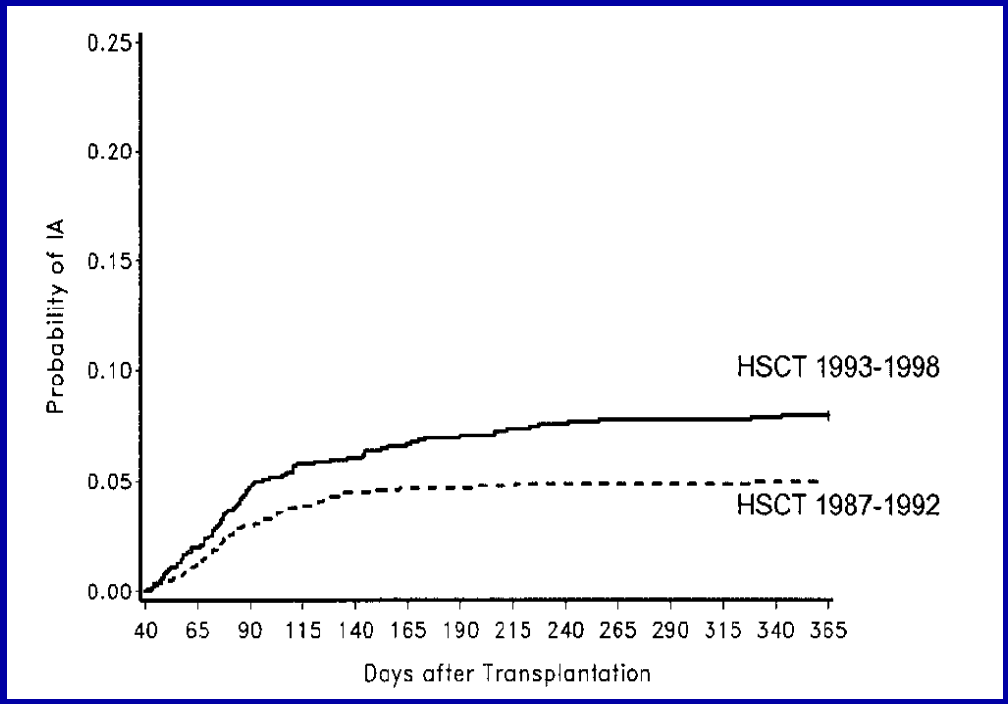


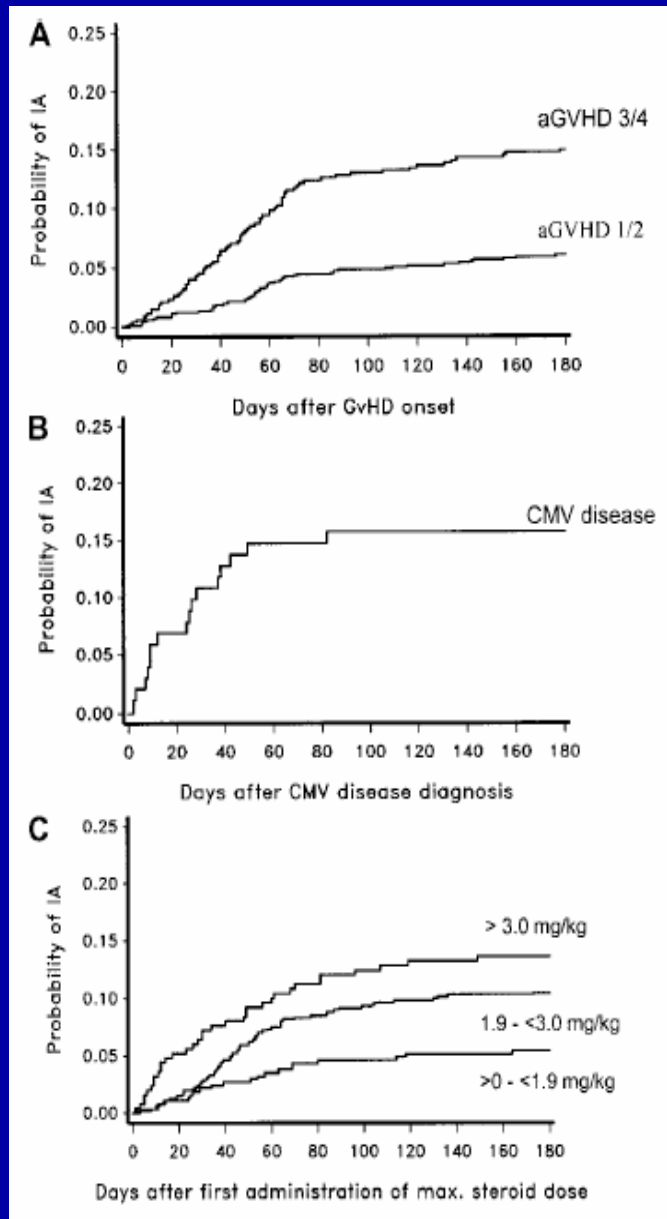
Case in Point: TNF-α



Tsiodras N and Kontoyiannis DP. Mayo Clinic Proceedings, in press

Steroids : A Major Risk Factor for IA in Allogeneic Stem Cell Recipients





Marr et al. *Blood* 2002;100:4358-66.

Corticosteroid-Associated IA

"Emerging" or less common risk groups

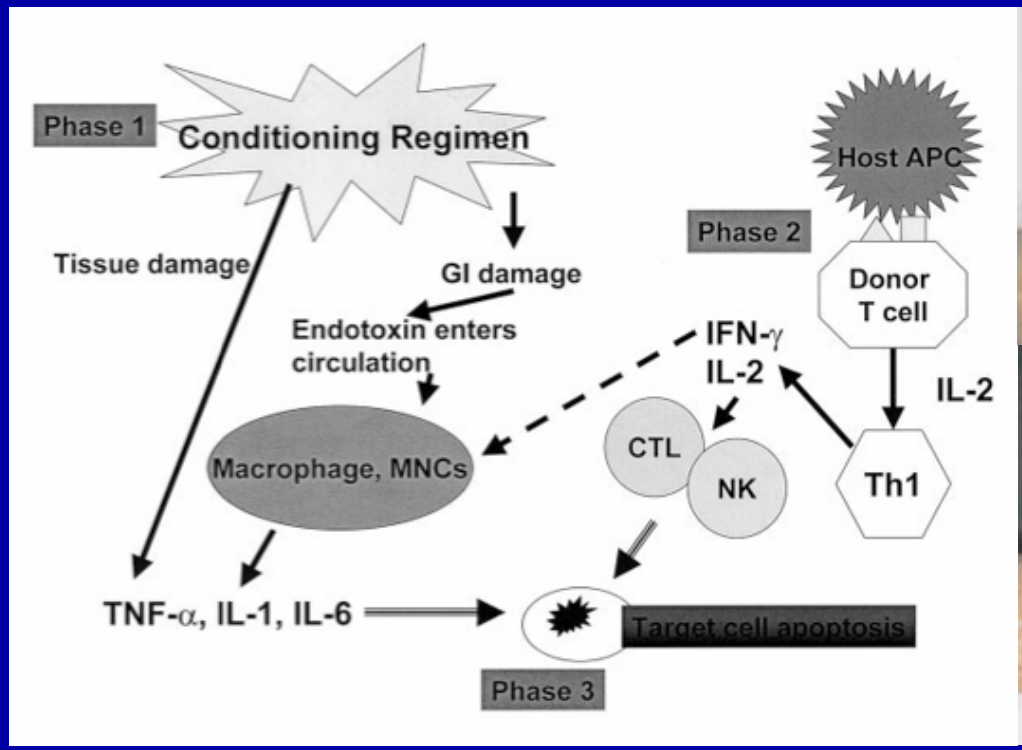
- **Multiple myeloma (Lotholary O et al. CID 2000)**
- **Solid tumors and lymphoma**
- **SLE (Iriya SM et al. Arch Int Med 2001), Wegener's and other illnesses on chronic steroids (e.g., NS, ITP)**
- **AIDS (Khoo SH & Denning DW. CID 1994)**
- **Solid organ transplantation (Patterson JE. Trans Inf Diseas 1999)**
- **Inhaled high potency corticosteroids for asthma or COPD (Peter E et al. CID 2002)**

Steroids-rarely come as a sole risk factor in Hematology patient: Hyper-CVAD

- **Hyper-CVAD** (Course 1,3,5,7)
  - Cyclophosphamide 300 mg/m^2 over 3° q12h x days
    - MESNA 600 mg/m^2/d CI days 1-3
    - Vincristine 2 mg IV days 4,11
    - Adriamycin (Doxorubicin) 50 mg/m^2 IV day 4
    - Dexamethasone 40 mg PO daily (day 1-4, 4-11)
    - G-CSF support

- **MTX/HIDAC** (Courses 2,4,6,8)
  - MTX 200 mg/m^2 IV x 2° followed by 800 mg/m^2 on day#1
  - Leucovorin rescue (15 mg q6°x 8doses)
  - Ara-C 3g/m^2 IV x 2° q12h x 4 doses, day #2,3
  - Methylprednisolone 50 mg IV q12h, Days 1-3

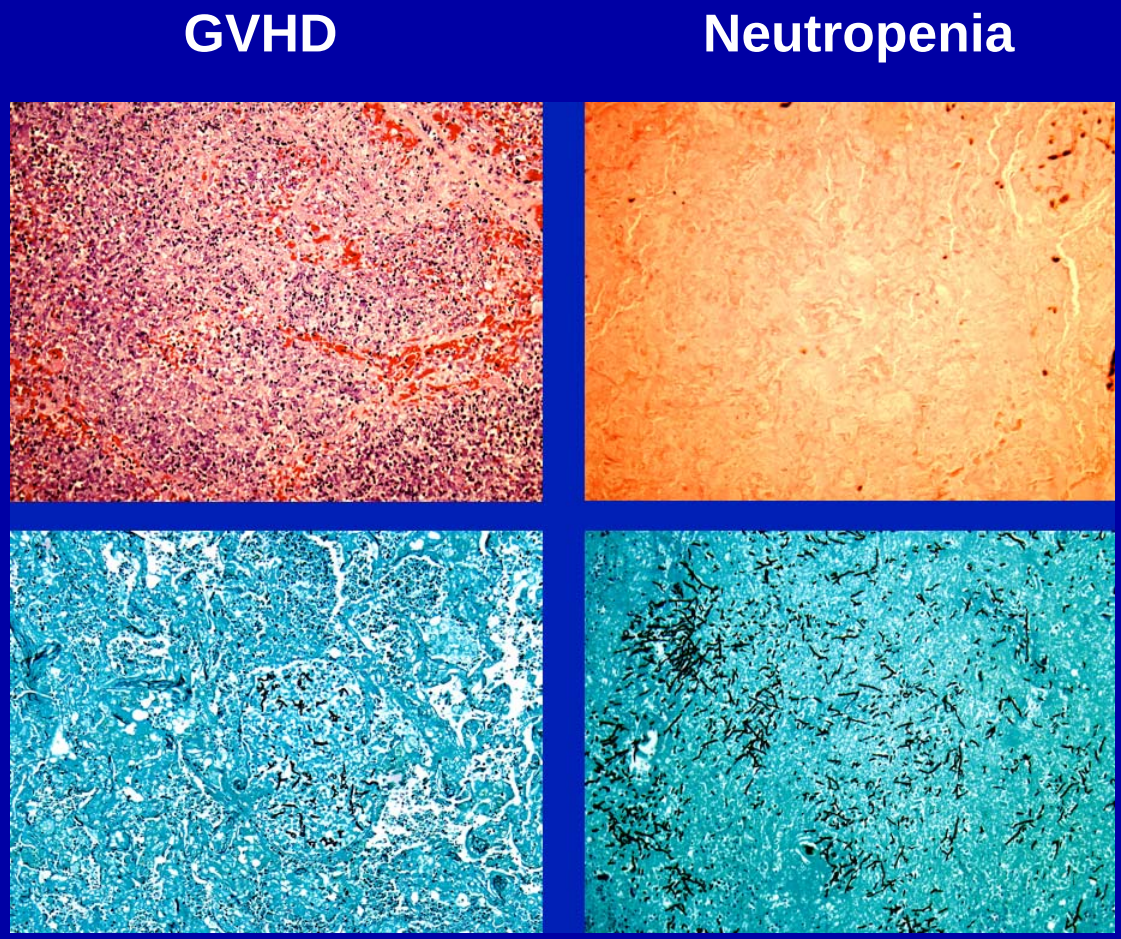
Steroids Rarely Come as the Sole Risk Factor in The SCT Patient: acute GvHD



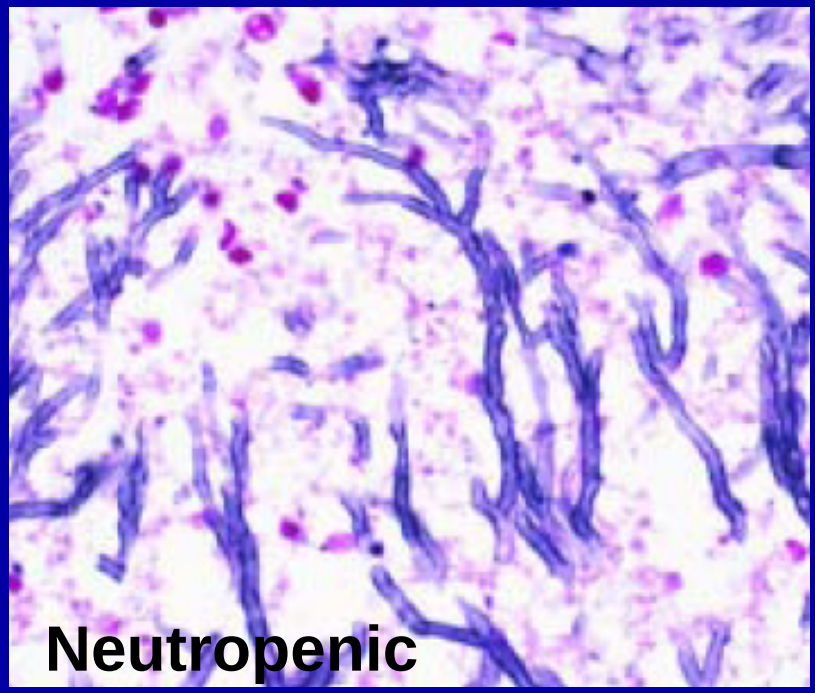
Severe Immunosuppression !

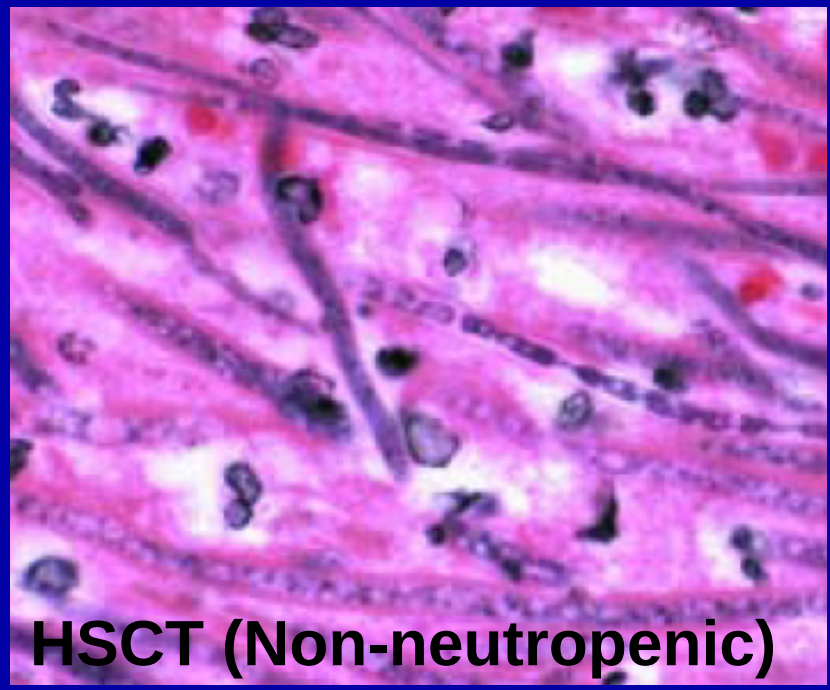
Couriel et al. Cancer 2004;101:1936-46.

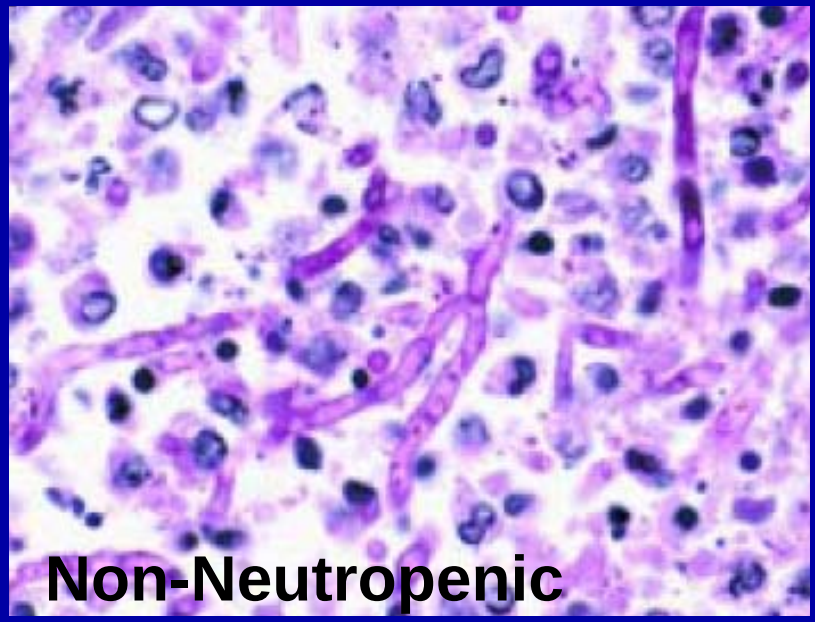
Representative Histopathology of IPA at Autopsy in Neutropenia vs. GVHD



Chamilos et al. *Haematologica* 2006;91:986-9.







Disabled PMN trafficking in GVHD pts treated with steroids?

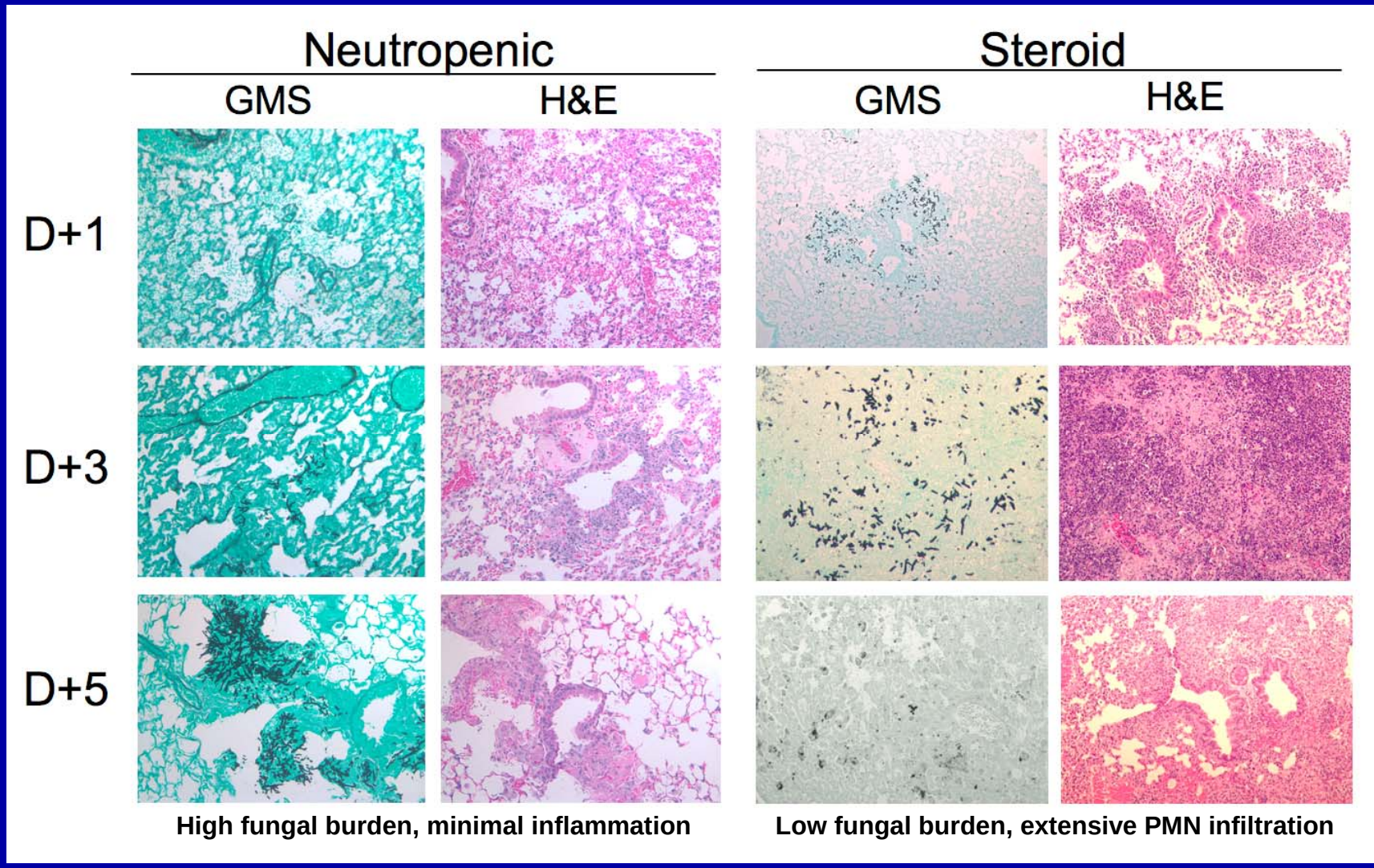
Stergiopoulou T et al. AJCP 2007

Differences in the Pathogenesis of Experimental Invasive Pulmonary Aspergillosis

	Corticosteroid-induced immunosuppression	Chemotherapy-induced neutropenia
Cellular trafficking in BALF	Rapid and extensive increase in PMN	No influx of PMN
TNF-alpha concentration in BAL	Not detected	High
IL-10 concentration in BALF	Low	High
Histological features	Inflammation +++	No inflammatory exudate Necrosis with hyphae +++
Presence of fungal elements	Small numbers of conidia Paucity of angioinvasion	Large numbers of invading, frequent dissemination
Chitin levels in organs	Low in al organs	High in all organs
Galactomannan levels in organs	Low to very low	High
Dominant mechanism	**Adverse host response**	**Fungal development**

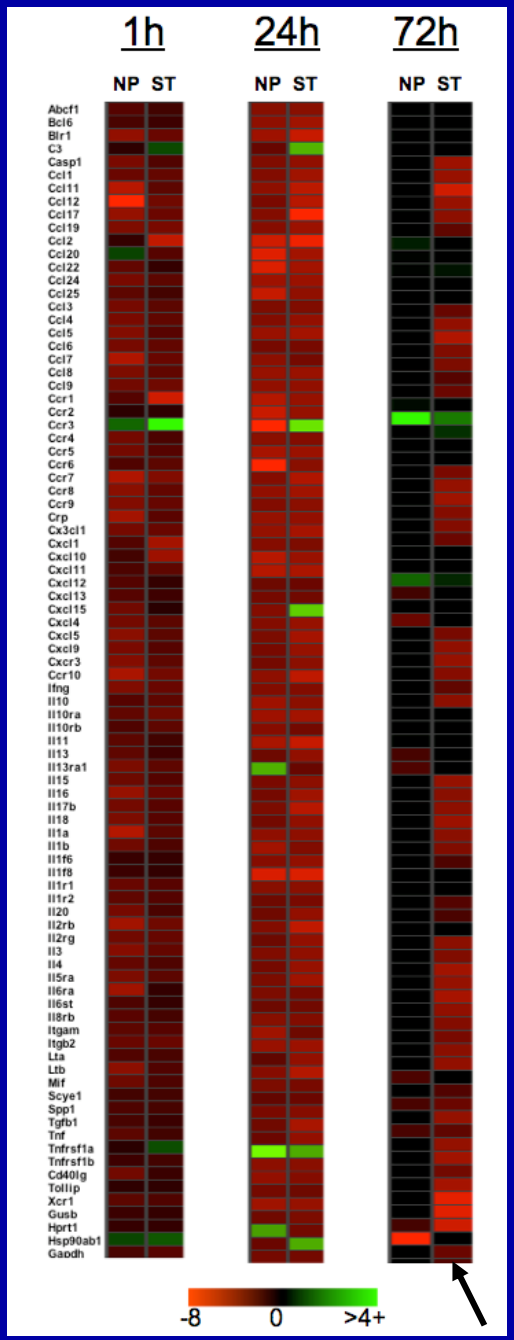
Berenguer J et al. Am J Resp Crit Care Med 1995, Balloy et al. Infection and Immunity 2005, Maertens et al. Med Mycol, 2006

Transcriptional Profile of the Innate Immune Response in Cyclophosphamide vs. Steroid Immunosuppressed Mice with IPA

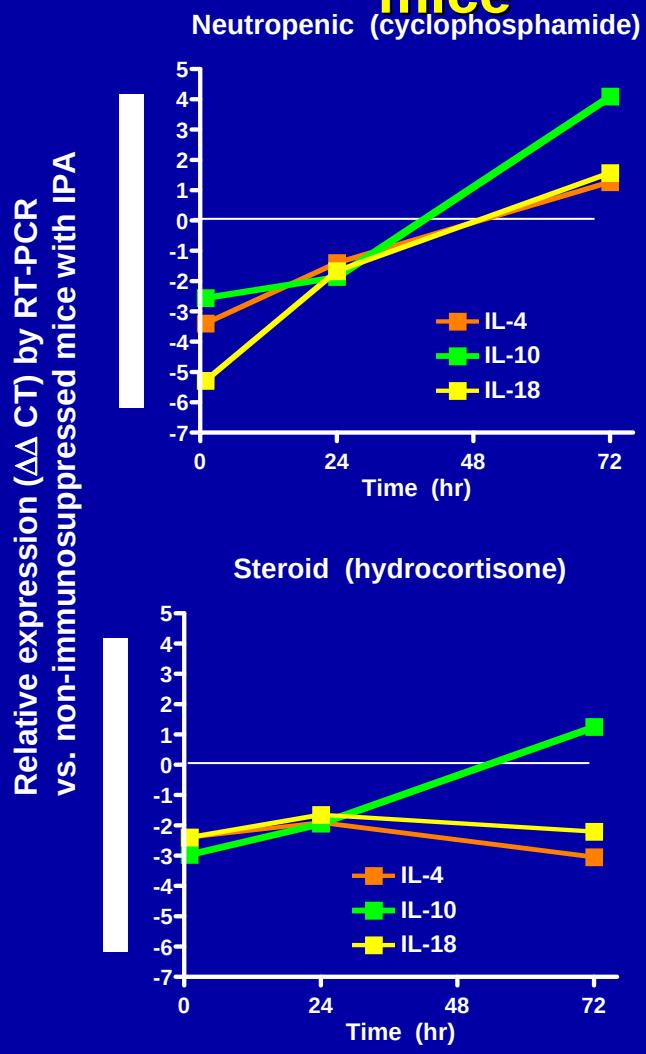


Lewis et al. *Personal communication*

Persistent suppression of anti-inflammatory/ Treg cytokines is a feature of IPA in steroid-immunosuppressed mice

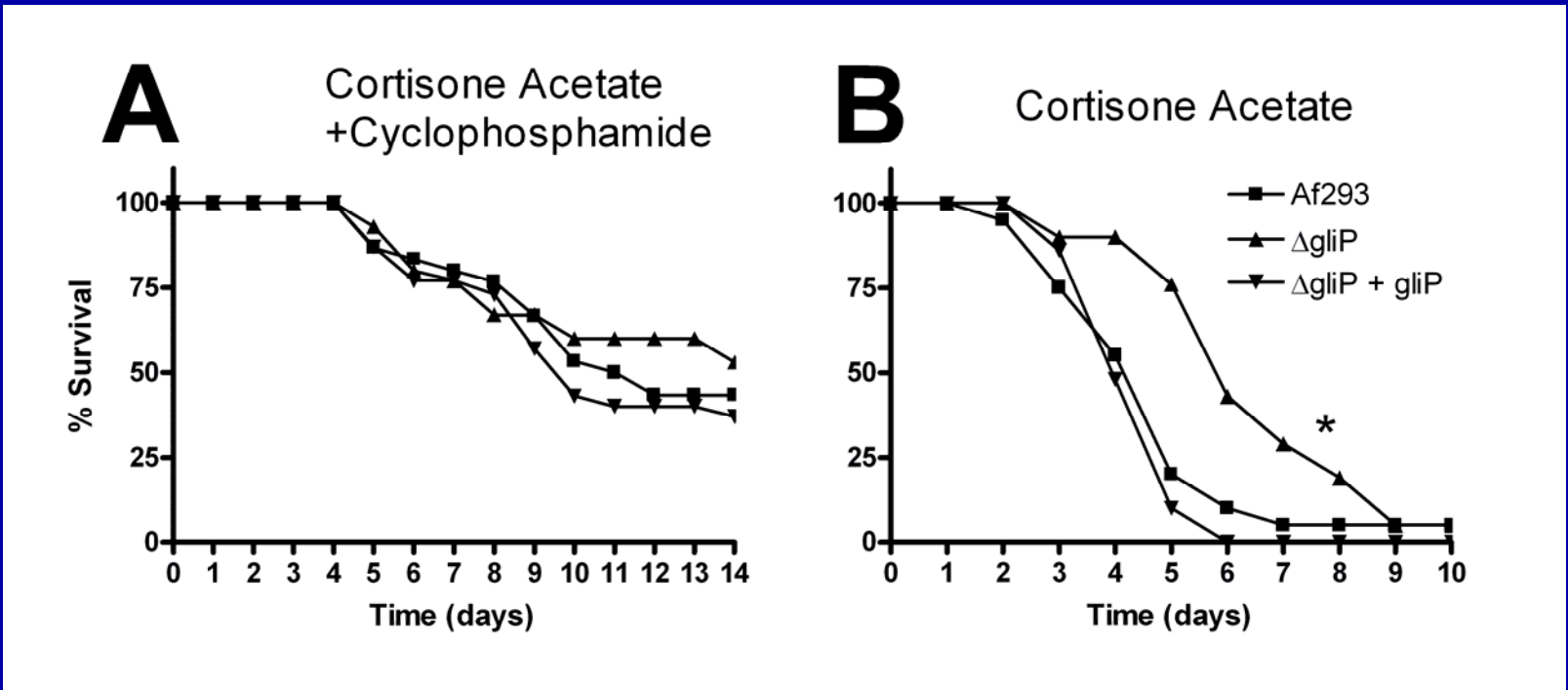


NP= Neutropenic
ST= Steroid



Lewis et al. *Personal communication*

Is *Aspergillus* virulence influenced by the mechanism of immunosupression? Gliotoxin



Sungui JA et al. Eukaryot Cell 2007, Spikes S et al. JID, in press

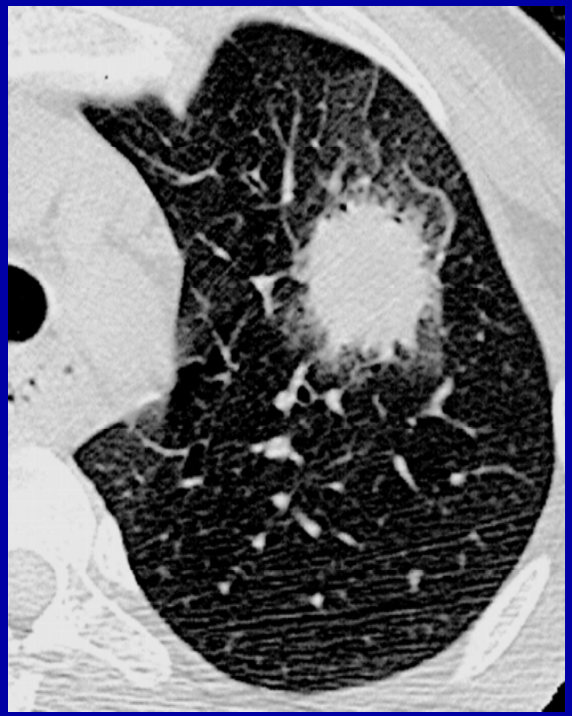
Common clinical features in steroid-associated IA

- Fever is a delayed sign
- Common co-infections associated with profound T-cell immunity (PCP, other moulds, Nocardia, CMV)
- Hyperglycemia, malnutrition

Controversies in management of steroid-associated IA-1

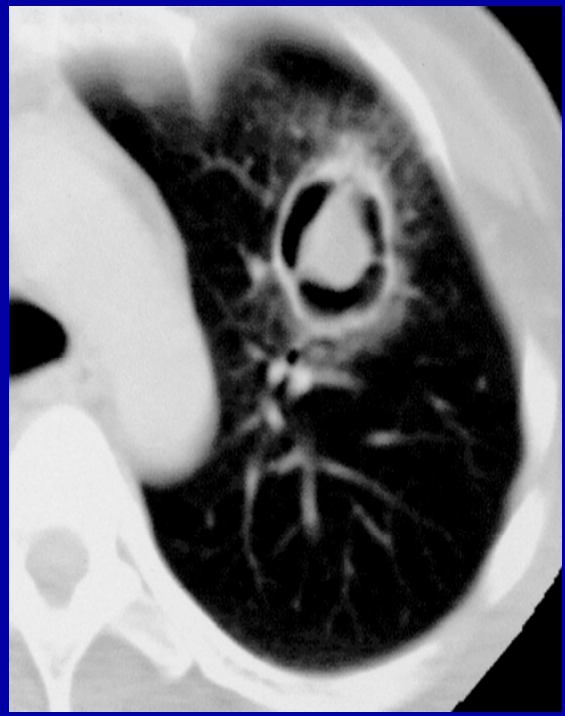
- What is the predictive value of halo sign by CT and the evolution of fungal volume following treatment?
- Could a combination of non-culture based markers (GM PCR, G-glucan) increases the diagnostic yield?
- Is there an immune-reconstitution syndrome?

Evolution of Invasive Aspergillosis in the Neutropenic patient



Halo sign (day 0)

Non-specific (day 4)



Air crescent (day 7)
neutrophil recovery

Caillot et al. *J Clin Oncol* 2001; 19:253-59

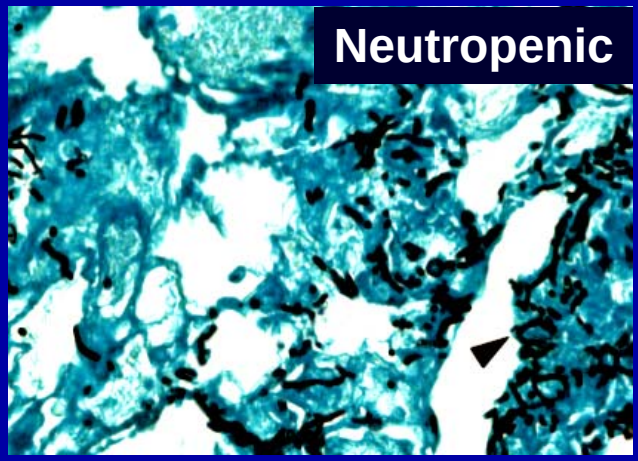
Controversies in Management of Steroid-associated IA-2

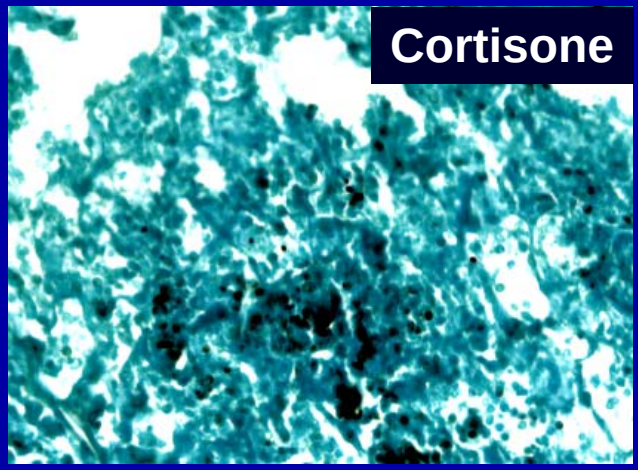
- How to deal with voriconazole failures?
  - Role of antifungal drug monitoring
  - Alternative agents (Posa, Lipid AMB, candins or their combination)
- What is the best primary or secondary prophylaxis? Is there a concern about cross-resistance between triazoles?
- What is the role of adjunctive surgery?
- What is the role steroid-tapering in outcome?
  - What is the role of immune adjunct therapy? (Schaffner A. JCI 1985)
- Are we focusing enough in indirect metabolic effects of corticosteroids in IA outcome (glucose control)

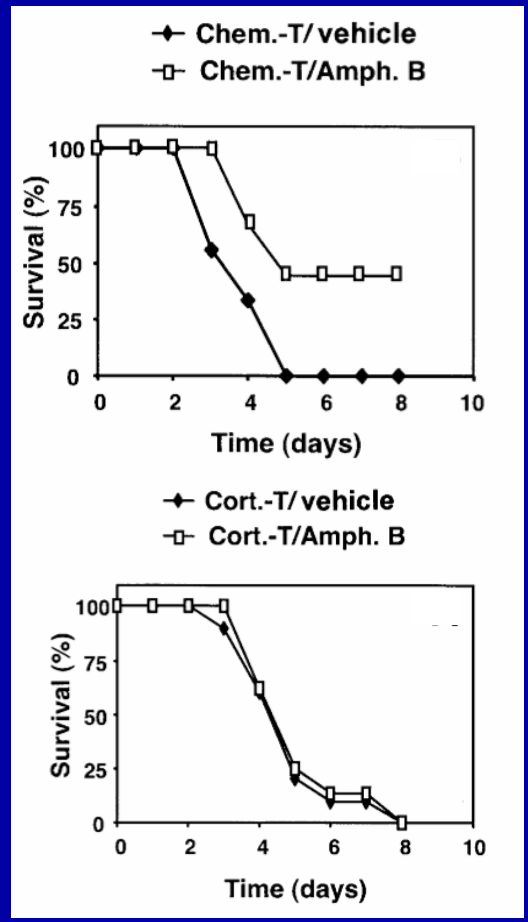
Future Research Directions

- Are they steroid-responsive receptors in *Aspergillus*? (Ng TT et al. Microbiology 1994)
- Can we dissect the contributions of underlying disease?
- Can we “index” the functional immune incompetence in steroid-treated patients?
- What are the interactions of antifungals with the host immune response in steroid-associated IA?

Inflammation in the lung decreases activity of AMB-deoxycholate







30% less fungal burden; similar mortality

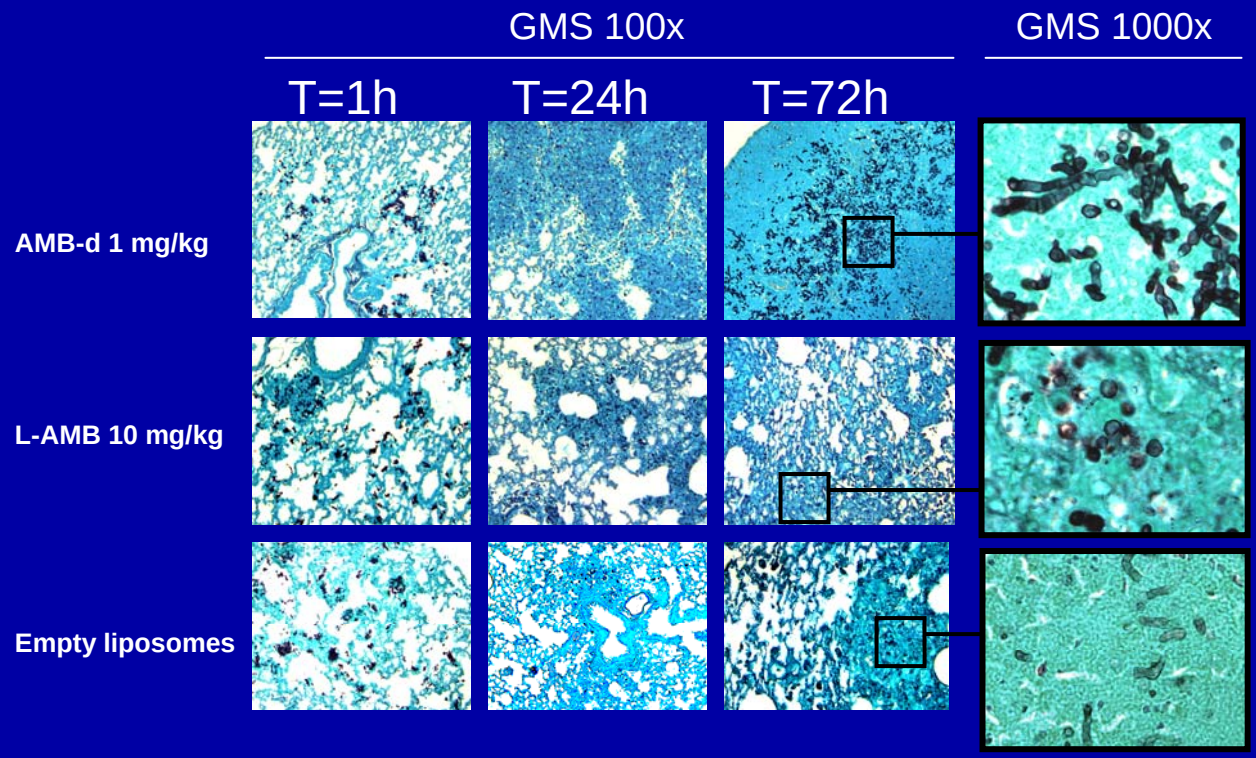
Berenguer et al. Am J Respir Crit Care Med 1995;152:1079-1086
Balloy et al. Infection and Immunity 2005;73:494-503.

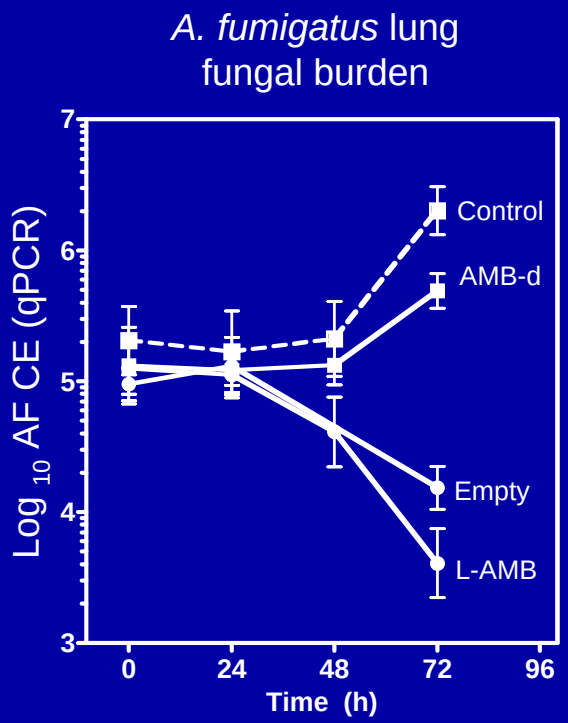
Overview of the immunological activity of antifungals

AmB-deoxy	↑ monocyte/ macrophage TNF-α, IL-1β, ↑ PMN TLR2, $H_20_{2,}$ IL-8, CD11b	Augmentation of macrophage, neutrophil killing
ABLC	↑ monocyte/ macrophage $H_20_{2,}$	Augmentation of macrophage, neutrophil killing
Ambisome	↑ monocyte/ macrophage TNF-α, IL-1β, ↑ PMN TLR4	Augmentation of macrophage, neutrophil killing
Triazoles	Cytokine-independent mechanisms?	Augmentation of macrophage, PMN killing
Echinocandins	ß-glucan “unmasking”	Enhanced macrophage, DC and PMN recognition and killing

Comparison of lung injury and fungal clearance in corticosteroid-immunosuppressed mice with IPA

72 hour pretreatment with AmB-d, L-AMB, or empty liposomes





Lewis et al. Antimicrob Agent Chemother 2007;52:1078-81.

- Echinocandins enhance neutrophil- mediated hyphal damage in *Aspergillus* species
- Incubation of moulds with caspofungin leads to concentration dependent increases in β-glucan exposure
  - Anti β-glucan antibodies appear to play a role in enhancing antifungal immunity against moulds

Lamaris G et al. JID, in press

CONCLUSION

Steroid-induced changes in immunobiology of IA mandate different approaches to diagnosis and management compared to neutropenia-associated IA

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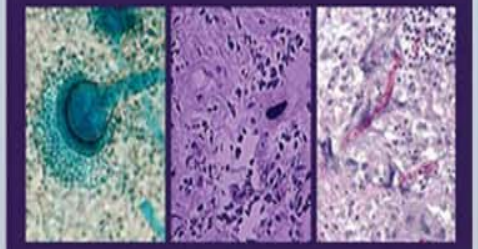

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