

Diagnostic Imaging in Experimental Invasive Pulmonary Aspergillosis

Introduction

- **Invasive pulmonary aspergillosis is an important cause of morbidity and mortality in immunocompromised patients.**
- **CT scan technology has greatly enhanced our capability for early diagnosis and for monitoring of therapeutic response.**
- **We have applied CT scan technology to the monitoring of therapeutic response in experimental pulmonary aspergillosis.**

Objectives

- Review basic concepts in CT imaging (CTI)
- Illustrate application of CTI
 - Pathophysiology
 - Monitoring of therapeutic response to AFT
 - Single agent
 - Combination therapy
 - Pathogenesis: *A. fumigatus* vs *A. terreus*
- MDVI
- Application to human IPA
- Future directions

Relationship to Pulmonary Pathophysiology

- **Pulmonary infiltrates in neutropenic hosts with invasive aspergillosis are caused by vascular invasion and hemorrhagic infarction.**
- **CT scan imaging may provide an objective parameter by which to serially measure organism-mediated tissue injury.**
- **We therefore have monitored the course of pulmonary infiltrates by serial ultrafast computerized tomography (UFCT) in persistently granulocytopenic rabbits with experimental invasive pulmonary aspergillosis.**

Ultrafast High Resolution CT Scan

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Ultrafast High Resolution CT Scan: Principles

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

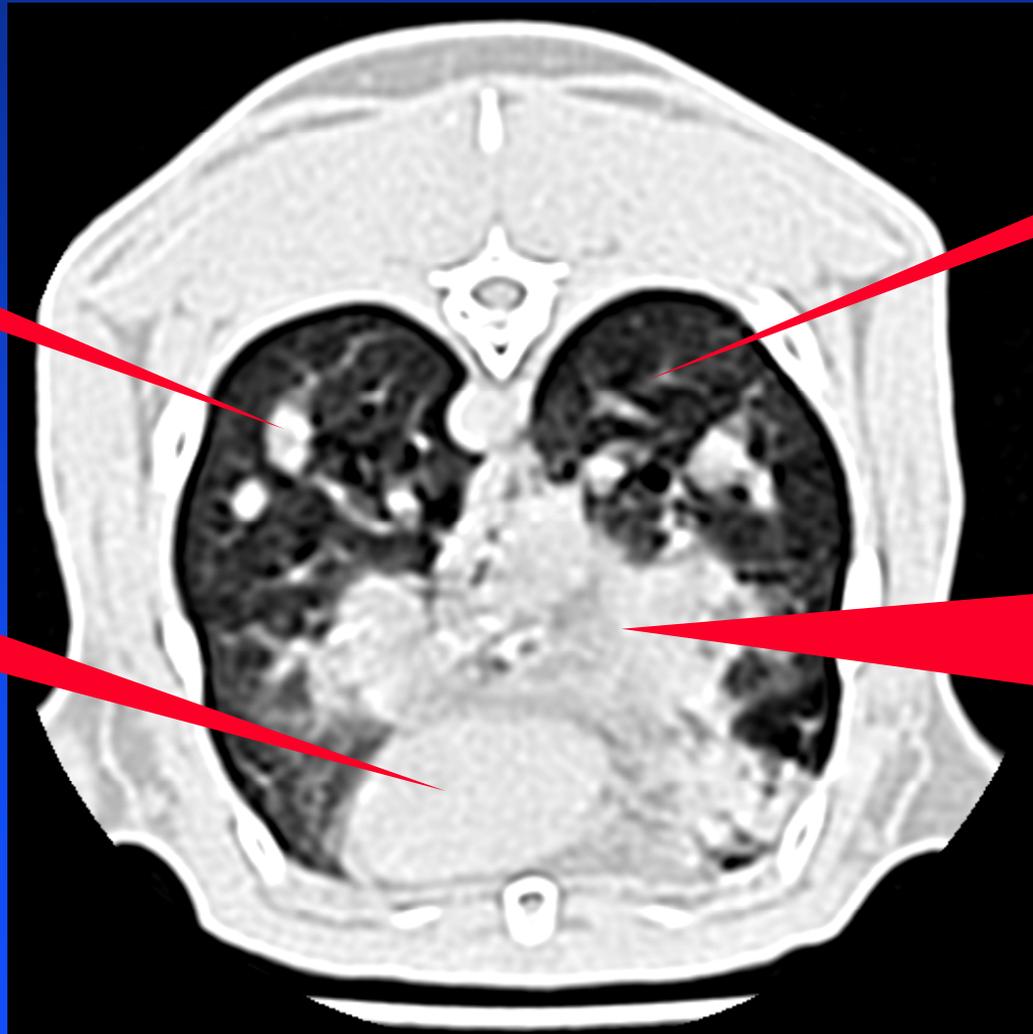
Two-dimensional image

Nodular pulmonary infiltrate

Normal lung tissue

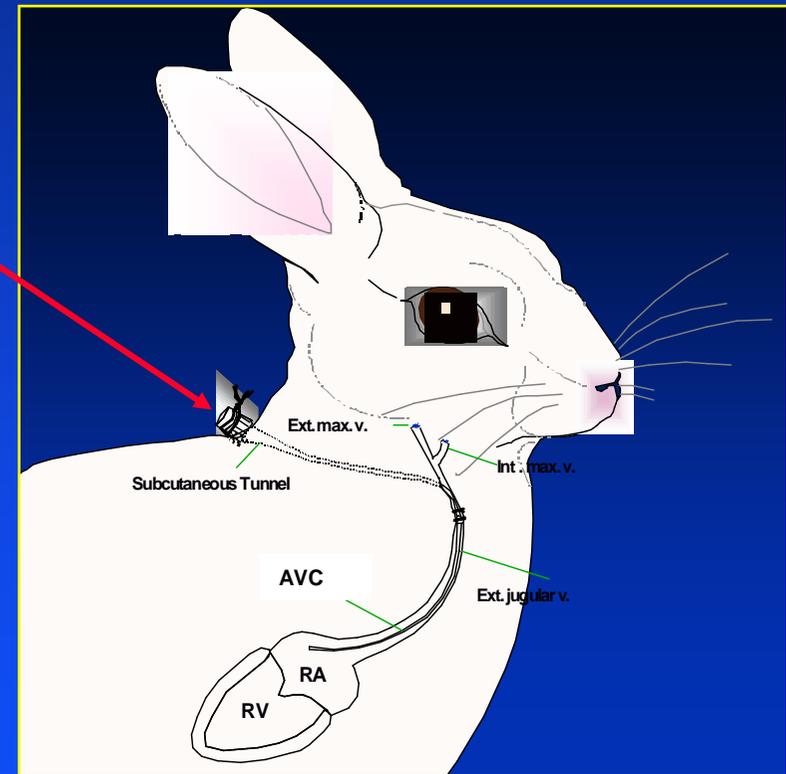
Bronchopneumonia with irregular boundaries caused by invasive pulmonary aspergillosis involving the right middle lobe and right lower lobe

Contour of the heart



Rabbit Models of Invasive Pulmonary Aspergillosis

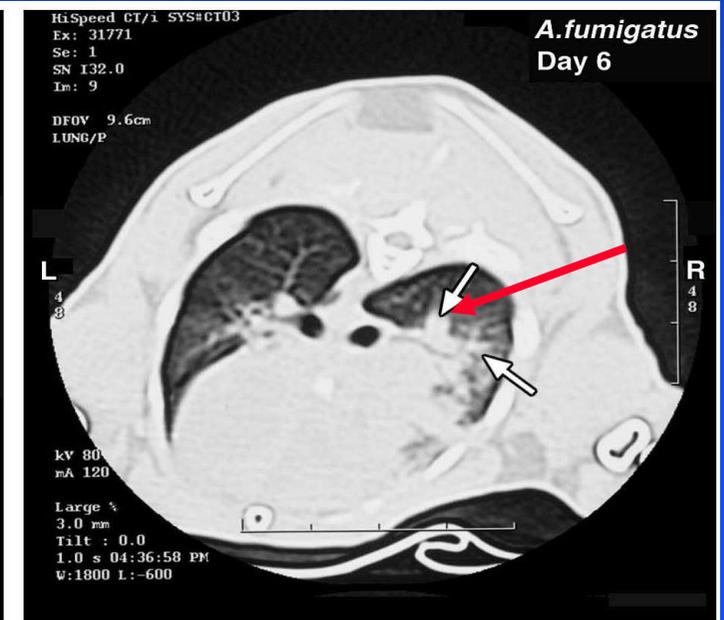
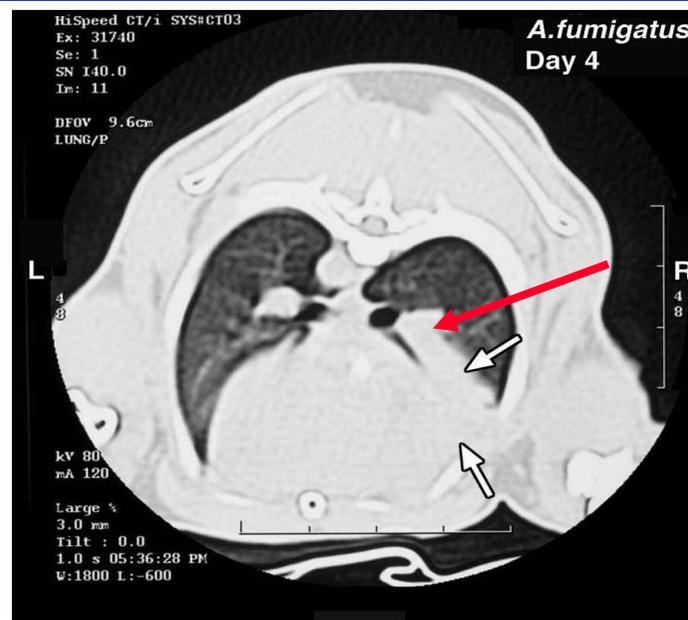
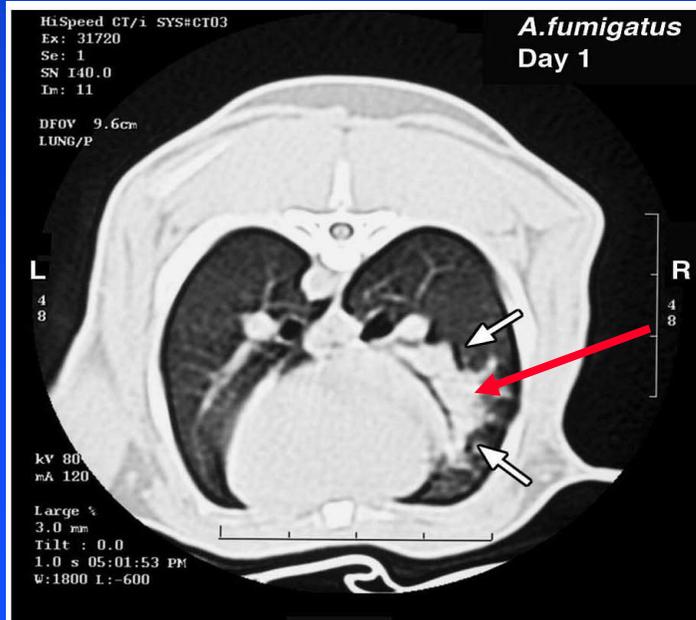
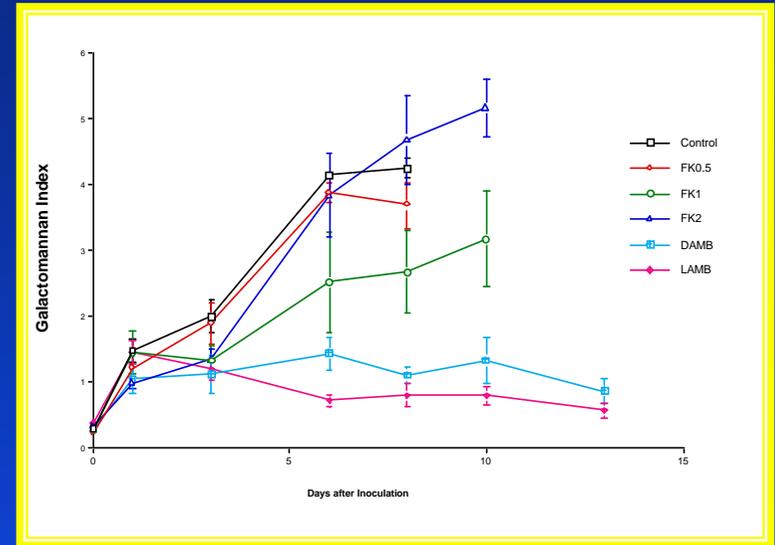
- Central silastic venous catheter permits atraumatic venous access
- Ara-C induction of profound and persistent neutropenia
- Further immunomodulation with CsA and methylprednisolone, where applicable
- Intensive supportive care with broad spectrum antibacterial antibiotics, twice daily monitoring, and 24/7 on-call schedule



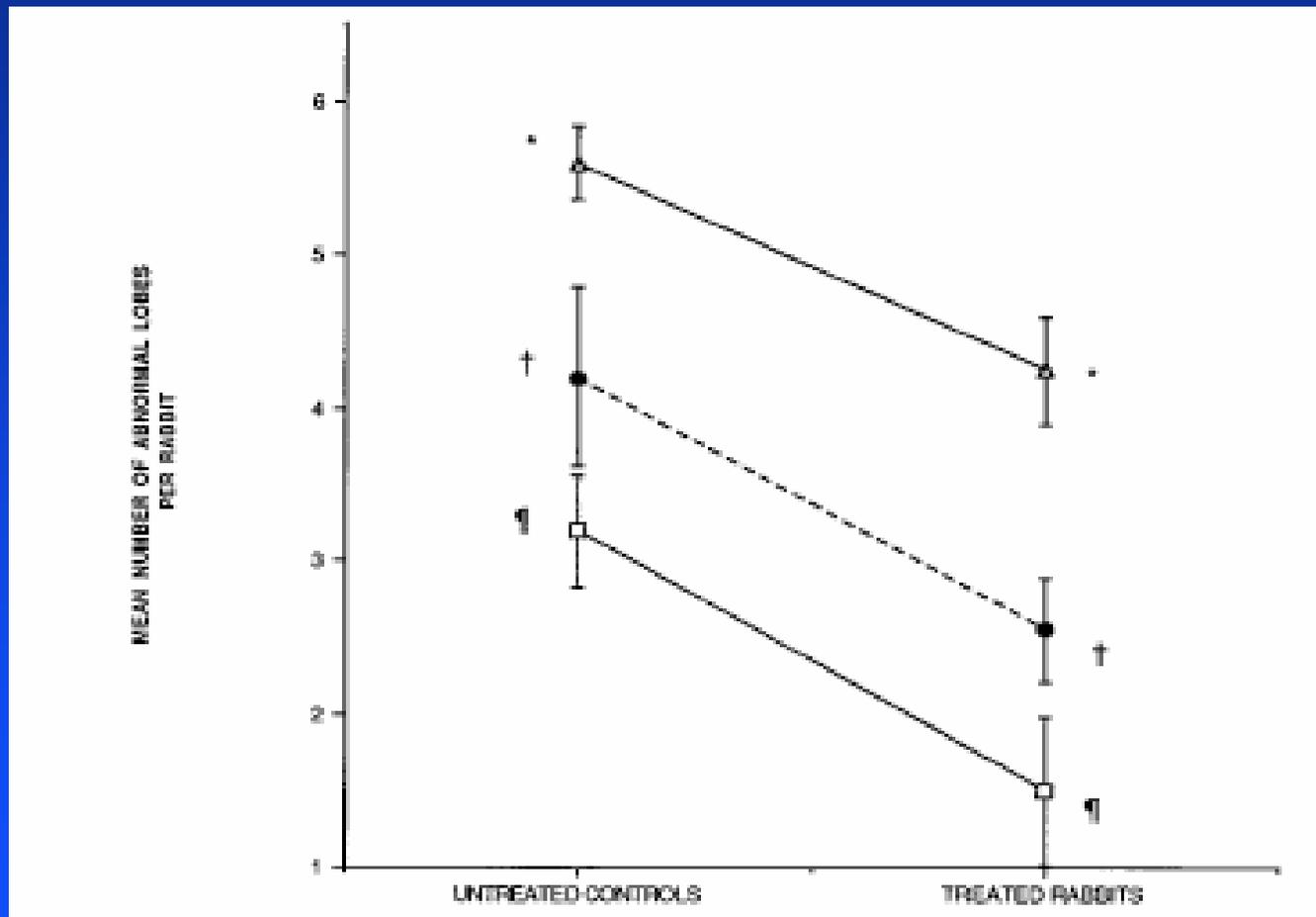
Real time Therapeutic Monitoring of Invasive Pulmonary Aspergillosis in Persistently Neutropenic Rabbits

Antigen, metabolite, and PCR
e.g. galactomannan antigenemia

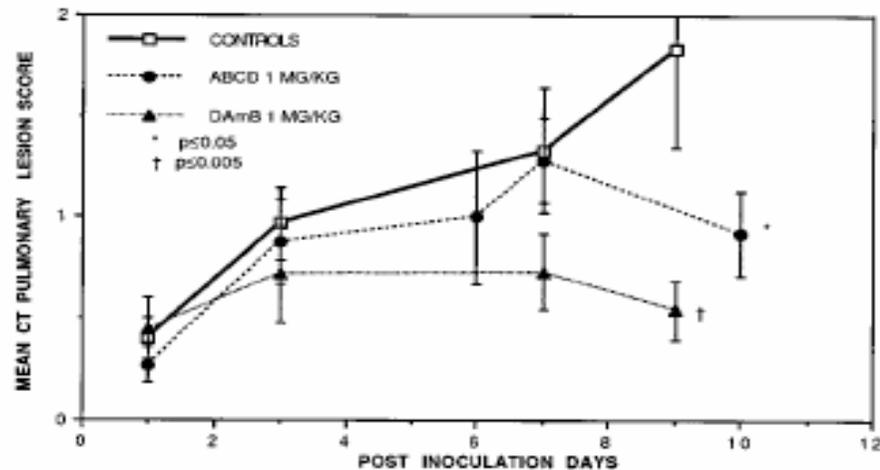
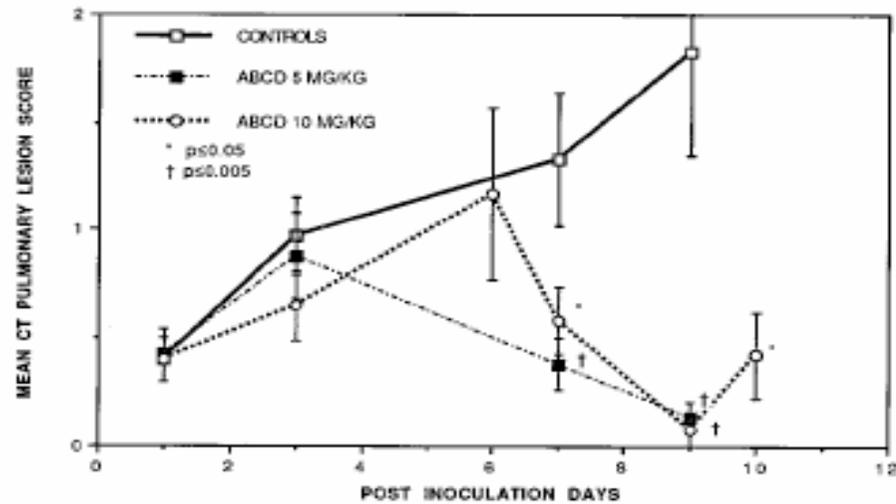
Serial CT and MRI scans



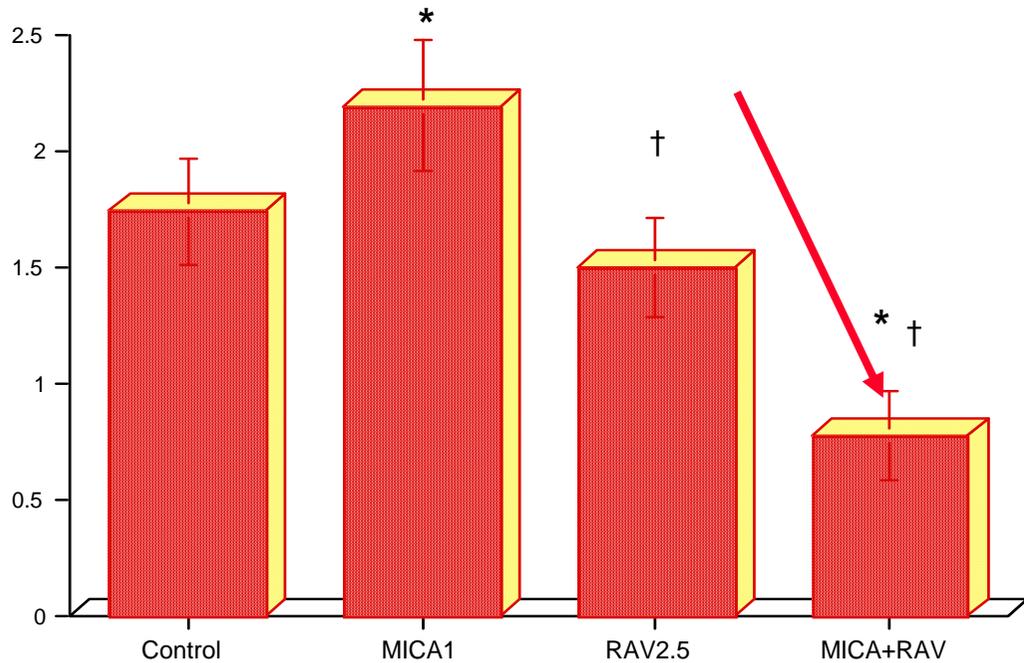
Correlation with Pulmonary Infarct Scores



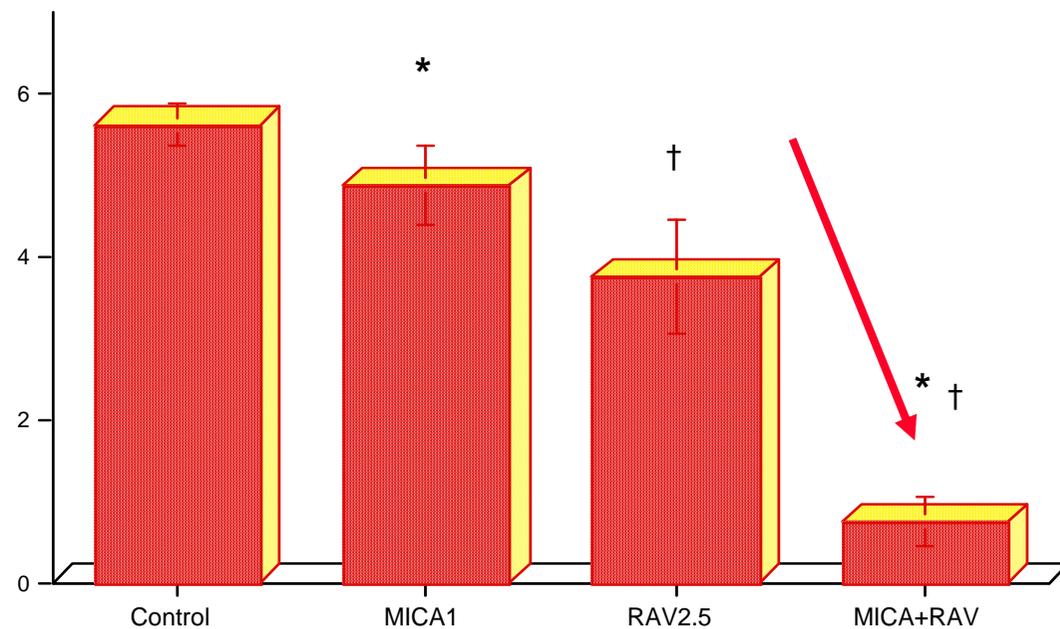
Dose Response Relationships to Amphotericin B Formulations



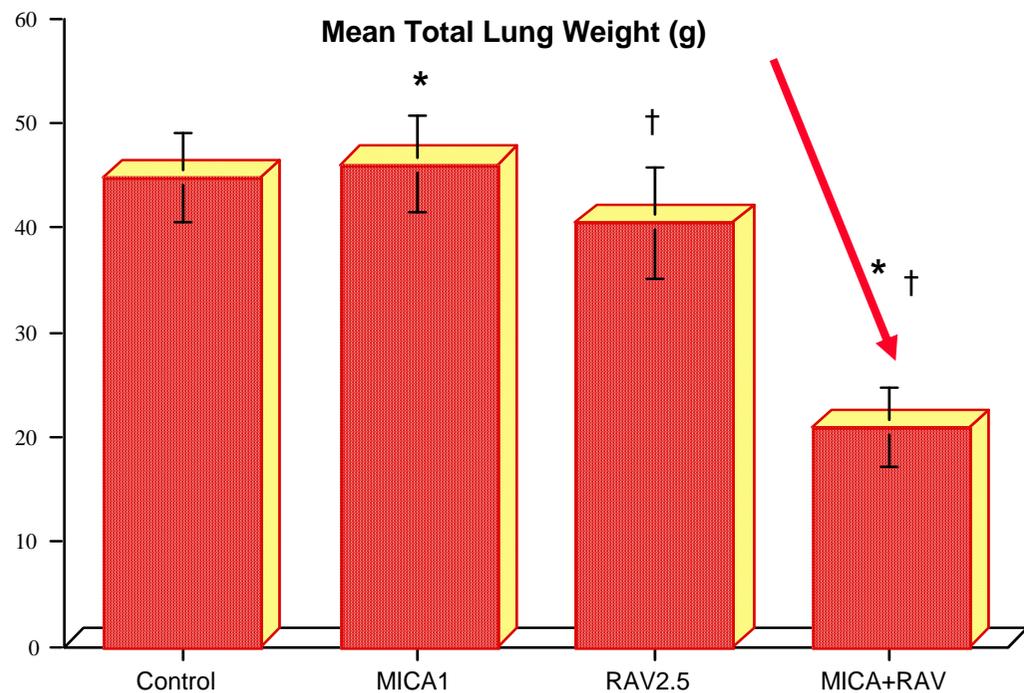
Mean Pulmonary LOG CFU/g



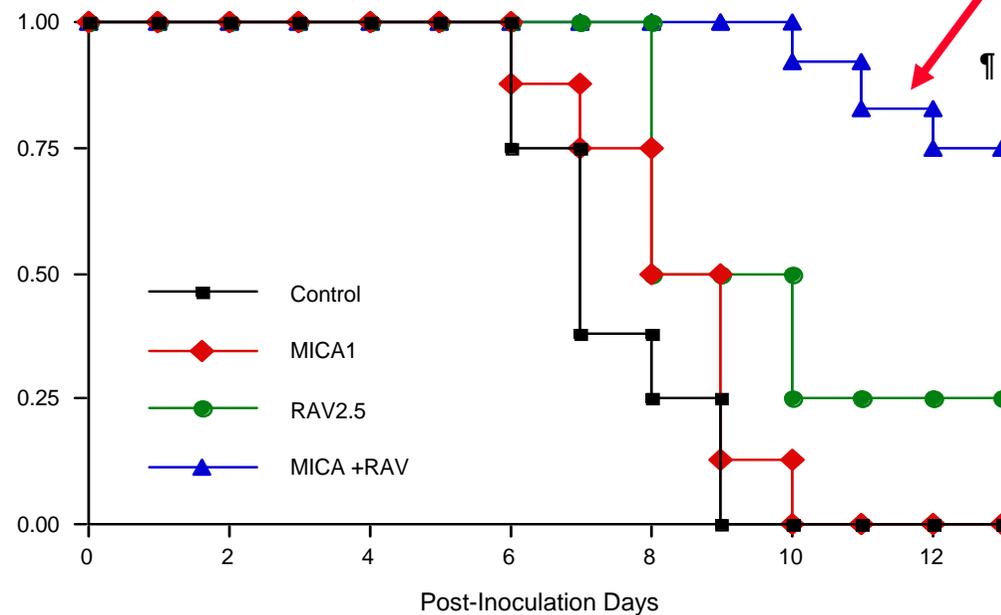
Mean Pulmonary Infarct Score



Mean Total Lung Weight (g)

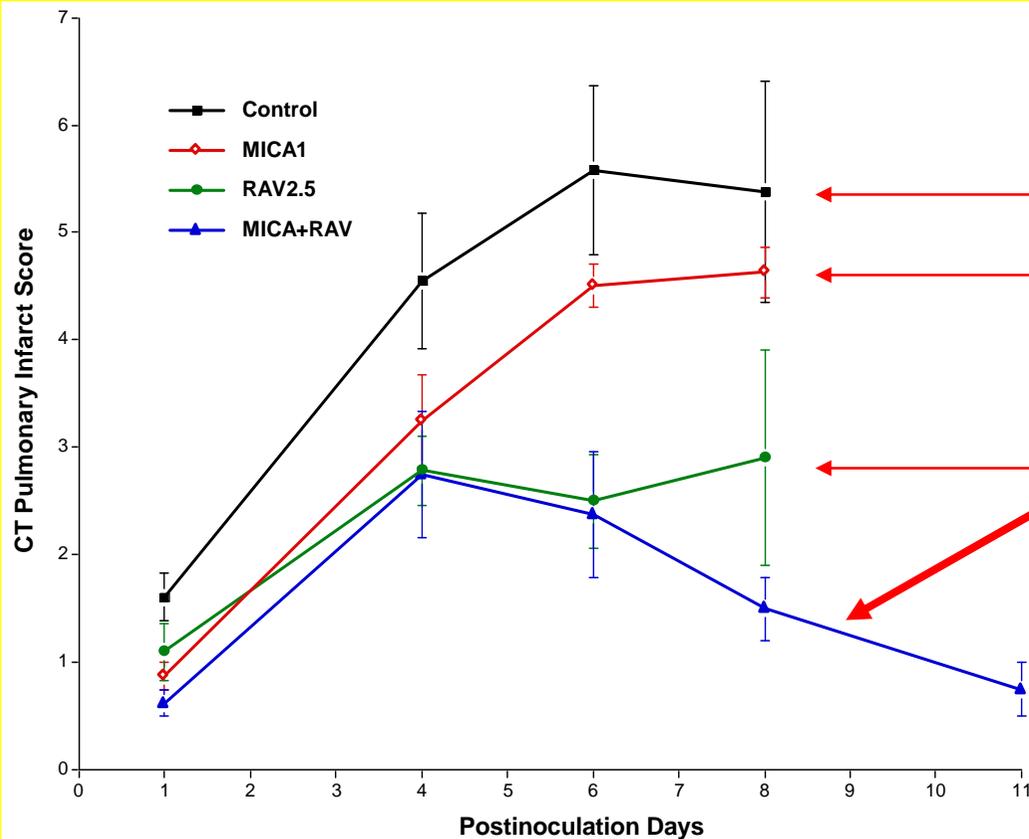


Survival

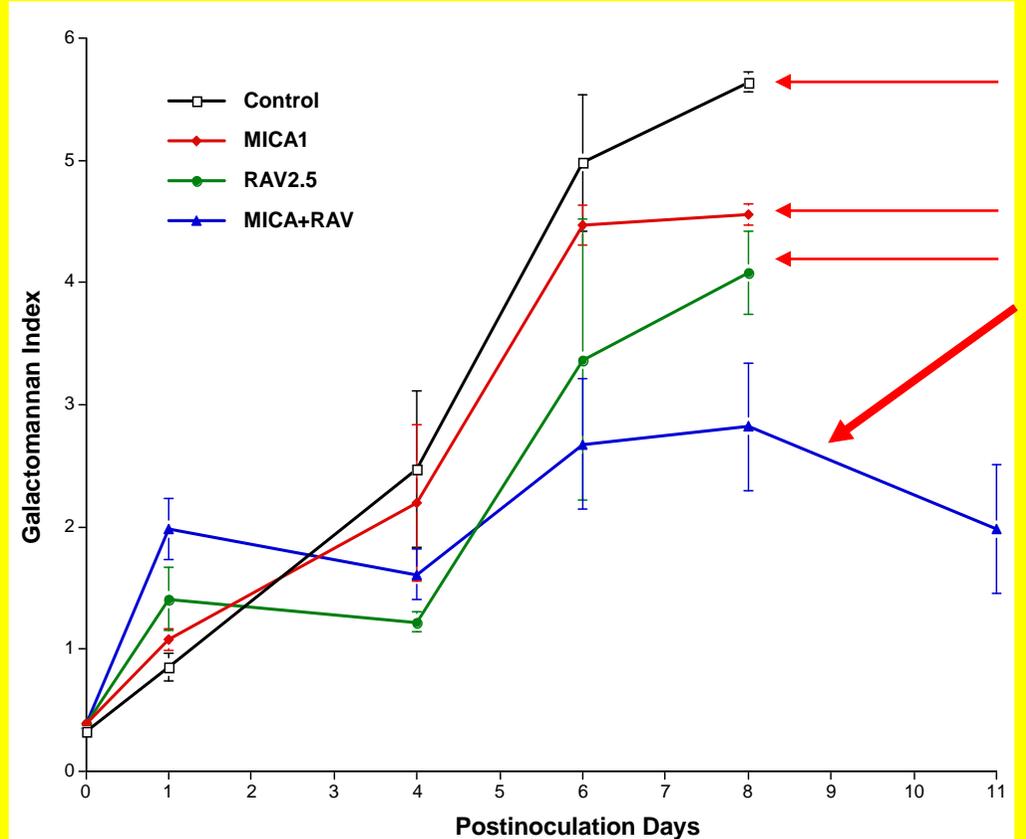


Echinocandin-Triazole Combination Therapy: Surrogate Markers of Therapeutic Response

CT Pulmonary Infarct Score

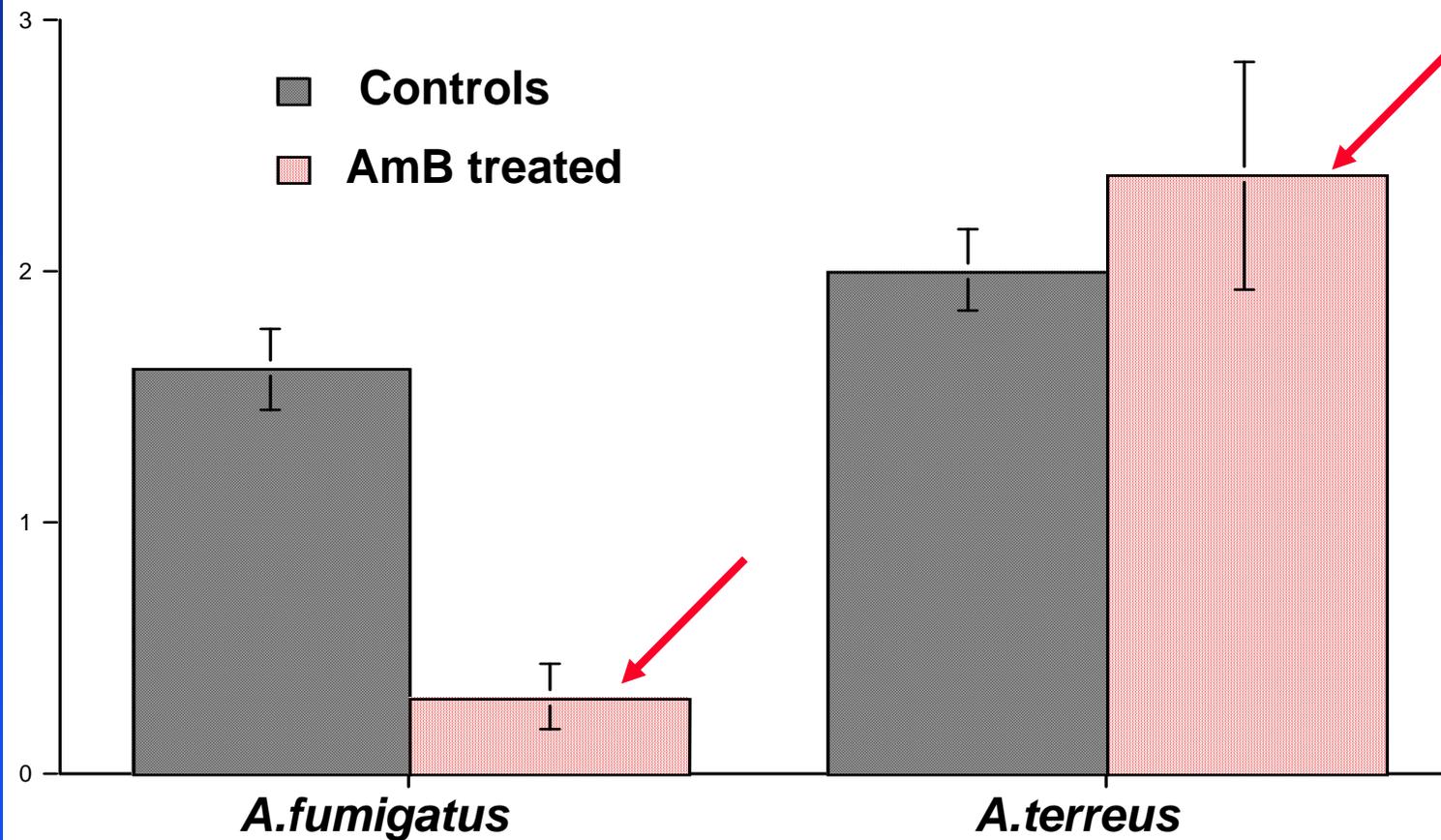


Galactomannan Antigenemia



Aspergillus terreus: In vivo Resistance to AmB

Persistence of viable *A. terreus* in lung tissue
(log CFU/g)



Experimental IPA: *A. fumigatus* and *A. terreus*

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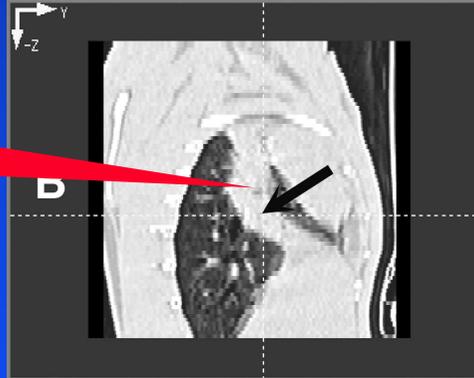
Multi-dimensional Volumetric Imaging of Pulmonary Infiltrates

CT volume used in the analysis software to generate a volume measurement

Transverse plane depicting pulmonary infiltrates in both lower lobes



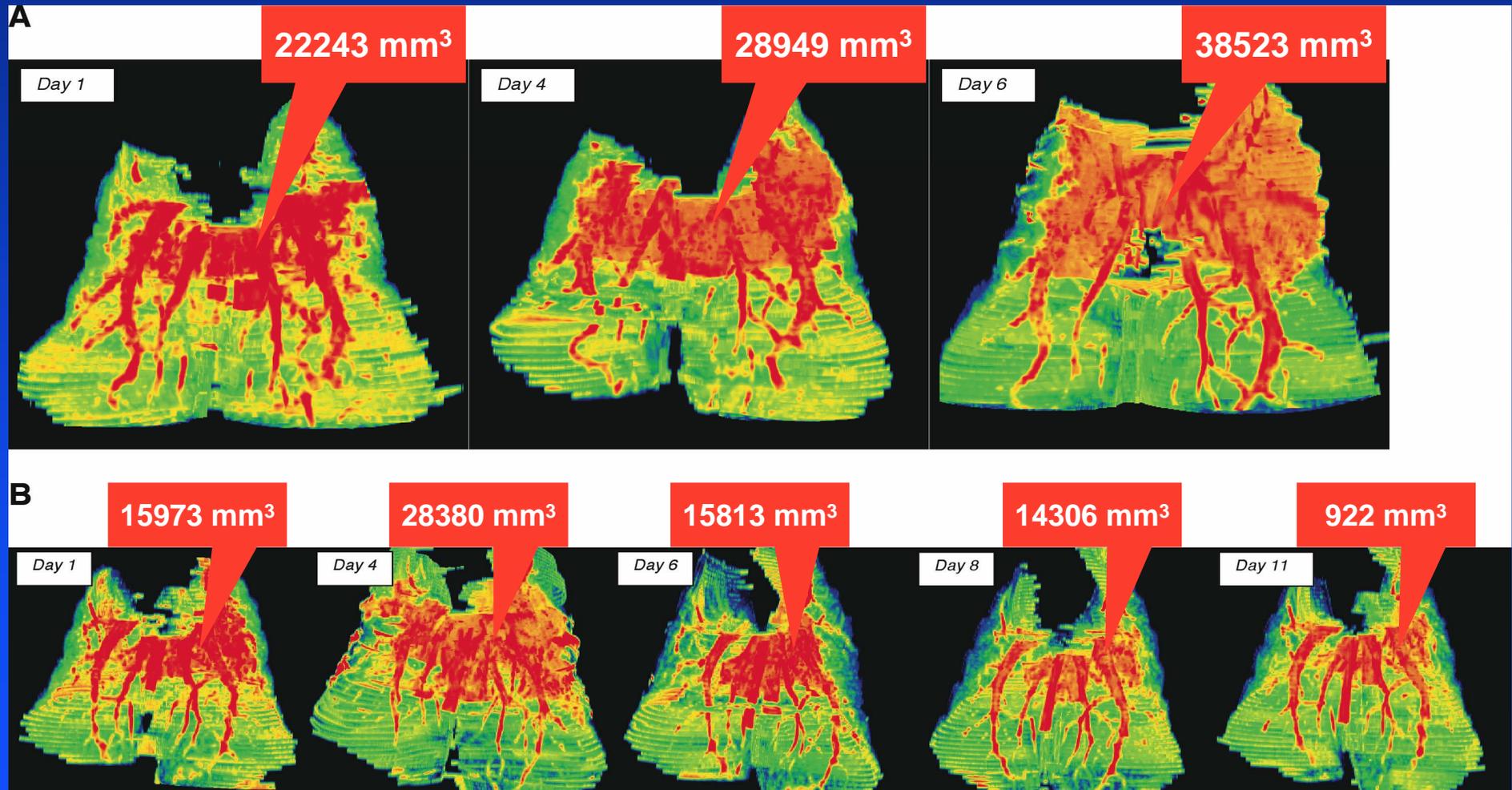
Sagittal plane depicts a column of infiltrate due to invasive pulmonary aspergillosis



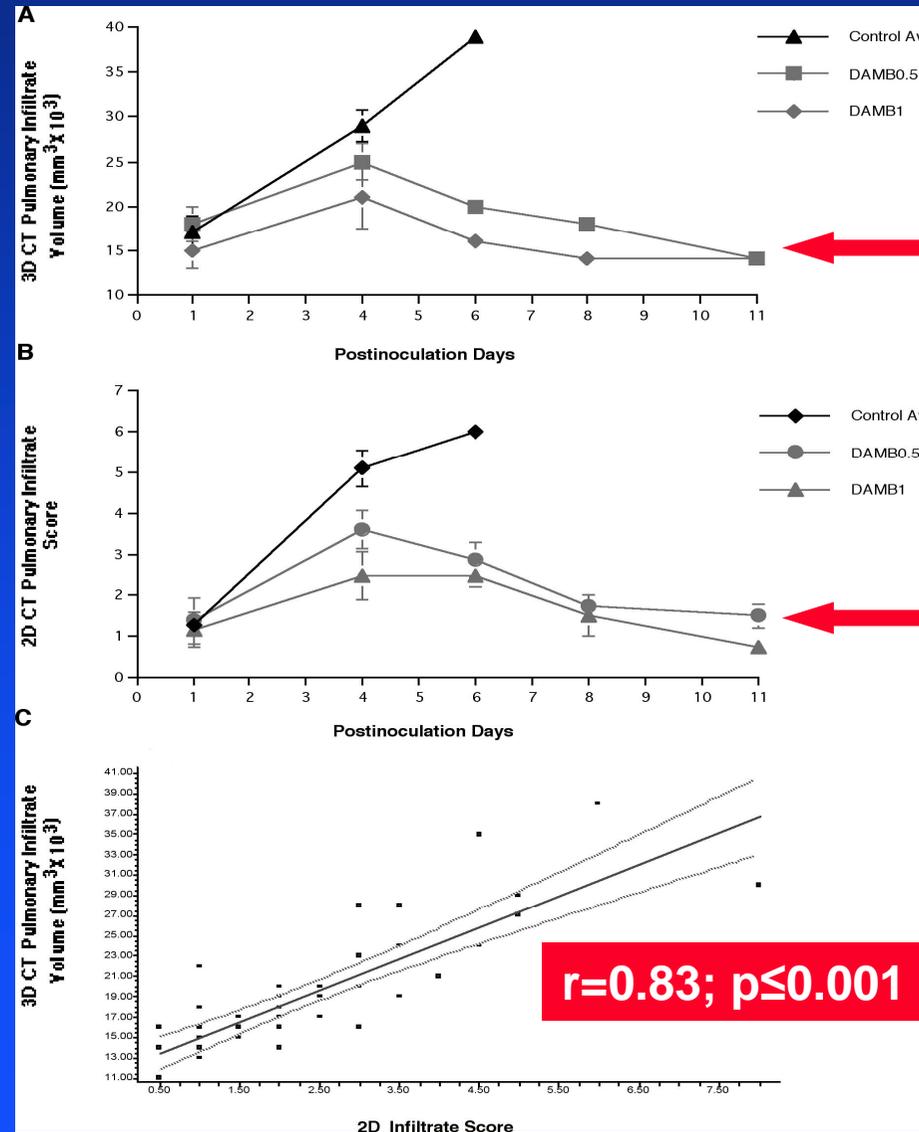
Coronal image depicting irregularly contoured pulmonary infiltrates



Representative maximum intensity projections (MIPs) from untreated control and DAMB-treated rabbits



The dynamics of the pulmonary infiltrate volume correlate with changes in the pulmonary infiltrate score measured using conventional UFCT

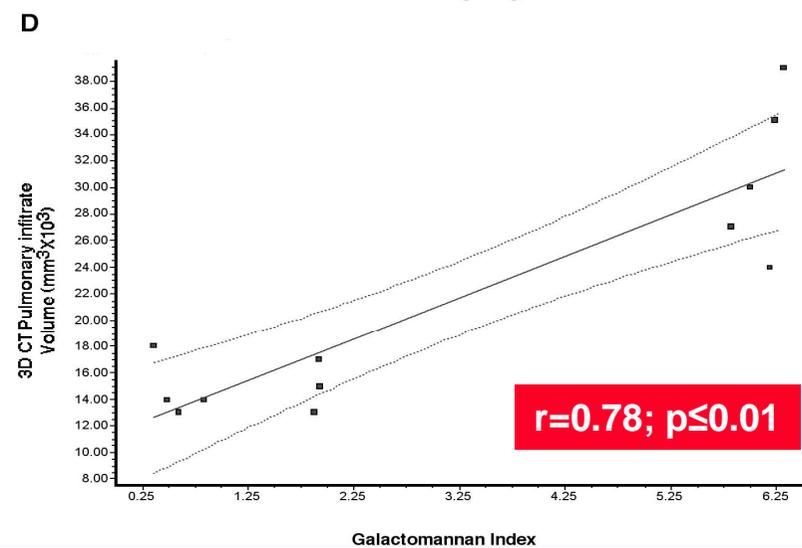
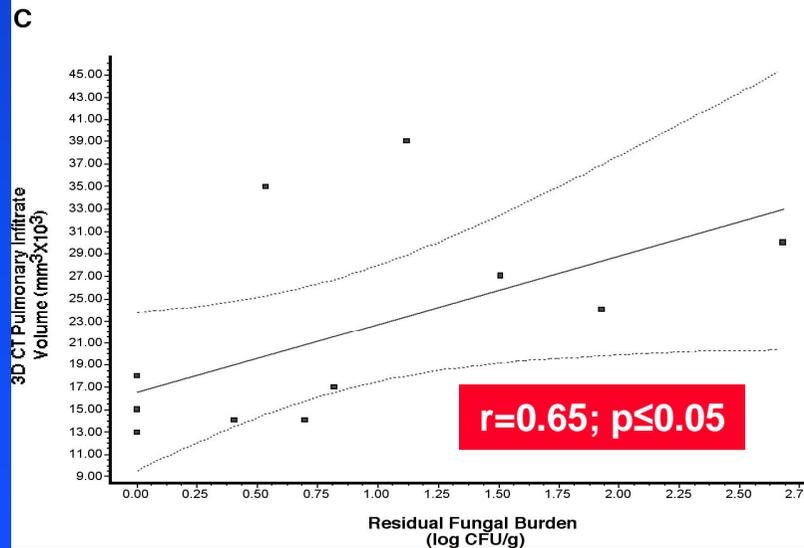
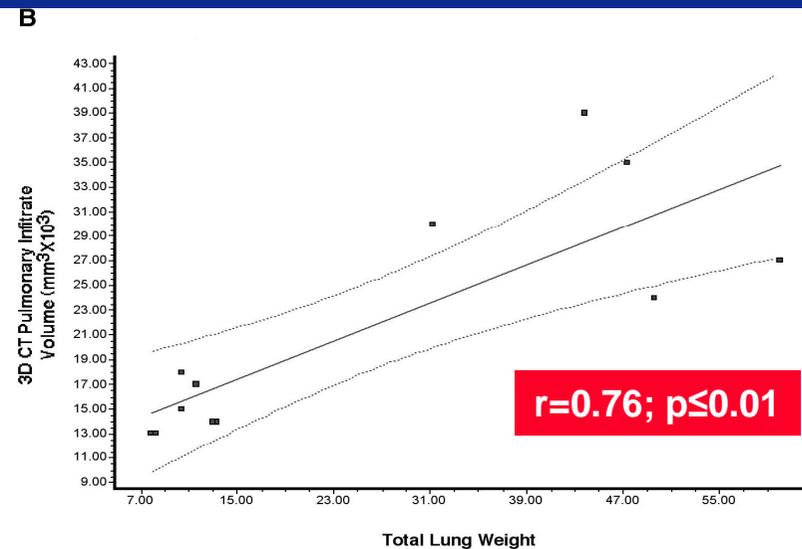
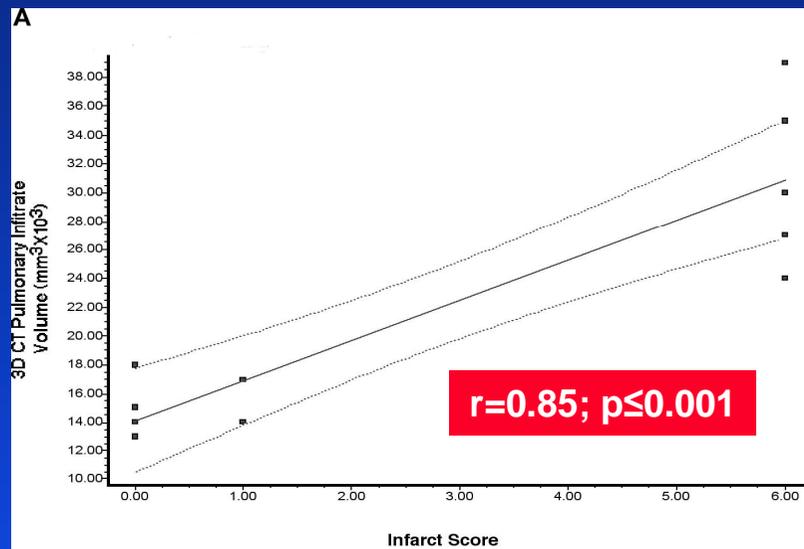


$p \leq 0.001$

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$r=0.83$; $p \leq 0.001$

Volume of pulmonary infiltrates correlate with pulmonary infarct score, total lung weights, residual fungal burden, and galactomannan antigenemia

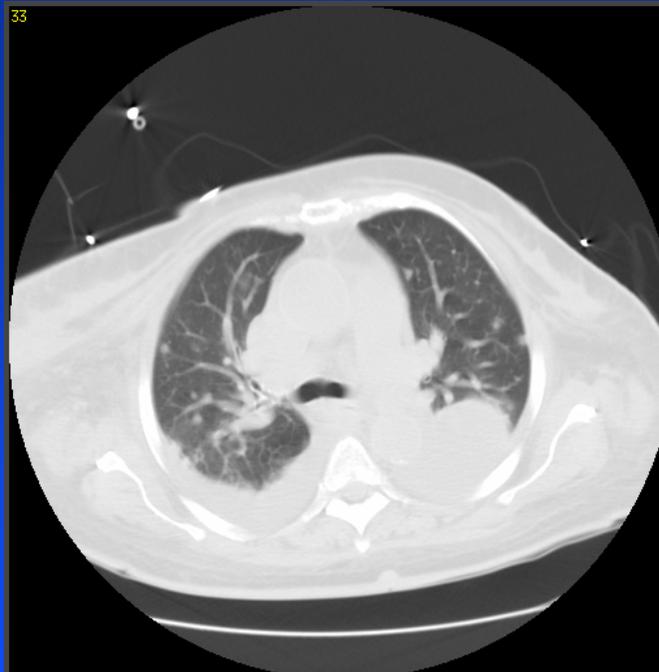


MDVI in Patients with Invasive Mycoses

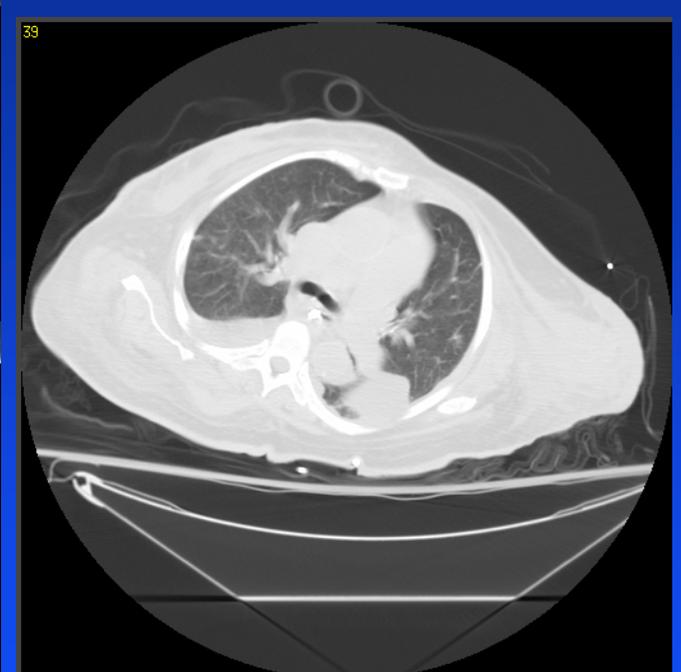
(Pyrgos et al: ICAAC 2007)



7219 (June
8)



29,747
(June 22)



15,101 (June
29)

Summary

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 - Pathophysiology
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Future Directions

- Further studies in experimental aspergillosis with different classes of antifungal compounds and immunomodulation using MDVI
- Correlation with new molecular and proteomic diagnostic markers
- Genetically modified *Aspergillus* spp.
- PET/CT
- Incorporation of MDVI into clinical trials
- Utility in other infectious causes of pneumonia

Gratitude

- **ICHS/NCI**
 - **Laboratory Animal Facility**
 - » Vidmantas Petraitis
 - » Ruta Petraitiene
 - » Robert Schaufele
 - » Tin Sein
 - » Lora Greene
 - » Molly Cotton
 - **Host Defense Research Unit**
 - » Emmanuel Roilides
 - » Vasilios Pyrgos
 - » Joanne Peter
 - » Shmuel Shoham
- **Diagnostic Imaging CC/NIH**
 - Nilo Avila
 - Jeff Solomon
 - Irwin Feurstein
- **Washington Hospital Center**
 - Shmuel Shoham
 - Vasilios Pyrgos