

Utility of Surrogate Markers in Serum and BAL Fluid

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INVASIVE ASPERGILLOSIS ANIMAL MODELS

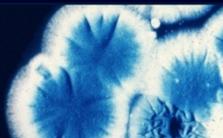
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Background

- Early diagnosis of invasive pulmonary aspergillosis and initiation of antifungal therapy improves outcomes
 - Galactomannan and (1→3)- β -D-glucan within serum
- Utility of the galactomannan assay using bronchial alveolar lavage (BAL) fluid
- Reduced sensitivity of assays in the presence of antifungal therapy

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Objectives

- Measure (1→3)- β -D-glucan and galactomannan within the BAL fluid in a guinea pig model of invasive pulmonary aspergillosis
 - Compare to results in serum
- Assess the utility of these assays in the presence of antifungal therapy

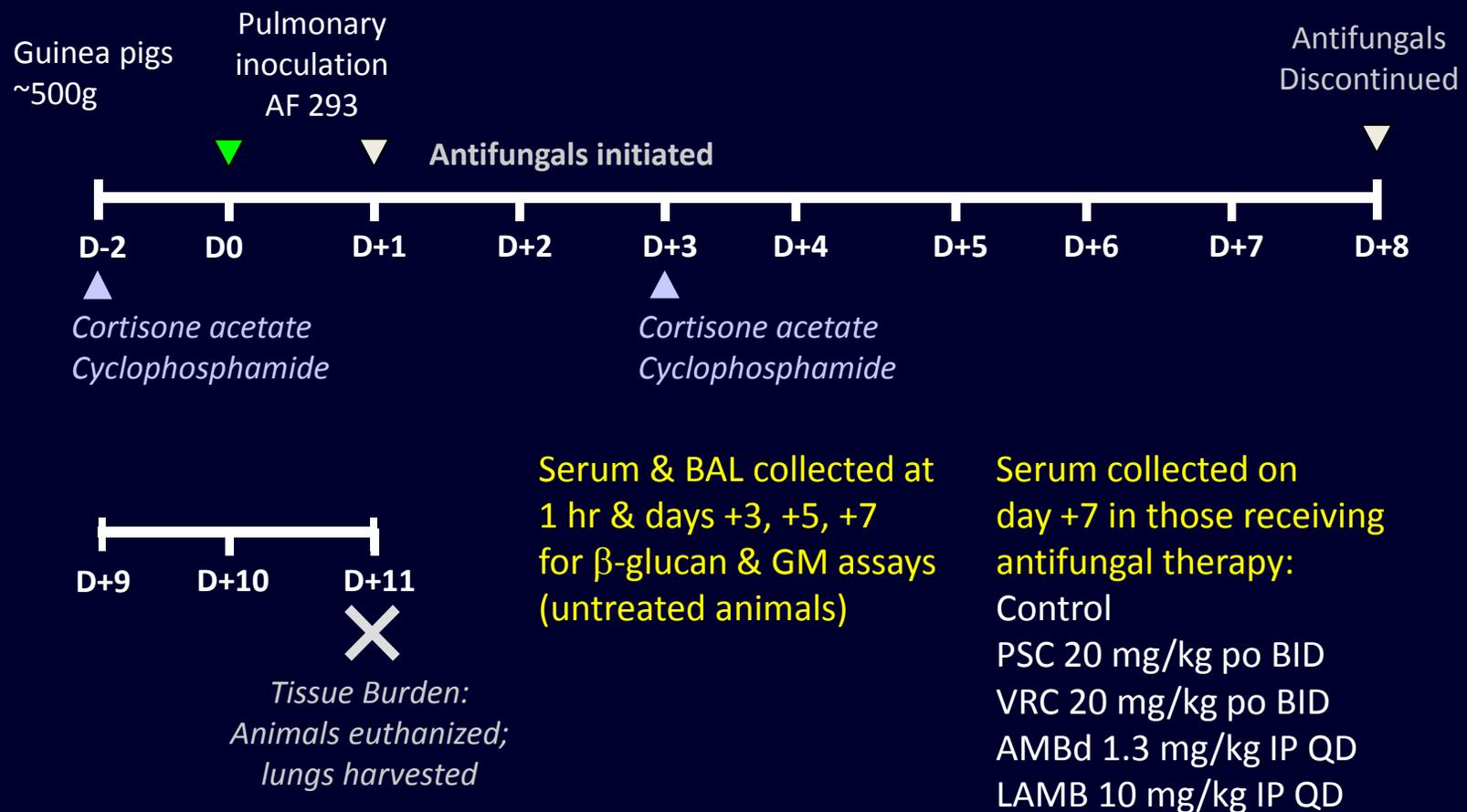
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Guinea Pig Model of Invasive Pulmonary Aspergillosis



(1→3)- β -D-glucan and Galactomannan Assays

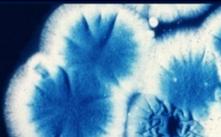
Fungitell (1→3)- β -D-glucan Assay

- Transferred to 96 well cell culture plate in duplicate
- Mean rate Δ O.D. (405 nm) over 40 minute period
- Unknowns compared to standard curve

Platellia Aspergillus EIA

- Samples treated with EDTA acid solution, heat treated, and transferred to microwells containing conjugate and EBA-2 antibody
- Optical density of sample, positive control, negative control, and cut-off control measured (450 and 630 nm)
- GMI calculated as OD of each sample divided by mean cut-off of control OD

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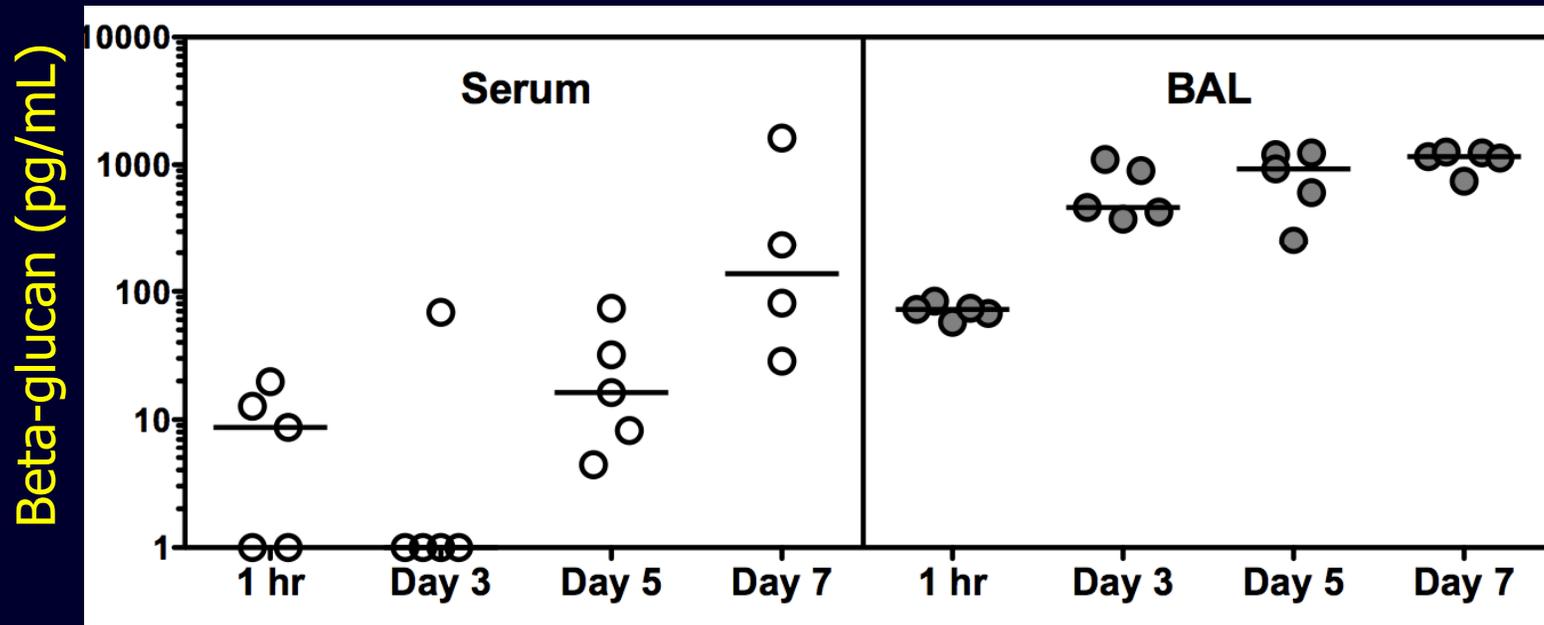
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(1→3)- β -D-glucan (Serum vs. BAL)



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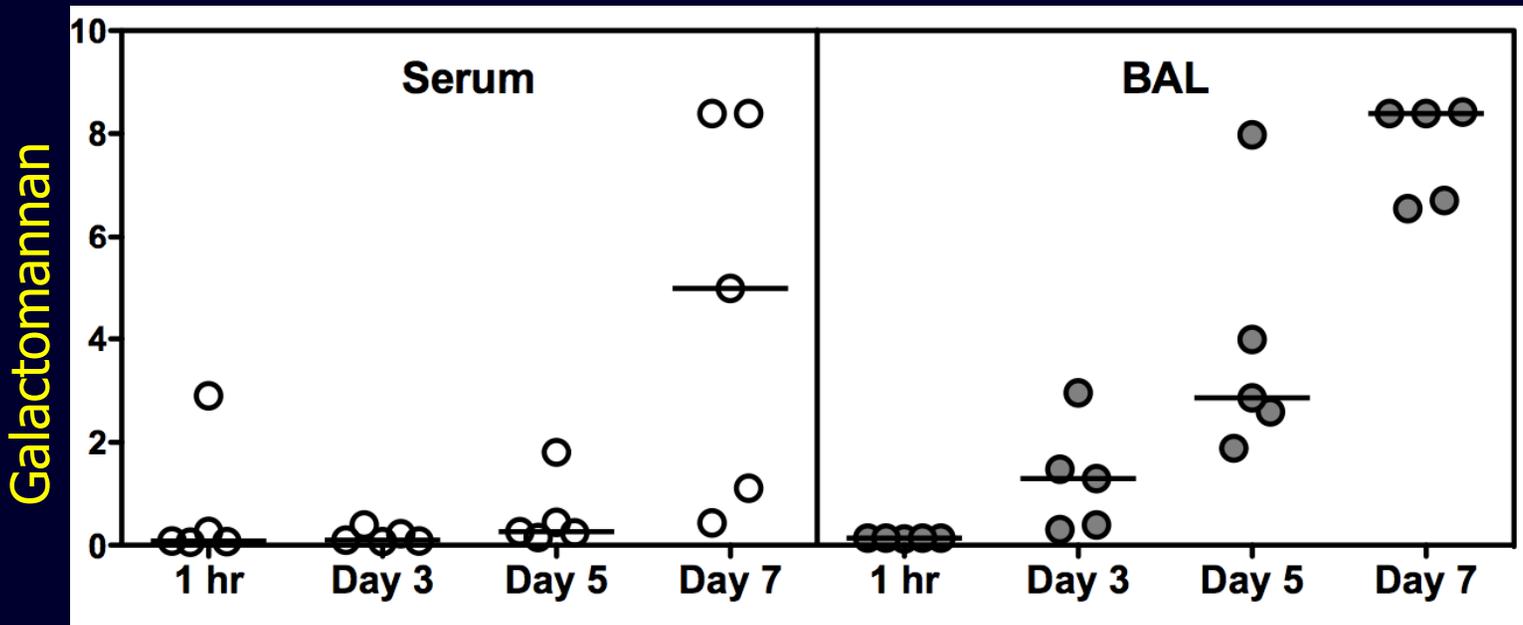
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Galactomannan

(Serum vs. BAL)



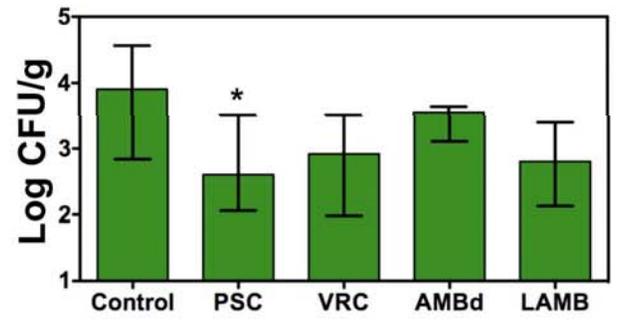
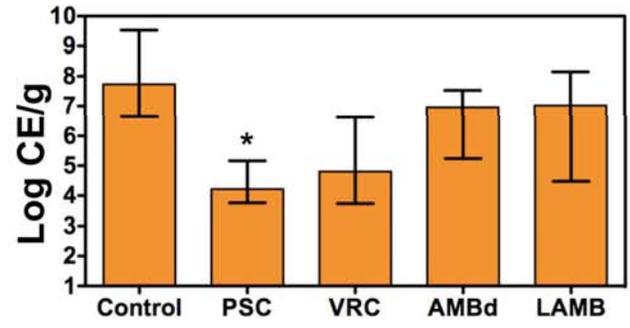
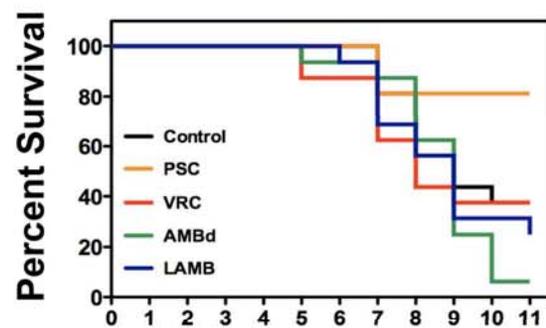
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Results – Survival & Fungal Burden

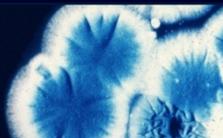


TX Group	Control	PSC	VRC	AMBd	LAMB
Median Survival	9 days	>11 days p = 0.02	8 days	9 days	9 days
Percent Survival	37%	81% p = 0.03	37%	6%	25%
Beta-glucan, pg/mL (range)	1407 (326 – 1682)	12.4 (0 – 371)	51.9 (0 – 941)	772 (520 – 1269)	25 (0 – 456)
GMI (range)	21.1 (0.64 – 39.6)	0.48 (0.11 – 0.62)	0.44 (0.23 – 0.60)	13.7 (3.76 – 35.1)	3.16 (0.5 – 23.5)

Conclusions

- Biomarkers detectable early in course of infection in BAL fluid versus serum
 - (1→3)- β -D-glucan > 60 pg/mL by day +3
 - GMI > 0.5 by day +3
 - Day 5 – 7 for biomarkers in serum
- Mixed association between (1→3)- β -D-glucan / galactomannan and survival with antifungal exposure
 - Changes in (1→3)- β -D-glucan were predictive of survival in animals treated with posaconazole and AMBd, but not voriconazole and LAMB
 - Sensitivity of the galactomannan assay reduced with voriconazole exposure

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