

# Diagnosics of Invasive Aspergillosis: From Experimental Models to Clinical Evaluation.

(1→3)- $\beta$ -D-Glucan and Galactomannan

Nathan P. Wiederhold, Pharm.D.

University of Texas at Austin

University of Texas Health Science Center at San Antonio

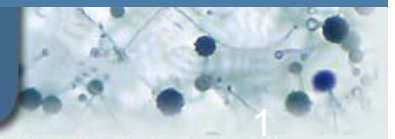
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INVASIVE ASPERGILLOSIS ANIMAL MODELS

ASTE C

ASPERGILLUS TECHNOLOGY CONSORTIUM



# Study Objectives

- Two surrogate markers accepted by EORTC/MSG
  - Galactomannan & (1,3)- $\beta$ -D-glucan
- Measure the serum kinetics of (1,3)- $\beta$ -D-glucan & galactomannan in murine and guinea pig models of IPA
- Examine (1,3)- $\beta$ -D-glucan assay as a surrogate marker of disease burden
  - Presence of antifungal therapy

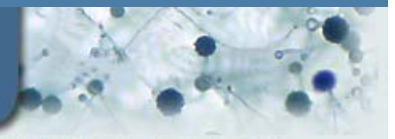
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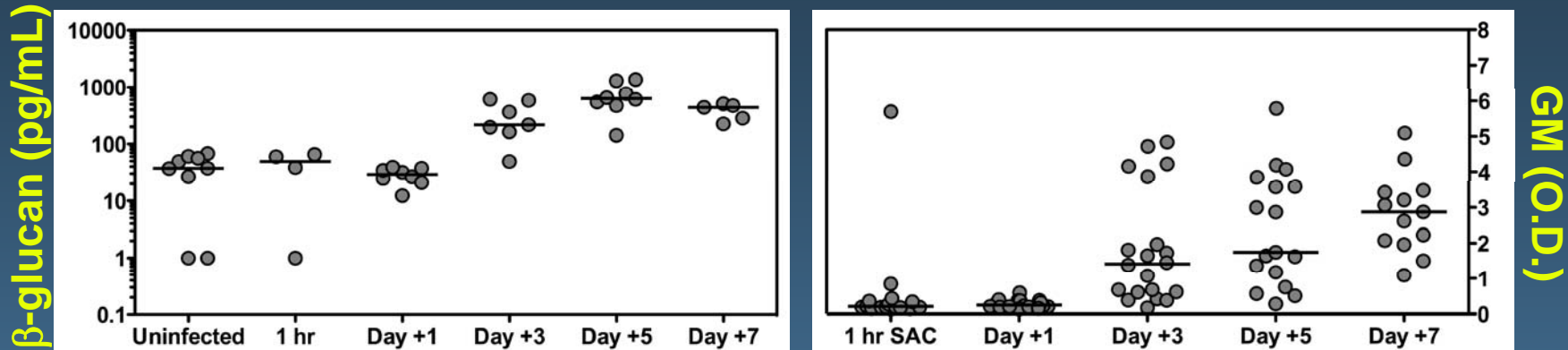
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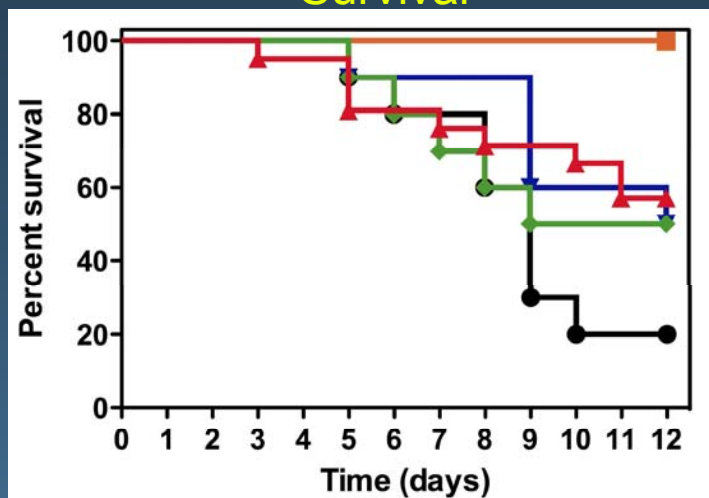
# (1→3)-β-D-Glucan and Galactomannan (neutropenic murine model)



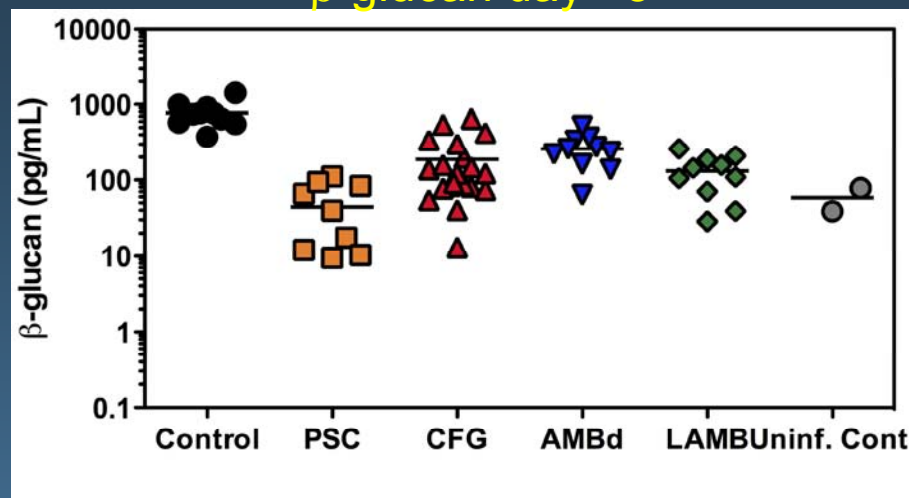
β-Glucan	Uninfected	1 hr SAC	Day +1	Day +3	Day +5	Day +7
Median	37.6	49.2	29.2	218	635	442
Range	56.0 - 68.3	0 - 65.8	12.3 - 39.2	49.2 - 609	142 - 1375	225 - 510
Galactomannan	1 hr SAC	Day +1	Day +3	Day +5	Day +7	
Median	0.21	0.24	1.42	1.75	2.87	
Range	0.14 - 5.70	0.14 - 0.59	0.17 - 4.84	0.28 - 5.79	1.09 - 5.10	

# (1→3)-β-D-Glucan & Therapy Response

Survival



β-glucan day +5



AF293	Control	PSC 40 mg/kg	CFG 2 mg/kg	AMBd 3 mg/kg	LAMB 10 mg/kg
Percent Survival (Median)	20 (9 days)	100 (>12 days)	57 (>12 days)	50 (10 days)	50 (10.5 days)
β-glucan (Range)	758 (377 - 1426)	28.5 (0 - 111)	121 (13.0 - 650)	250 (63.8 - 525)	127 (28.5 - 259)
Log CE/gm (Range)	10 (9.1 - 11)	3.6 (0 - 8.7)	6.9 (6.4 - 8.1)	9.6 (8.8 - 11)	8.9 (8.3 - 9.8)

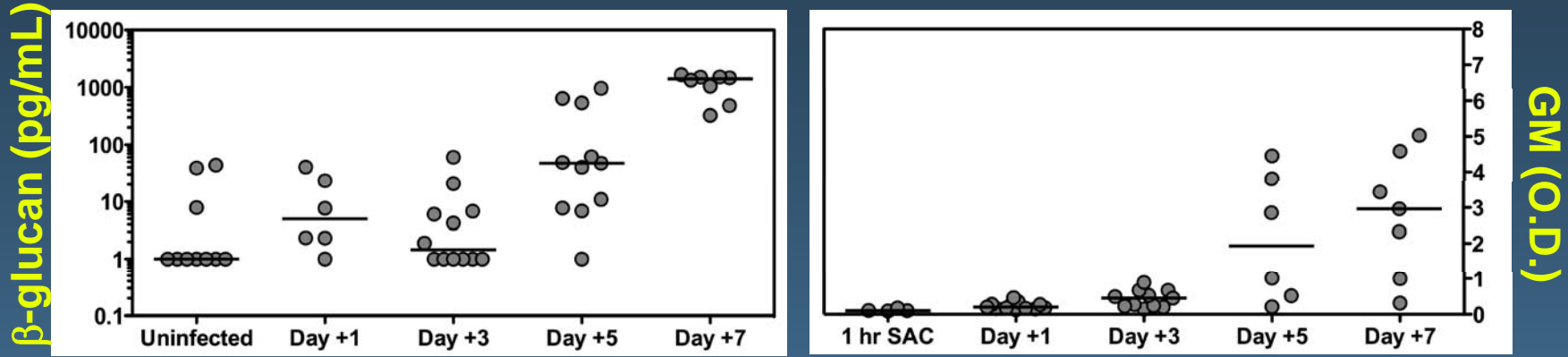
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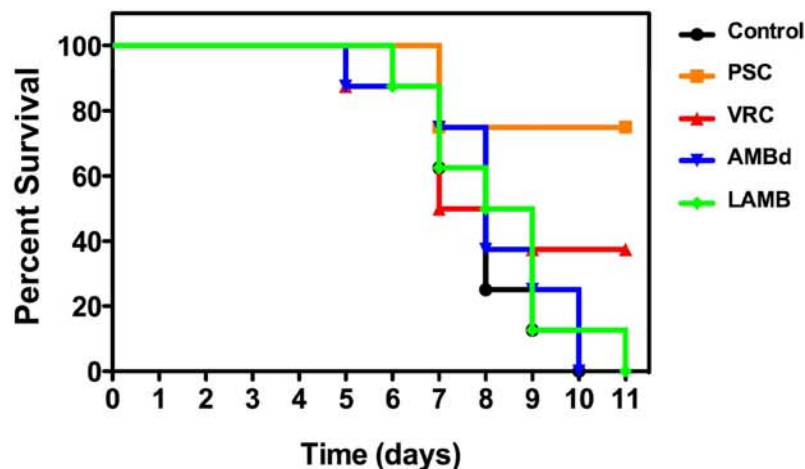
# (1→3)-β-D-Glucan and Galactomannan (neutropenic guinea pig model)



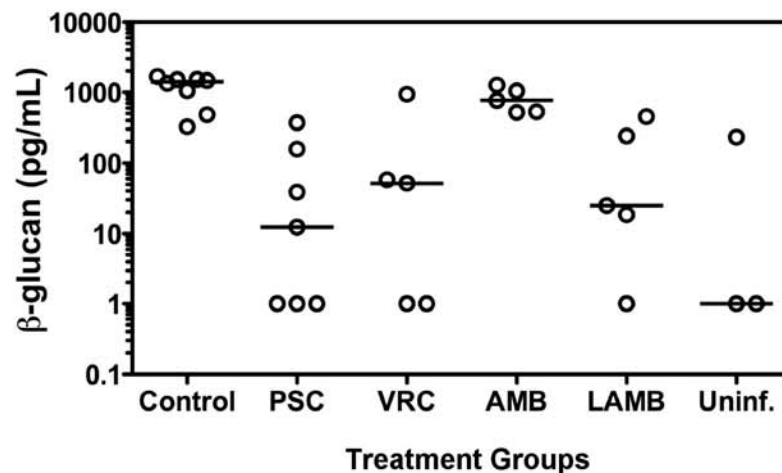
β-Glucan	Uninfected	Day +1	Day +3	Day +5	Day +7
Median	0	5.0	0.9	47.6	1407
Range	0 - 43.9	0 - 40.6	0 - 60.5	0 - 971	326 - 1682
Galactomannan	Day +1	Day +3	Day +5	Day +7	
Median	0.20	0.45	1.93	2.97	
Range	0.13 - 0.46	0.15 - 0.89	0.21 - 4.45	0.31 - 5.03	

# (1→3)- $\beta$ -D-Glucan & Therapy Response

Survival



$\beta$ -glucan day +7



## AF293

	Control	POS 20 mg/kg BID	VOR 20 mg/kg BID	AMB 1.3 mg/kg IP	LAMB 10 mg/kg IV
Percent Survival	0	75	37.5	0	0
(Median Survival)	(8)	(>11)	(8)	(8)	(8.5)
Median $\beta$ -glucan	1407	12.4	51.9	772	25.0
(Range)	(325 - 1682)	(0 - 371)	(0 - 941)	(520 - 1269)	(0 - 456)

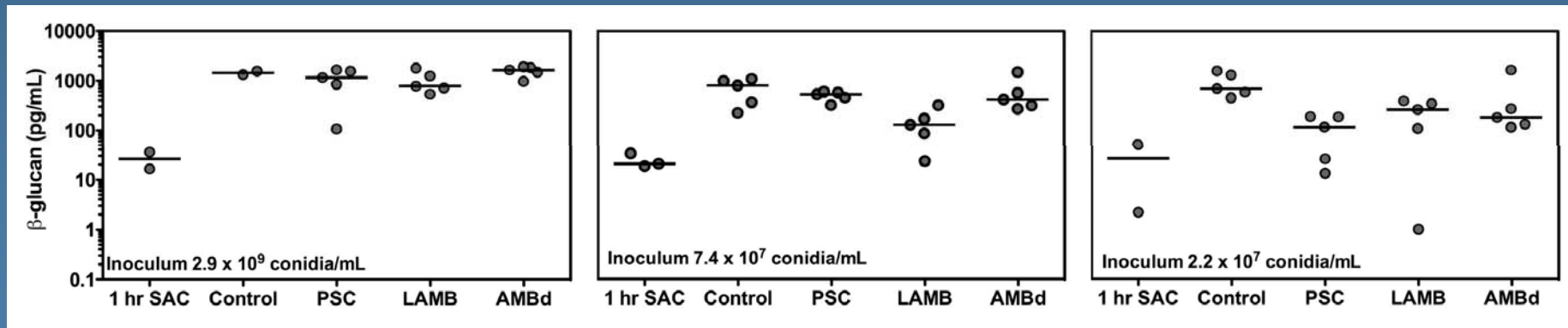
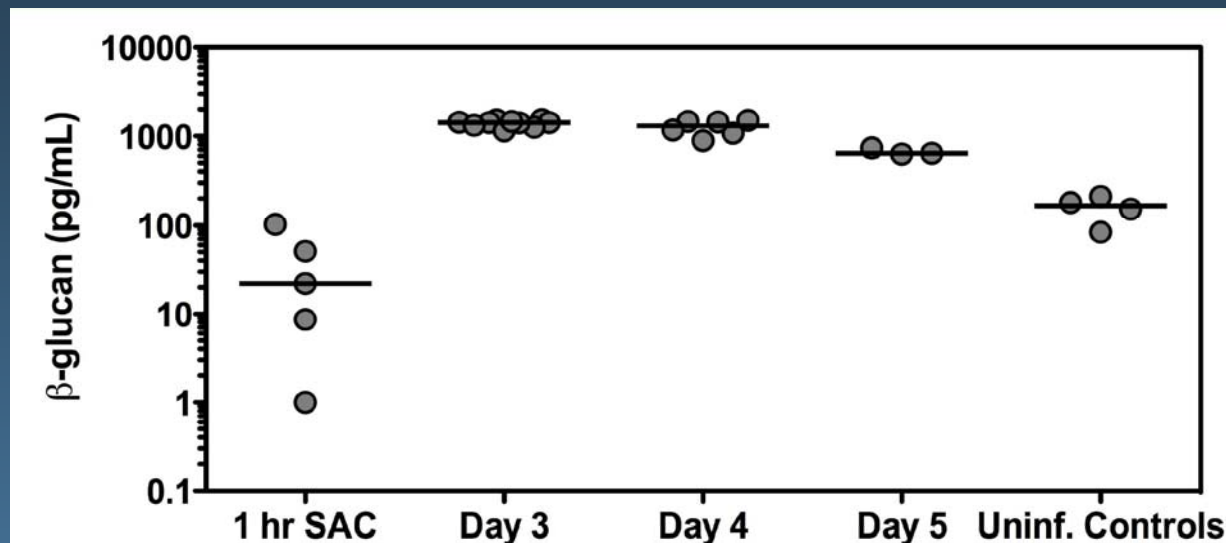
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# (1→3)-β-D-Glucan (murine non-neutropenic model)



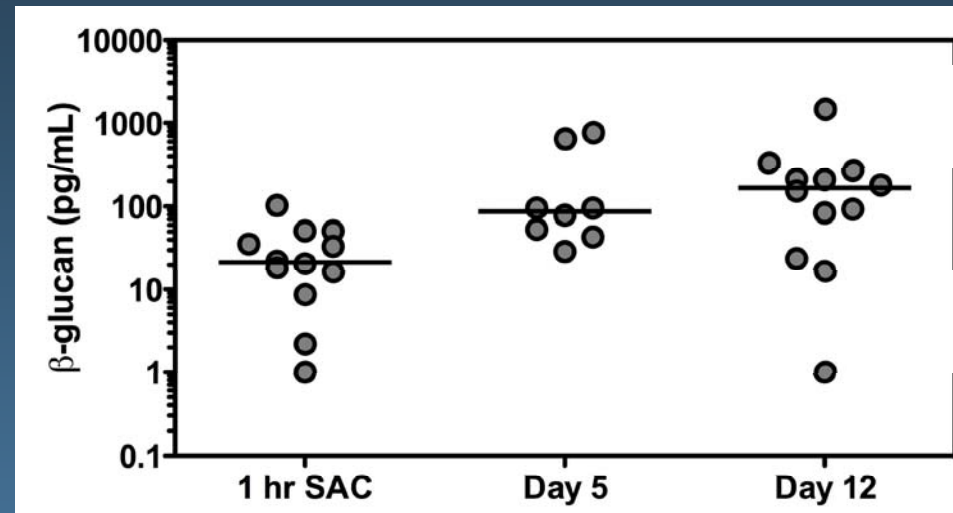
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# (1→3)-β-D-Glucan Uninfected Controls



β-Glucan (pg/mL)	Uninfect. D5 (Neutropenic)	Non-neutropenic		
		1 hr Sac	Day +5	Day +12
Median	37.6	21.4	87.0	167
Range	56.0 - 68.3	0 - 103	28.9 - 768	0 - 1458

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# Conclusions

- Serum (1,3)- $\beta$ -D-glucan & galactomannan detectable earlier in course of infection in neutropenic murine & guinea pig models
  - > 60 pg/mL by day +5
  - Later detection in guinea pig model (day 7)
- Early decreases in serum (1,3)- $\beta$ -D-glucan were predictive of survival in murine model
  - Median values of < 60 pg/mL on day +5 associated with 100% survival in posaconazole group
  - Reductions associated with improved survival in amphotericin B groups
- (1,3)- $\beta$ -D-glucan detected early in non-neutropenic murine model
  - Levels above threshold for positivity in uninfected controls

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