

Galaktomannan, Beta-D-Glucan und PCR-basierte Tests für die frühzeitige Diagnose von IFI bei Kindern mit Krebserkrankungen und bei Kindern nach HSZT

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Interessenskonflikte

Vortragshonorar:

Astellas, Gilead Sciences,
Merck/MSD, Pfizer

Advisory board:

Astellas, Basilea, Gilead
Sciences, Merck/MSD

Forschungsunterstützung:

Gilead Sciences

Hintergrund und Methoden (I)

- Biomarker wichtiger Bestandteil in der Diagnostik von IFI als auch (GM/BG) mikrobiologisches Kriterium in der Definition der IFI
- Fragestellung: Wertigkeit von GM, BG, und Pilz-PCR in der Diagnostik von IFI bei Kindern mit Krebserkrankungen oder nach HSZT
 - Im Screening während der Neutropenie / schweren Immunsuppression
 - In der Diagnostik bei Patienten mit Fieber bei Neutropenie oder mit Symptomen, die auf IFI hinweisen

Methoden (II)

- Ausschluss von Studien die “possible IFI” als invasive Pilzinfektionen eingruppiieren
- Biomarker:
 - GM: Cut-off OD ≥ 0.5 ein- bzw. zweimal, ≥ 0.7 einmal
 - BG: Cut-off 80 pg/mL (Fungitell[®])
- Kriterien der Definition einer IFI oder IA
 - “Proven or probable” nach EORTC/MSG Kriterien

Galactomannan, β -D-Glucan, and Polymerase Chain Reaction-Based Assays for the Diagnosis of Invasive Fungal Disease in Pediatric Cancer and Hematopoietic Stem Cell Transplantation: A Systematic Review and Meta-Analysis

Thomas Lehrnbecher,¹ Paula D. Robinson,² Brian T. Fisher,³ Elio Castagnola,⁴ Andreas H. Groll,⁵ William J. Steinbach,⁶ Theoklis E. Zaoutis,³ Zelalem F. Negeri,⁷ Joseph Beyene,^{7,8} Bob Phillips,^{9,10} and Lillian Sung¹¹

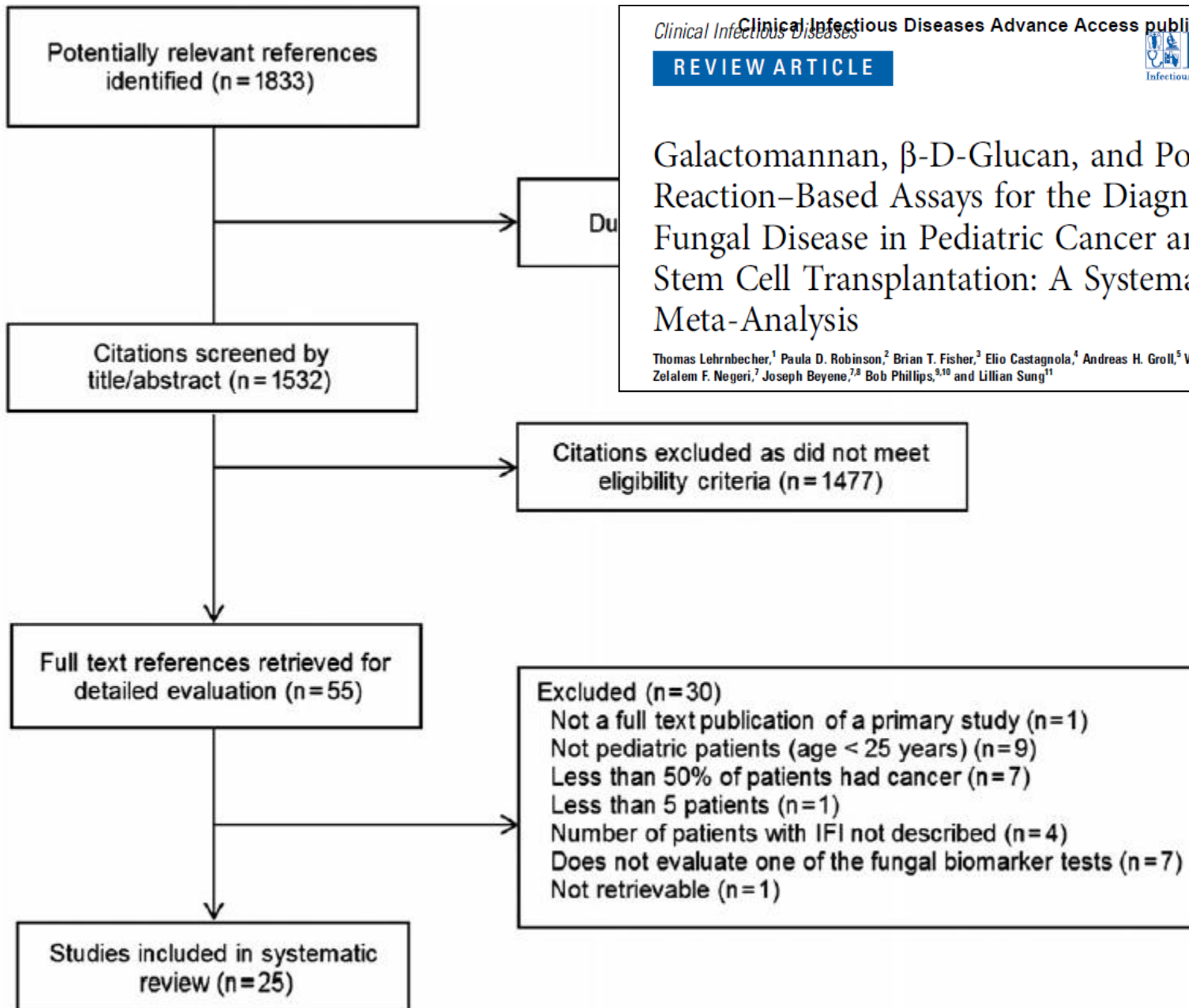


Figure 1. Study flowchart. Abbreviation: IFI, invasive fungal illness.

Galactomannan (GM)

GM: - 18 studies enrolled 1,421 patients (184 proven/probable IFDs)

- 10 studies on surveillance during neutropenia and 8 studies on GM as diagnostic tool in patients with persistent FN / symptoms suggestive for IFD

Pooled results	Pediatrics*				Adults			
	Sensitivity		Specificity		Sensitivity ¹		Specificity ¹	
Galactomannan								
Screening (n=5)	68%	(51 to 81)	91%	(86 to 94)				
Diagnostic Test (n=5)	89%	(79 to 95)	85%	(51 to 97)				
Total	81%	(69 to 89)	88%	(75 to 95)	82%	(73 to 90) [1]	81%	(72 to 90) [1]

Leeflang Cochrane Database Syst Rev 2015

Lehrnbecher et al, CID 2016

Galactomannan (GM)

10 studies - surveillance

- PPV* < 70% in 8/10
- NPV** good - excellent ($\geq 85\%$) in all

8 studies – diagnostic test

- PPV* $\leq 75\%$ in 7/8 and <50% in 4/8
- NPV** good – excellent ($\geq 84\%$) in all

*PPV- if have a positive test, chance you have disease

**NPV: if you have a negative test, chance you don't have the disease

BG in Blood (n=3)

3 studies enrolled 226 patients, 38 proven/probable IFD

First Author	No. Patients	Prevalence	Specificity*	Sensitivity*	Positive Predictive	Negative Predictive
Koltze	34	17.6	29% (13-49)	83% (36-100)	20% (7-41)	89% (52-100)
Zhao	130	16.9	82% (74-89)	82% (60-95)	49% (32-66)	96% (89-99)
Badiee	62	16.1	52% (38-66)	50% (19-81)	17% (6-35)	84% (67-95)

*synthesis not possible due to low number of patients

PCR in blood

- PCR: - 11 studies enrolled 686 patients (86 proven/probable IFDs)
- 3 studies on surveillance and 8 studies on PCR as diagnostic tool
 - 6 studies using *Aspergillus*-PCR, 5 studies “Pan”-fungal PCR

Pooled results	Pediatrics		Adults	
	Sensitivity	Specificity	Sensitivity ¹	Specificity ¹
PCR				
Screening (n=1)	NA	NA		
Diagnostic Test (n=6)	76% (62 to 86)	58% (42 to 72)		
Total			80.5% (73 to 86.3) *	78.5% (67.8 to 86.4) *

Cruciani Cochrane Database Syst Rev 2015

PCR in blood

- PCR for screening
 - PPV $\leq 50\%$ in all; NPV variable 60-96%
- PCR as diagnostic test
 - PPV $\leq 50\%$ in 7/8; NPV good ($\geq 85\%$) in all

Important Observations

- Predictive values similar with possible IFD classified as not having IFD or when patients with possible IFD were excluded from analysis
- Predictive values did not clearly differ based upon use in screening or diagnostic testing setting
- Test characteristics did not systematically improve as disease prevalence increased
- Antifungal prophylaxis in most studies not standardized- no conclusion possible

BIOMARKERS-Updated Recommendations

Evaluation

Consider **not** using serum GM **for surveillance or for early diagnosis** to identify invasive aspergillosis in patients at high risk for IFD

2B
Weak recommendation
Moderate-quality
evidence

In IFD low-risk patients, do not implement routine galactomannan screening.

1C
Strong recommendation
Low-quality evidence

All patients: **Perform GM in BAL** to support diagnosis of pulmonary aspergillosis.

1C
Strong
recommendation
Low-quality evidence

In children, **do not use BG or PCR testing for surveillance or early diagnosis** of IFD

1B
Strong recommendation
Moderate-quality
evidence

Danke für die
Aufmerksamkeit

PCR in Blood as Screening Test (n=3)

11 studies enrolled 686 patients, 86 proven/probable IFD
(multi-fungal PCR n=5, Aspergillus PCR n=6)

First Author	No. Patients	Prevalence	Positive Predictive	Negative Predictive
Badiee	62	16.1	50% (25-75)	96% (85-99)
Bialek	17	5.0	20% (3-56)	86% (42-100)
Armenian	68	4.4	22% (3-60)	60% (44-75)

PCR in Blood as Diagnostic Test (n=8)

First Author	No. Patients	Prevalence	Positive Predictive	Negative Predictive
Lin	42 (83 episodes)	40.5	71% (49-87)	100% (81-100)
El-Mahallawy	91	30.8	66% (47-81)	88% (77-95)
Dendis	24	20.8	50% (19-81)	100% (77-100)
Cesaro	62	12.9	17% (7-32)	95% (76-100)
Hummel	71	7.0	19% (5-42)	98% (89-100)
Landlinger	125 (150 episodes)	6.7	14% (7-25)	100% (95-100)
Mandhaniya	29	3.4	0% (0-19)	91% (59-100)
Reinwald	95 (253 episodes)	0.0	0% (0-8)	100% (93-100)

BIOMARKERS - Original Recommendations

Evaluation

Consider prospective monitoring of serum galactomannan twice per week in IFD high-risk hospitalized children for early diagnosis of invasive aspergillosis

2B
Weak recommendation
Moderate-quality evidence

In IFD low-risk patients, do not implement routine galactomannan screening.

1C
Strong recommendation
Low-quality evidence

All patients: Consider galactomannan in BAL and CSF to support diagnosis of pulmonary or central nervous system aspergillosis.

2C
Weak recommendation
Low-quality evidence

In children, clinical decisions should not be based on BG testing until further pediatric evidence has accumulated.

1C
Strong recommendation
Low-quality evidence

Blood Fungal PCR

11 studies enrolled 686 patients, 86 proven/probable IFD
(multi-fungal PCR n=5, Aspergillus PCR n=6)

	Sensitivity	Specificity	PPV	NPV
Screening (n=3)	11-80%	43-85%	20-50%	60-96%
Diagnostic test (n=8)*	0-100%	36-83%	0-71%	88-100%
Pooled Diagnostic (n=6)	76% (62 to 86)	58% (42 to 72)		

For screening and diagnostic test – ranges shown. For pooled, mean and 95% CI
*e.g., FN, clinical symptoms suggestive for IFD

GM in Blood as Screening Test (n=10)

First Author	No. Patients	Prevalence	Specificity	Sensitivity	Positive Predictive	Negative Predictive
Hayden	56	30.4	87% (73-96)	65% (38-86)	69% (41-89)	85% (70-94)
Rohrlich	37	27.0	93% (76-99)	100% (69-100)	83% (52-98)	100% (86-100)
Koltze	34	17.6	100% (88-100)	83% (36-100)	100% (48-100)	97% (82-100)
Badiee	62	16.1	90% (79-97)	90% (56-100)	64% (35-87)	98% (89-100)
Gefen	46	8.7	66% (49-80)	80% (28-99)	22% (6-48)	96% (82-100)
Tabone	76	7.9	87% (77-94)	100% (54-100)	40% (16-68)	100% (94-100)
Bialek	17	5.0	50% (23-77)	100% (29-100)	30% (7-65)	100% (59-100)
Hovi	98 (117 episodes)	2.0	90% (84-95)	50% (1-99)	8% (0-38)	99% (95-100)
Steinbach	64	1.6	87% (77-94)	0% (0-98)	0% (0-37)	98% (90-100)
Fisher	198	0.5	95% (91-98)	0% (0-98)	0% (0-31)	99% (97-100)

GM in Blood as Diagnostic Test (n=8)

First Author	No. Patients	Prevalence	Specificity	Sensitivity	Positive Predictive	Negative Predictive
El-Mahallawy	91	30.8	49% (36-62)	79% (59-92)	41% (28-55)	84% (68-94)
Choi	99	23.2	82% (70-90)	91% (72-99)	66% (47-81)	96% (87-100)
Dinand	145 (211 episodes)	13.8	72% (65-78)	95% (75-100)	26% (17-38)	99% (96-100)
de Mol	38	10.9	100% (85-100)	87% (60-98)	100% (75-100)	92% (74-99)
Armenian	68	4.4	98% (88-100)	14% (3-35)	75% (19-99)	70% (58-81)
Castagnola	119 (195 episodes)	3.6	98% (95-100)	100% (59-100)	70% (35-93)	100% (98-100)
Jha	78 (100 episodes)	2.0	35% (25-45)	100% (16-100)	3% (0-11)	100% (90-100)
Reinwald	95 (253 episodes)	0.0	90% (82-96)	NC	0% (0-37)	100% (95-100)

PCR in Blood as Screening Test (n=3)

First Author	No. Patients	Prevalence	Specificity	Sensitivity	Positive Predictive	Negative Predictive
Badiee	62	16.1	85% (72-93)	80% (44-97)	50% (25-75)	96% (85-99)
Bialek	17	5.0	43% (18-71)	67% (9-99)	20% (3-56)	86% (42-100)
Armenian	68	4.4	79% (61-91)	11% (1-33)	22% (3-60)	60% (44-75)

PCR in Blood as Diagnostic Test (n=8)

First Author	No. Patients	Prevalence	Specificity	Sensitivity	Positive Predictive	Negative Predictive
Lin	42 (83 episodes)	40.5	72% (51-88)	100% (80-100)	71% (49-87)	100% (81-100)
El-Mahallawy	91	30.8	83% (71-91)	75% (55-89)	66% (47-81)	88% (77-95)
Dendis	24	20.8	74% (49-91)	100% (48-100)	50% (19-81)	100% (77-100)
Cesaro	62	12.9	37% (24-51)	88% (47-100)	17% (7-32)	95% (76-100)
Hummel	71	7.0	74% (61-84)	80% (28-99)	19% (5-42)	98% (89-100)
Landlinger	125 (150 episodes)	6.7	57% (49-65)	100% (69-100)	14% (7-25)	100% (95-100)
Mandhaniya	29	3.4	36% (19-56)	0% (0-98)	0% (0-19)	91% (59-100)
Reinwald	95 (253 episodes)	0.0	54% (43-64)	NC	0% (0-8)	100% (93-100)