Medical University of Graz

Risk Assessment in the Haemato-Oncologic Patient

Acute Leukemia

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TIMM
Trends in Medical Mycology

Disclosures:

MSD Pfizer

Research grants
(investigator initiated studies)

Pfizer MSD astellas

Speakers honorarium

Genericon Pharma

Epidemiology Haemato-Oncologic (1)

Table 1. Stratification of immunocompromised patients in risk categories for invasive fungal disease according to incidence and mortality rates obtained from current literature[2–7,9–11]

Low risk	Intermediate risk	High risk
autologous HSCT	acute lymphoblastic leukaemia	acute myeloid leukaemia (above all in first induction)
Hodgkin's lymphoma	chronic lymphocytic leukaemia	allogeneic HSCT (particularly with cord blood source)
chronic myeloproliferative disorders (CML and Ph− diseases)	lymphoma	heart, lung, liver transplantation
solid cancer	COPD	
myeloma	AIDS	
kidney transplantation	myelodysplastic syndromes	
chronic immunological disease		
systemic lupus erythematosus		

CML, chronic myeloid leukaemia; COPD, chronic obstructive pulmonary disease; Ph−, Philadelphia negative.

Pagano L, JAC 2011

Epidemiology Haemato-Oncologic (2)

Table 1. Patient populations considered to be at high risk of invasive mould diseases

Patients	Example
With uncontrolled underlying disease	relapsed acute leukaemia
	prolonged MDS
Undergoing treatment	remission induction therapy for acute leukaemia or MDS
	monoclonal antibodies, e.g. etanercept, alemtuzumab
	prolonged treatment with corticosteroids (prednisolone or equivalent mean minimum dose of 0.3 mg/kg/day or for >3 weeks)
Receiving an allogeneic HSCT	
Post-allogeneic HSCT	corticosteroids to manage GVHD
	GVHD with or without CMV disease
History of previous invasive mould disease	probable or proven invasive aspergillosis

MDS, myelodysplastic syndrome; GVHD, graft-versus-host disease; CMV, cytomegalovirus.

Agrawal S, JAC 2011

Epidemiology Haemato-Oncologic (3)

Table 1. Demographic data and host factors of study groups

	Group A, patients with probable/ proven IFI	Group BI, patients with systemic antifungal therapy, but without IFI	*P* value, comparison between groups A and BI, if significant	Group BII, patients without systemic antifungal therapy and without IFI	*P* value, comparison between groups A and BII, if significant
n	58	116		116	
Sex, male/female	40 (69%)/18 (31%)	73 (63%)/43 (37%)		80 (69%)/36 (31%)	
Age (years), range (median)	18–80 (50.78)	21–80 (53.64)		18–80 (52.63)	
Room of care					
HEPA-filtered room	14 (24%)	19 (16%)		9 (8%)	0.004
standard room	44 (76%)	101 (87%)		107 (92%)	0.004
Underlying disease					
AML	24 (41%)	48 (41%)		13 (11%)	<0.001
NHL	7 (12%)	24 (21%)		48 (41%)	<0.001
MDS	4 (7%)	12 (10%)		3 (3%)	
MM	2 (3%)	4 (3%)		17 (15%)	0.036
CLL	4 (7%)	8 (7%)		16 (14%)	
ALL	10 (17%)	9 (8%)		3 (3%)	0.001
others	7 (12%)	11 (9%)		16 (14%)	
Chemotherapy					
high dose	38 (66%)	63 (54%)		56 (48%)	0.046
low dose	8 (14%)	17 (15%)		31 (27%)	
none	11 (19%)	36 (31%)		29 (25%)	
GVHD grade III/IV	10 (17%)	19 (16%)		0	
Three or more host factors present	19 (33%)	15 (13%)	0.003	1 (1%)	<0.001
Neutropenia (0.05×10^9/mL)					
no	17 (29%)	51 (44%)		97 (84%)	<0.001
<10 days	6 (10%)	36 (31%)	0.002	13 (11%)	
>10 days	35 (60%)	29 (25%)	<0.001	6 (5%)	<0.001
median (days) in case of neutropenia	17	8		5	
T cell suppressants within 90 days	41 (71%)	69 (59%)		29 (25%)	<0.001
Use of corticosteroids (minimum dose of 0.3 mg/kg/day of prednisone equivalent)					
no	32 (55%)	77 (66%)		64 (55%)	
<14 days	8 (14%)	30 (26%)		45 (39%)	<0.001
>14 days	18 (31%)	9 (8%)	<0.001	4 (3%)	<0.001
>21 days	13 (22%)	6 (5%)	0.001	3 (3%)	<0.001
HSCT[a]					
allogeneic recent	11 (19%)	12 (10%)		0	<0.001
allogeneic previous	9 (16%)	22 (19%)		16 (14%)	
allogeneic all	20 (34%)	34 (29%)		16 (14%)	0.003
autologous recent	2 (3%)	5 (4%)		8 (7%)	
autologous previous	3 (5%)	2 (2%)		3 (3%)	

ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; HSCT, haematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma.
[a]Definition: recent HSCT: IFI/admission <6 months after SCT; previous HSCT: IFI/admission >6 months after SCT.

Single centre study

- **5-year-period**
- **58 cases of probable/proven IFI**
- **14 yeasts, 49 moulds**
- **2 control groups**
- **With/without AF therapy**
- **Retrospective matching 2:1 for sex and age**

Hoenigl M et al J Antimicrob Chemother 2012

Epidemiology Haemato-Oncologic (4)

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Hoenigl M et al J Antimicrob Chemother 2012

Epidemiology Haemato-Oncologic (5)

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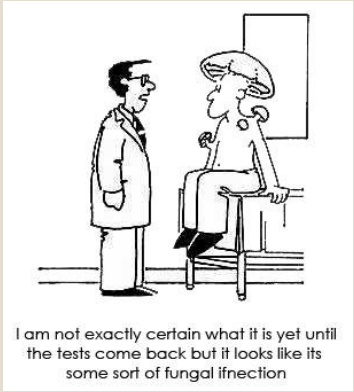
Hoenigl M et al J Antimicrob Chemother 2012

Why Early Diagnosis? (1)

- **Diagnosis of IPA difficult**
  - **Clinical signs, symptoms & radiological findings often unspecific**
  - **Conventional culture methods lack sensitivity**
  - **Only one fourth of autopsy proven IMI diagnosed pre-mortem**



Chamilos et al, Haematologica 2006

Hoenigl et al, CID 2010

Why Early Diagnosis? (2)

- **Crude mortality of 80-90% in absence of adequate treatment**

Key factors in successful treatment

- **Timely diagnosis**
- **Early start of antifungal therapy**

Various studies have shown that early initiation of antifungal therapy may improve IFI survival to above 80%

Greene et al, CID 2007

Lass-Flörl et al, CID 2007

Why Early Diagnosis? (3)

Assessment of individual risk factors for IFD may facilitate a more rapid & precise diagnostic approach in individual patients

In pts at risk, GM, BDG screening/ prophylaxis; early chest CT, BAL

Greene et al, CID 2007

Lass-Flörl et al, CID 2007

BAL Lateral Flow Device Test for IA

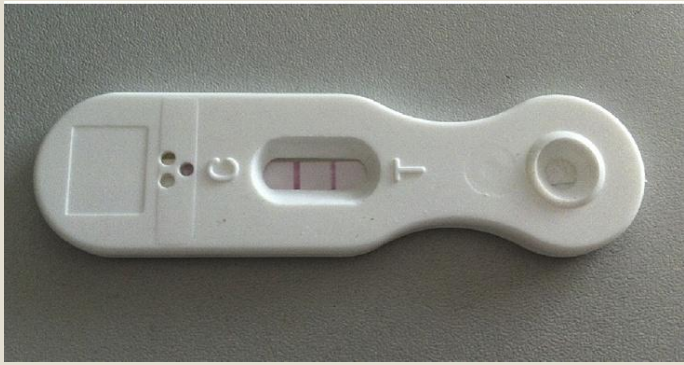
• Point-of-care test for invasive aspergillosis

• Detects an extracellular glycoprotein secreted during active growth of *Aspergillus* via mAB JF 5

• Developed byChristopher Thornton, University of Exeter, UK

• Simple, rapid (15 min), single-use test
  – Can be performed in rudimentary facilities using BAL or serum specimens

• http://www.jove.com/video/3721/



39 BALs from 37 pts

Sensitivity compared to GM 100%; Specificity 81%

Table 1 Demographic data, underlying diseases and test results of Study Cohort.

Pat No.	Underlying disease	Patient's age (years)/sex	BAL GM value*	BAL LFD result	Fungal growth in BAL culture	IPA according to EORTC 2008 criteria
SOT patients						
1	LTx 2012	43/m	0.52	–	No	No
2	HTx 2004, KTx 2011	48/m	0.42	+	*Aspergillus fumigatus*	Probable
3	KTx 2011	34/m	1.22	++	No	Probable
4	LTx 2008	67/m	0.7	+	*Aspergillus fumigatus*	Probable
5	KTx 2011	55/f	4.66	+++	*Aspergillus fumigatus*	Probable
6	LTx 2011	65/m	0.73	++	No	Possible
7	LTx 2012	58/m	19.86	++	*Aspergillus fumigatus*	Probable
8	LTx 2007	63/m	Negative	–	*Lichtheimia corymbifera*	No
9	HTx 2012	30/m	Negative	–	*Candida albicans*	No
10	KTx 1999	67/f	Negative	–	No	No
Haematological malignancy patients						
11	AML	64/m	Negative	–	No	No
12	NHL, HSCT	46/f	1.5	+	No	Probable
13	MM, HSCT	52/m	19.3	+++	No	Probable
14	AML	36/m	18.45	+++	No	Probable
15	NHL	72/m	2.8	++	No	Probable
16	AML	14/f	1.23	+	No	Probable
17	NHL	62/m	Negative	–	No	No
18	Autoimmune haemolytic anaemia	50/f	Negative	–	No	No
19	MM, HSCT	69/m	Negative	–	No	Possible
			Negative	–	No	No
20	MM	58/m	Negative	–	No	No
			Negative	–	No	No
21	AML	56/m	Negative	–	No	Possible
22	NHL	75/f	Negative	–	No	No
23	NHL	71/m	22	++	*Aspergillus fumigatus*	Probable
24	ALL	49/f	Negative	–	No	No
25	AML	41/f	Negative	+	No	Possible
26	MM, HSCT	67/m	0.6	+	*Candida glabrata*	Possible
27	AML	55/m	Negative	–	No	No
28	Sezary Syndrome, HSCT	56/m	0.63	+	No	Possible
29	AML, HSCT	43/m	Negative	+	No	Possible
30	NHL	56/m	3.2	++	*C. guilliermondii*, *Penicillium* sp.	Probable
31	NHL	62/m	Negative	–	No	No
32	MDS	21/m	Negative	–	No	No
33	AML	51/f	Negative	–	No	Possible
34	NHL	45/m	Negative	–	No	Possible
35	Morbus Hodgkin	40/f	0.47	–	No	No
36	AML	68/f	Negative	–	No	No
37	AML	68/m	Negative	–	No	No

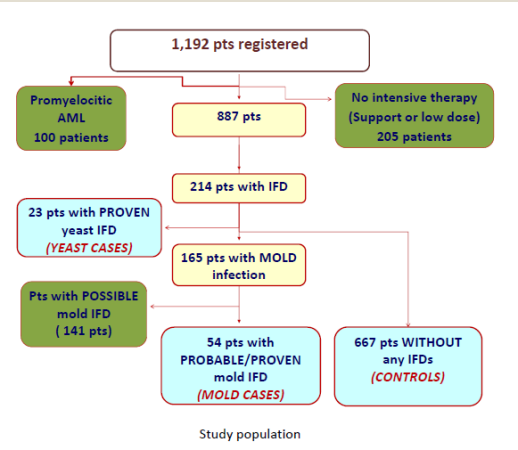
Hoenigl et al. J Infect. 2012 Dec;65(6):588-91.

Risk Factors Pre-hospital (1)

- **Genetic**
- **Environment (Markus Ruhnke)**
  - **Activities/Hobbies**
- **Underlying Diseases**
- **Advanced Age**

Risk Factors Pre-hospital (2)

- **SEIFEM 2010 - (April 2012)**
- **Italy 1192 newly diagnosed AML pts from 31 centres in Italy**
  - **305 pts with promyelocitic AML or low dose PCT excluded**
  - **141 with possible IFD excluded**
  - **23 pts proven yeast infection**
  - **54 probable/proven mould infection**
  - **667 controls**



Study population

Caira M et al, ICAAC 2013 Poster#

Risk Factors Pre-hospital (3)

Table 1. univariate analysis of main risk factors for proven/probable IFDs at time of admission

PRE-TREATMENT VARIABLES	CONTROLS 667 pts	MOLDS 54 pts	P-value	YEASTS 23 pts	P-value
Age - <50 yy - >50yy	217 (33%) 450 (67%	9 (17%) 45 (83%)	0.015	18 (78.2%) 5 (21.8%)	0.27
PERFORMANCE STATUS * - 0-2 - 3-4	607 (91%) 60 (9%)	41 (76%) 13 (24%)	<0.001	20 (87%) 3 (13%)	0.50
Diabetes - yes - no	43 (6.5%) 624 (93.5%)	9 (16.7%) 45 (83.3%)	0.005	2 (8.7%) 21 (91.3%)	0.66
COPD -yes -No	23 (3.4%) 644 (96.6%)	6 (11.1%) 48 (88.9%)	0.005	1 (4%) 22 (96%)	0.81
Smoking -yes -no	196 (29.9%) 471 (70.1%)	24 (44.4%) 30 (55.6%)	0.006	1 (4.3%) 22 (95.7%)	0.14
Type of job -Highly exposing* -non highly exposing	41 (6.1%) 626 (93.9%)	11 (20.3%) 43 (79.7%)	<0.001	1 (2%) 22 (96%)	0.72
Hobbies -Highly exposing** -non highly exposing	58 (8.7%) 609 (91.3%)	10 (18.5%) 44 (81.5%)	0.017	4 (17%) 19 (83%)	0.15

* including those activities more likely exposing to fungal spores, such as construction workers, farmers, gardeners, florists, forestry workers

** including those activities more likely exposing to fungal spores, such as hunting, gardening, fishing, hiking

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Risk Factors Pre-hospital (4)

Background
Early diagnosis
Acute leukemia
RF pre hospital
RF in hospital
Conclusion

Table 2. multivariate analysis of risk factors for proven/probable IMIs and proven yeast infections

	MOLD CASES			YEAST CASES		
VARIABLES	OR	*P value*	CI 95%	OR	*P value*	CI 95%
PRE-HOSPITAL						
1. PERFORMANCE STATUS ≥2	2.69	0.002	1.44-5.00	---	---	---
2. HOUSE RENOVATION	3.93	<0.001	1.83-8.40	---	---	---
3. HIGHER BODY WEIGHT	0.31	0.007	0.13-0.72	---	---	---
4. HIGHLY EXPOSING JOB	3.14	0.006	1.38-7.17	---	---	---
5. COPD	3.54	0.022	1.19-10.5	---	---	---

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Genetic Risk Factors (1)

Genetic risk factors influence susceptibility to, and outcome of IFD

- **e.g. polymorphism within IL-10 production**

a.) ACC haplotype -> decreased IL-10 production

-> 9-fold lower risk of developing IA

b.) ATA haplotype -> increased IL-10 production

-> sign. higher risk for IA

Romani, Nat Rev Immunol 2011
Seo, BMT 2005

Genetic Risk Factors (2)

Other genetic risk factors polymorphisms in

- **TNF-α production**
- **Toll-like receptors (TLR 2, 4; TLR 1, 6)**
- **Plasminogen gene**
- **Dectin-1 deficiency**

.....

Pagano L, JAC 2011
Mezger M, Crit Rev Microbiol 2010
Metzger, Blood 2008
Seo, BMT 2005
Bochud PY; NEJM 2008
Lambourne; Clin Infec Dis 2009
Zaas; Plos Genet 2008
Cunha, Blood 2010

Environmental Risk Factors (1)

Table 2. Environmental risk factors

Risk factor
Seasonal incidence
Weather variation
temperature
rainfall
humidity
wind speed
Personal habits
smoking
living in countryside
fungus exposure
type of work (e.g. farmer, agriculture)
Exposure outside
pets
dusty household
construction work
Exposure inside
potted plants
absence of HEPA-filtered rooms
water

HEPA, high-efficiency particulate air.

Pagano L, JAC 2011
Lambourne J, CID 2009
Brenier-Pinchart, Am J Infect Contr 2009
Lass Flörl, ECCMID 2009, O243
Panackal, CID 2009
Benet, CID 2007
Lass-Flörl, J Hosp Infect 2000

Potted Plants? (1)

Acapulco, Mexico: Springbreak 2001

Potted Plants? (2)

- **More than 200 American college students pulmonary syptoms at springbreak**
- **All in the same hotel in Acapulco**
- **Risk factor: frequent use of the staircase**

→ **Transmission: potting soil!!!**

CDC. MMWR Morb Mortal Wkly Rep 50:359–360.

Taylor ML, FEMS Immunol Med Microbiol 2005; 45: 435–441.

Histoplasmosis

- Background
- Early diagnosis
- Acute leukemia
- RF pre hospital
- RF in hospital
- Conclusion

→ **Reactivation in immigrants from countries where histoplasmosis is endemic (often after decades)**

Risk Factors for other Moulds

Mucorales

- **Neutropenia**
- **Metabolic acidosis (ketoacidotic diabetes)**
- **Iron overload (therapy??)**

Fusariosis, Scedosporiosis

- **Risk factors identical with IA**

Pagano L, Br J Haematol 2009.

Risk Factors after Chemotherapy

Background
Early diagnosis
Acute leukemia
RF pre hospital
RF in hospital
Conclusion

Multivariate

- **Moulds**

Neutropenia
Esophagitis
Urinary Catheter
Protective: Posa prophylaxis

- **Yeasts**

PLUS Central Venous Catheter

Table 2. multivariate analysis of risk factors for proven/probable IMIs and proven yeast infections

	MOLD CASES			YEAST CASES		
AFTER CHEMOTHERAPY						
6. SEVERE NEUTROPENIA	1.03	0.039	1-1.06	---	---	---
7. ESOPHAGITIS	3.49	0.006	1.43-8.48	4.24	0.013	1.35-13.3
8. URINARY CATHETER	2.29	0.022	1.12-4.68	10.3	<0.001	4.1-26
9. CENTRAL VENOUS CATHETER	---	---	---	7.25	0.058	0.93-56
10. POSACONAZOLE PROPHYLAXIS	0.39	0.003	0.21-0.72	0.22	0.006	0.08-0.65

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Risk Factors at Hospital (1)

Table 3. Common risk factors for IFDs observed in the different groups of patients (including aspergillosis, zygomycosis, fusariosis)

	Neutropenia depth and duration	Monocytopenia	Lymphocytopenia	Steroids	Iron overload	GvHD	CMV infection	Purine analogue or monoclonal antibodies	Renal failure	Advanced age
Haematological malignancy										
acute myeloid leukaemia	+	+	−	−	+	−	−	+	−	+
acute lymphoid leukaemia	−	−	+	+	+	−	−	−	−	+
multiple myeloma	−	−	−	+	−	−	−	−	−	+
Non-Hodgkin's lymphoma	−	−	−	+	−	−	−	+	−	+
Hodgkin's disease	−	−	−	+	−	−	−	−	−	+
chronic myeloid leukaemia	−	−	−	−	−	−	−	−	−	+
chronic lymphoid leukaemia	−	−	+	−	−	−	−	+	−	+

Pagano L, JAC 2011

Risk Factors at Hospital (2)

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T-cell suppressants: IMI vs Group BI (p=0.025)

Hoenigl M et al J Antimicrob Chemother 2012

Risk Factors at Hospital (3)

Table 2. ORs and 95% CIs for host factors

	Group A versus control group BI		Group A versus control group BII	
	OR	95% CI	OR	95% CI
Chemotherapy, high dose	1.59	0.83–3.07	2.04	1.06–3.91
GVHD grade III/IV	1.06	0.46–2.46	[a]	
Three or more host factors present	3.28	1.52–7.09	56.03	7.26–432.36
Neutropenia (0.05×10^9/mL) >10 days	4.57	2.33–8.95	27.90	10.52–74.02
T cell suppressants within 90 days	1.64	0.84–3.23	7.24	3.58–14.64
Use of corticosteroids (minimum dose of 0.3 mg/kg/day of prednisone equivalent)				
>14 days	5.35	2.22–12.88	12.60	4.02–39.48
>21 days	5.29	1.90–14.80	10.88	2.96–40.01

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Risk Factors at Hospital (4)

Current cut-off for corticosteroid treatment in revised EORTC/MSG criteria 21 days

- **Change to cut-off of 14 days may be of benefit for differentiating patients with IFI from those without**

Hoenigl M et al J Antimicrob Chemother 2012
Thursky, BMT 2004

Risk Factors at Hospital (5)

Background
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The most important risk factors at hospital for invasive aspergillosis in patients with acute leukemiar are

- **Profound and sustained granulocytopenia (neutrophils <500/µL for more than 10 days)**
- **Intensive chemotherapy (e.g., high-dose cytosine-arabinosid)**
- **T-cell suppressive therapy**
- **Long-lasting corticosteroid treatment and/or refractory underlying malignant disease**

- **Absence of HEPA filter/construction work at the hospital**

Mikolajewska A , Mycoses 2011
Klastersky J, J Clkin Oncol 2000

Take Home Message

- **Important risk factor pre-hospital**
  - **Genetic predisposition**
  - **Environment**
  - **Activities/Hobbies (smoking, exposure)**
  - **Underlying Diseases (diabetes)**
  - **Advanced Age**
- **Important risk factors in the hospital**

→ **Diagnostic strategies according to risk stratification**

Medizinische Universität Graz


Thank you for your attention !!