Aspergillosis – new risks, new hosts

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EORTC
European Organisation for Research and Treatment of Cancer

MSG 2008
Mycoses Study Group

Table 2. Criteria for probable invasive fungal disease except for endemic mycoses.

Host factors[a]
Recent history of neutropenia (<0.5 × 10^9 neutrophils/L [<500 neutrophils/mm^3] for >10 days) temporally related to the onset of fungal disease
Receipt of an allogeneic stem cell transplant
Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for >3 weeks
Treatment with other recognized T cell immunosuppressants, such as cyclosporine, TNF-α blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogues during the past 90 days
Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency)

De Pauw B et al. CID 2008;46:1813

"host factor" criterion meant to ensure fairly homogeneous population for inclusion in clinical trials, but

… lack of a "host factor" should not be a reason to withhold anti-fungal therapy in someone with clinical, radiological, &/or mycological data suggesting IA

Herbrecht R et al. Ann NY Acad Sci 2012;1272:23

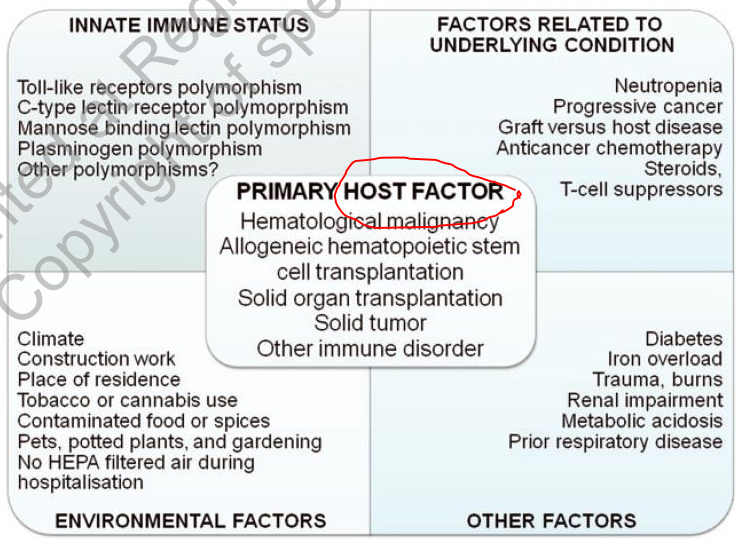


Figure 2. Diagram of the various risk factors affecting the primary host condition.

Herbrecht R et al. Ann NY Acad Sci 2012;1272:23

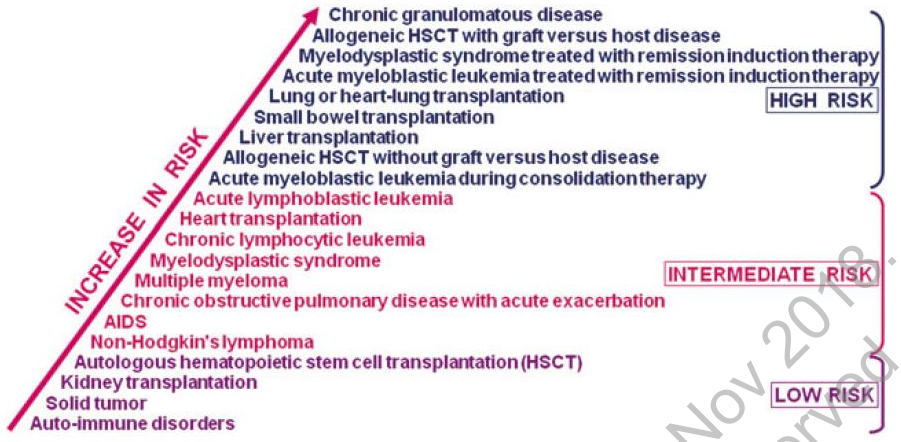


Figure 3. Risk of invasive aspergillosis based on the primary host factor.

Herbrecht R et al. Ann NY Acad Sci 2012;1272:23

"New" or just unfamiliar

- Unconventional
- Non-classical

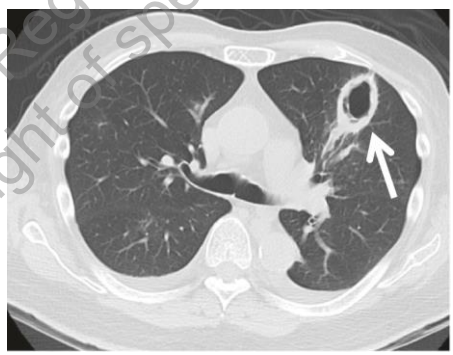
- Associations
- Risk factors

In what clinical circumstances, other than HSCT, SOTx, neutropenia, & steroids, should we also worry about IA?

A man with melanoma

- At age 48 – lesion on cheek – wide excision
- At age 68 – hypertension diagnosed; renal u/s – liver lesions –metastatic melanoma
- Started on ipilumumab → diarrhoea → colonoscopy showing colitis → infliximab x 2 doses, methylpred (2mg/kg) followed by prednisolone (1mg.kg.d)
- A few months later, while asymptomatic, CT chest had this:

Kyi C et al. J Immunother Cancer 2014;2:19



BAL grew *A. fumigatus*

Started on LamB

Kyi C et al. J Immunother Cancer 2014;2:19

So you mean patients with melanoma are at risk of IA?

Or is ipulimumab a risk for IA?

Wisdom of the EORTC!

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Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency)

It's the steroids!

Early-onset invasive aspergillosis and other fungal infections in patients treated with ibrutinib

Identified 33 cases of IFI in patients on ibrutinib
30 of these were on ibrutinib for CLL

- 27/33 were IA
- 40% of IA involved brain
- 18/33 had other, conventional risk factors for IA (eg neutropenia)
- Most of the cases occurred within 3 months of starting ibrutinib
- 17/33 died (9/17 of IFI)

Ghez D et al. Blood 2018;131:1955

IA in ibrutinib-treated patients

Likely results from complex immunodeficiency
Likely classic example of "net state of immunosuppression"

- Environmental exposure to fungal conidia
- Synergism with other immunosuppressive therapies
- Inhibition of BTK on monocytes, macrophages
- Off-target binding of ibrutinib to other kinases
- Genetic predisposition

Off-target binding
✓ Some effect of ibrutinib on other malignancies, eg, breast
✓ Non-infectious AEs associated with binding to other targets, eg, cardiac arrhythmia, bleeding

Chamilos G et al. Clin Infect Dis 2018;66:140

Invasive Pulmonary Aspergillosis Associated with Infliximab Therapy

- 25yo man, fistulizing Crohns, fever, dyspnoea and cough 5d after single dose of infliximab
- Not at that time on steroids or other immunosuppressants
- Required intubation; D7 ETT *A. fumigatus* – contaminant (?)
- Steroids for ARDS
- D13 – ett and BAL – *A. fumigatus*
- Hemothorax – thoracotomy – samples *A. fumigatus*
- Expired – PM – IPA, with samples growing *A. fumigatus*

Warris A et al. NEJM 2001;344:1099

Infliximab use in patients with severe graft-versus-host disease and other emerging risk factors of non -*Candida* invasive fungal infections in allogeneic hematopoietic stem cell transplant recipients: a cohort study

Out of 270 HSCTs done at the Dana-Farber

Overall incidence rate (IR) of IFI: 0.22/1,000 days post-HSCT
IR of IFI (no GVH, or only Grade 1,2 GVH) 0.11/1,000 patient-days
IR of IFI (severe GVH) 0.78/1,000 patient-days

Focusing only on patients with severe GVH
(10 pts with severe GVH developed IFI, 5 of those 10 on infliximab)
Overall IR of IFI 0.99/1,000 GVH patient-days
IR of IFI (severe GVH, received infliximab) 6.78/1,000 GVH patient-days*
IR of IFI (severe GVH, no infliximab) 0.53/1,000 GVH patient-days*

No diffce in cumulative doses of steroids, by "prednisone-equivalents"

Marty FM et al. Blood 2003;102:2768

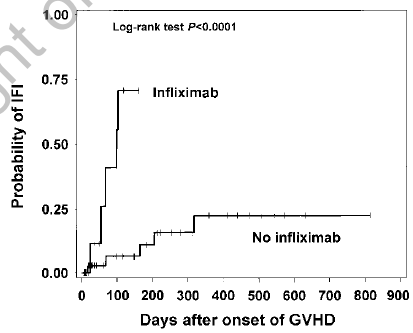


Figure 1. Time to IFI from onset of GVHD among HSC transplant recipients who developed severe GVHD.

Marty FM et al. Blood 2003;102:2768

A personal take

- New hosts but with standard risk factors, eg, steroid exposure (look out for checkpoint inhibitors and "autoimmune" complications!)

- New risk factors (eg ibrutinib) –

More "new" hosts with IA?

Invasive Aspergillosis in Critically Ill Patients without Malignancy

- University Hosp, Leuven, 1/1/2000 – 1/1/2003
- 1700-bed hospital
- 1850 admissions to ICU during study period, 528 deaths (28%)
- 357 of deaths autopsied (68%)
- Aspergillus found in 52 cases (15% of all autopsies)

Role of steroids?

Meerssemann W et al. AJRCCM 2004;170:621

Invasive Aspergillosis in Critically Ill Patients without Malignancy

38 patients with underlying malignancy
(37 haem malig)

Mortality	100%
Autopsy	30/38

Invading hyphae seen in 25/30 (83%) autopsies

89 patients no malignancy

COPD	35 (42%)
SOTx	9 (10%)
AI disease, with IS	17 (19%)
Cirrhosis	6 (7%)
Miscellaneous	22 (25%)

(14/22 – colonization only)

Mortality	71 (80%)
Autopsy	46/71
Invading hyphae	25/46 (59%)

5/30 proven cases without EORTC host factors: cirrhosis (3), 95yo pneumonia (1), ARDS + shock (1)

Meerssemann W et al. AJRCCM 2004;170:621

The *Asp*ICU diagnostic criteria – "PUTATIVE"

❖ **Lower respiratory tract culture with Aspergillus** – ***entry criterion***

➢ **Compatible signs/symptoms** – (any 1 of 7)
- Fever refractory to at least 3 days of appr abx
- Fever recrudescent after 48hr afebrile hr, while still on abx, with no app cause
- Dyspnoea
- Hemoptysis
- Pleuritic chest pain
- Pleural rub
- Worsening resp status while on vent support, despite appr abx

➢ **Abnormal CXR or CT chest**

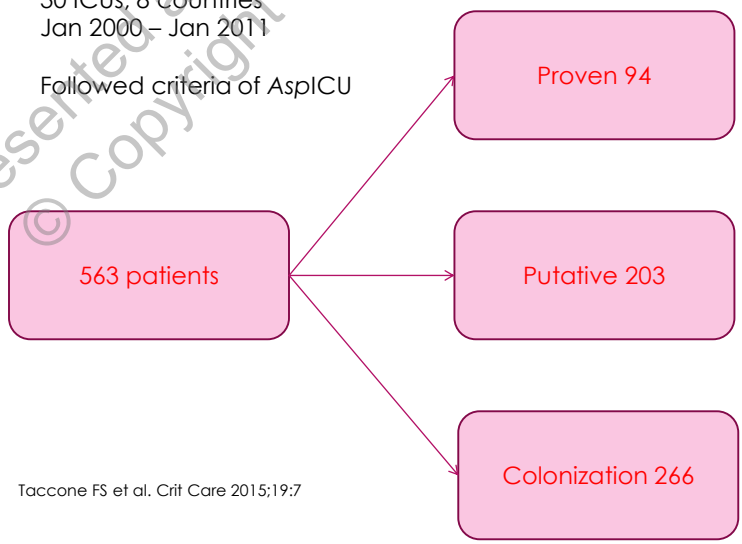
➢ **Either or both**
- Host (neutropenia, malig treated with chemo, steroids, congen/acqd immunodef)
- BAL with Aspergillus (+ or ++) with no bacterial growth AND hyphae seen on cytological smear

Taccone FS et al. Crit Care 2015;19:7

The *Asp*ICU study

30 ICUs, 8 countries
Jan 2000 – Jan 2011

Followed criteria of *Asp*ICU



Taccone FS et al. Crit Care 2015;19:7

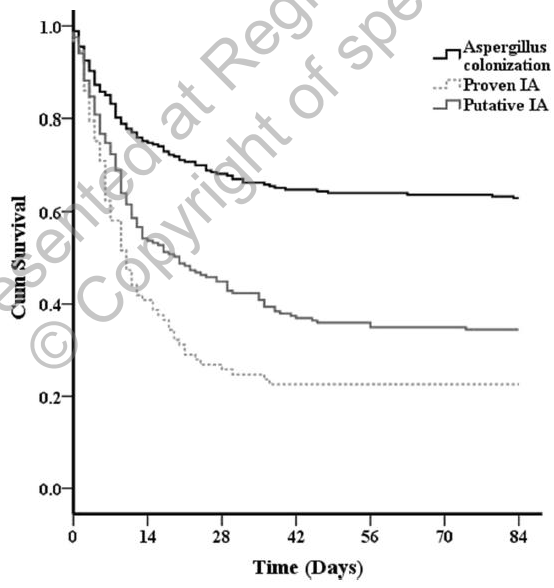
438 (77%) of patients in *Asp*ICU study <u>not classifiable</u> by EORTC/MSG criteria

Underlying diagnoses in proven/putative cases

COPD* Solid tumour Haem malignancy/BMT* Neutropenia*
Liver disease* Chronic CCF SOTx* ESRD
ETOH abuse HIV On IS*

* Stat sig cf colonization

Taccone FS et al. Crit Care 2015;19:7



Survival curves

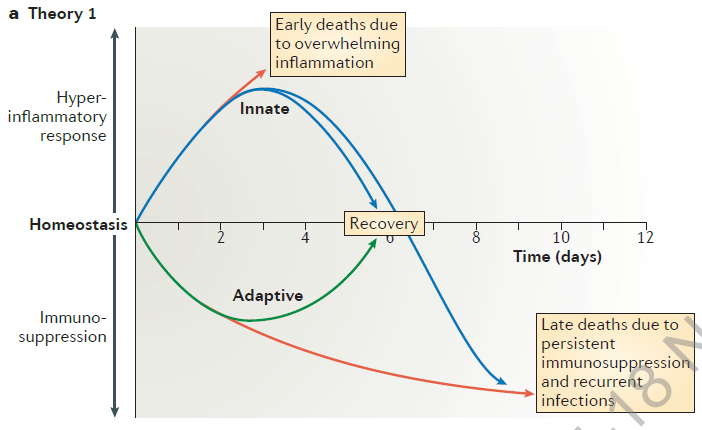
12-wk mortality

Proven IA = 79%
Putative IA = 67%
Colonized = 38%

Putative/Proven vs colonization $p<0.001$

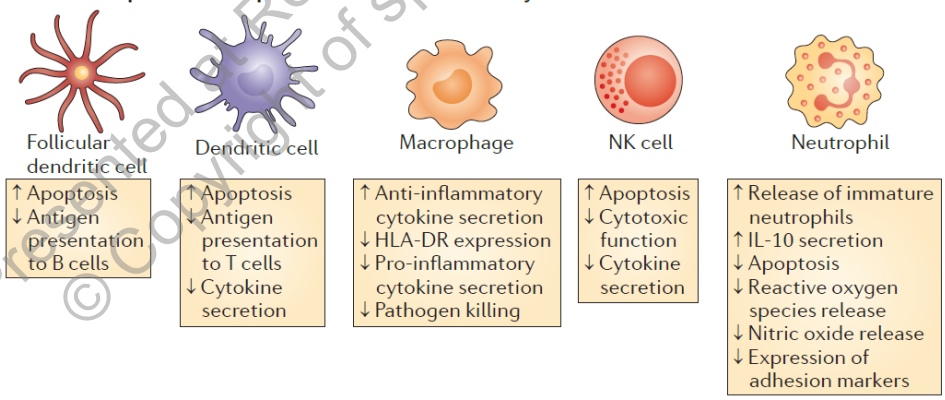
Putative vs proven $p=0.156$

Taccone FS et al. Crit Care 2015;19:7



Fever
Shock

Hotchkiss RS et al. Nat Rev Immunol 2013;13:862



Neutrophil dysfunction precedes nosocomial sepsis

Hotchkiss RS et al. Nat Rev Immunol 2013;13:862

Sepsis-induced immunoparalysis

It is now becoming clear that many patients survive the initial hyperinflammatory phase of sepsis, but die in an immunosuppressive state. This state, called immunoparalysis, is characterized by both innate and adaptive immunodysfunction, resulting in ineffective clearance of septic foci, increased vulnerability towards secondary infections, and reactivation of latent infections.[4]

Hamers L et al. Minerva Anestesiol 2015;81:426

Is it merely immunoparalysis?

2 guys in the ICU

- 8 Mar: known COPD admitted, started on IV Augmentin & prednisolone
- 10 Mar: ICU, intubated
- 11 Mar: ETT asp – *A. fumigatus*
- 16 Mar: BAL, also grew *A. fumigatus*
- 19 Mar: Ampho B
- 26 Mar: RIP
- 23 Mar: known COPD admitted, started on IV Augmentin & prednisolone
- 26 Mar: ICU, intubated; from this point on *A. fumigatus* grew from all ETT c/s (daily)
- 11 Apr: Ampho B
- 17 Apr: RIP

Pittet D et al. AJRCCM 1996;154:541

Experimental air filter change

- Logbook of maintenance reviewed
- Air filters in that room had been replaced on 8 Mar
- 12 days after the 2nd pt died, experimental replacement of filters performed
- Cultures of inside surface of filter yielded heavy growth of *A. fumigatus*
- Cultures of clean surface of air filter no growth
- Air sampling before filter replacement: no growth of fungi
- Air sampling during filter replacement: *A. fumigatus* (64 ± 42 cfu/ml)

Pittet D et al. AJRCCM 1996;154:541

COPD seems to be common "host" getting IPA in the ICU

Invasive Pulmonary Aspergillosis in Patients with Chronic Obstructive Pulmonary Disease: Report of Eight Cases and Review

16 [7] 59/M	*A. fumigatus*	*Strongyloides stercoralis*	Yes	NA	Sputum	NA	Died	Autopsy	Yes	NA
17 [8] 71/F	*A. fumigatus*	None	Prednisone, 40 mg (2 y)	Yes	LB	NA	Died	Autopsy	No	NA
18 [8] 73/M	*Aspergillus* species	*Klebsiella pneumoniae* *Staphylococcus aureus*	Prednisone, 20 mg (2 y)	Yes	LB	NA	Died	Autopsy	No	NA
19 [8] 64/M	*Aspergillus* species	*S. aureus*	Prednisone, 20 mg (>2 y)	No	LB	NA	Died	Autopsy	Yes	NA
20 [8] 51/F	*Aspergillus* species	*P. aeruginosa*	Prednisone, 20 mg (>2 y)	No	LB	NA	Died	Autopsy	Yes	NA
21 [8] 66/F	*A. fumigatus*	None	Prednisone, 30 mg (>2 y)	No	Sputum	NA	Died	Autopsy	Yes	NA
22 [9] 54/M	*A. fumigatus*	CMV	MP, 20–240 mg	Yes	Sputum	AmB	Died	Autopsy	Yes	9
23 [9] 61/M	*A. fumigatus*	*K. pneumoniae*	MP, 50 mg/d (>2 y)	NA	PSB	NA	Died	Autopsy	No	22
24 [9] 61/M	*A. fumigatus*	NA	NA	NA	BAS, LB	AmB	Died	Autopsy	No	16

Only 3 of 24 had not been on steroids

Rello J et al. Clin Infect Dis 1998;26:1473

Aspergillosis complicating COPD – a case series

65 cases (60 from lit, 5 of the authors')

Criteria used 2002 EORTC/MSG criteria, 43 proven

- Mean age 65 (45 – 83)
- Mean duration of smoking 59 pack-years
- Mean FEV1 1.18litres
- 34% had recent exacerbation of COPD (1 – 16 wk prior to diag)
- 75% had been on systemic steroids prior to diag
- 8% only on inhaled steroids before diagnosis
- Duration of steroids prior to diag: 3 wk – 10 yrs
- Symptoms and signs inconsistently reported in literature

Samarakoon P et al. Chr Resp Dis 2008;5:19

TABLE 1 Definitions of invasive pulmonary aspergillosis (IPA) in chronic obstructive pulmonary disease (COPD) patients

Proven IPA	Histopathological or cytopathological examination, from needle aspiration or biopsy specimen obtained from any pulmonary lesion present for <3 months, showing hyphae consistent with Aspergillus and evidence of associated tissue damage, if accompanied by any one of the following: 1) Positive culture of Aspergillus spp. from any LRT sample. 2) Positive serum antibody/antigen test for *A. fumigatus* (including precipitins). 3) Confirmation that the hyphae observed are those of Aspergillus by a direct molecular, immunological method and/or culture.
Probable IPA	As for proven IPA but without confirmation that Aspergillus is responsible (points 1, 2 and 3 are not present or tested). OR COPD patient, usually treated with steroids and severe according to GOLD (stage III or IV), with recent exacerbation of dyspnoea[#], suggestive chest imaging[¶] (radiograph or CT scan; <3 months[+]) and one of the following: 1) Positive culture[§] and/or microscopy for Aspergillus from LRT. 2) Positive serum antibody test for *A. fumigatus* (including precipitins). 3) Two consecutive positive serum galactomannan tests.
Possible IPA	COPD patient, usually treated by steroids and severe according to GOLD (stage III or IV), with recent exacerbation of dyspnoea[#], suggestive chest imaging[¶] (radiograph or CT scan; <3 months[+]), but without positive Aspergillus culture or microscopy from LRT or serology.
Colonisation	COPD patient with positive Aspergillus culture from LRT *without* exacerbation of dyspnoea, bronchospasm or new pulmonary infiltrate.

Data from references [23] and [38]. LRT: lower respiratory tract; *A. fumigatus*: *Aspergillus fumigatus*; GOLD: Global Initiative for Chronic Obstructive Lung Disease; CT: computed tomography. [#]: Exacerbation of dyspnoea and/or bronchospasm resistant to appropriate treatment including antibiotics; [¶]: pulmonary lesion(s) unresponsive to appropriate antibiotics (refers to dose, route, spectrum and activity against cultured bacteria); [+]: pulmonary lesions, especially cavitary, present for >3 months are better classified as chronic pulmonary aspergillosis (see text), unless direct tissue invasion is demonstrated; [§]: standard or sabouraud culture, or molecular detection test when licensed.

Bulpa P et al. Eur Resp J 2007;30:782

Risk factors for IA in COPD admitted to ICU

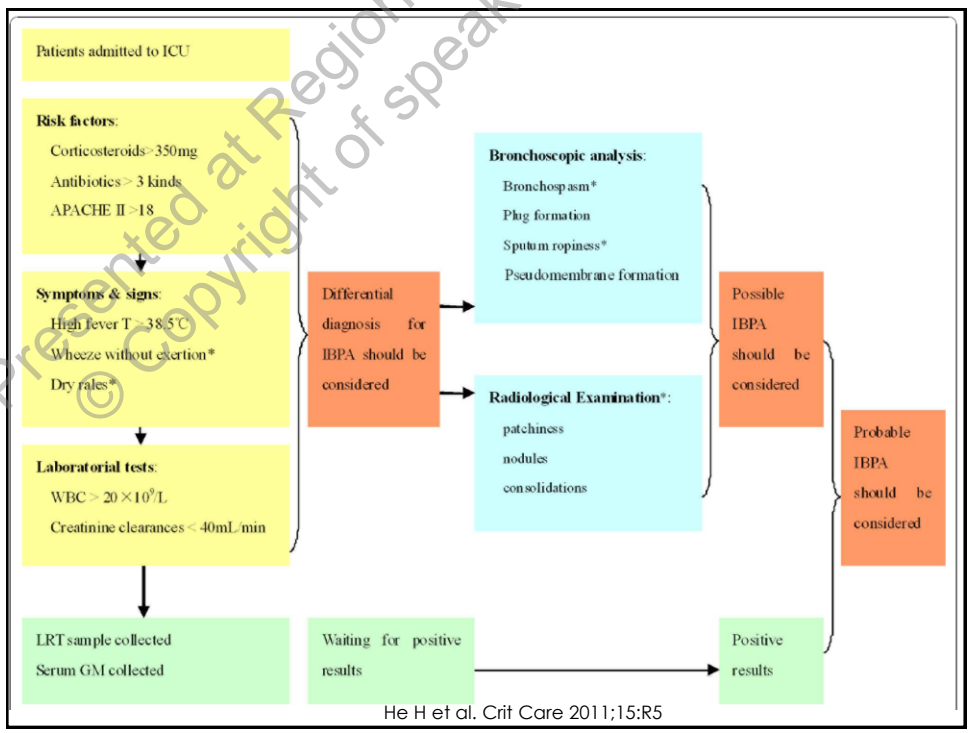
Pre-ICU independent predictors
APACHE >18
>3 antibiotics before ICU admission
Accumulated steroid dose >350mg before ICU admission

After ICU admission
Dry rales
Wheeze without exertion
Temp > 38.5^{0}C
Lower MAP (77 vs 90)
Higher WBC (21 vs 9)
Lower CCT (33 vs 67)

During BAL
Sputum ropiness

Imaging
Progression from nodules to consolidation in 7d

He H et al. Crit Care 2011;15:R5



He H et al. Crit Care 2011;15:R5

Use of GM to diagnose IPA in COPD

Table 2 Results of BALF and serum GM detection and isolation of *Aspergillus* from LRT in critically ill COPD patients.

	BALF GM (95%CI) (cut-off 0.8)	BALF GM (95%CI) (cut-off 0.5)	Serum GM (95%CI) (cut-off 0.5)	Isolation of *Aspergillus* from LRT (95%CI)
Sensitivity (%)	88.9 (76.8 to 101)	88.9 (76.8 to 101)	77.8 (61.8 to 93.8)	66.7 (48.6 to 84.8)
Specificity (%)	100 (100 to 100)	47.1 (27.9 to 66.3)	100 (100 to 100)	100 (100 to 100)
PPV (%)	100 (100 to 100)	47.1 (27.9 to 66.3)	100 (100 to 100)	100 (100 to 100)
NPV (%)	94.4 (85.6 to 103.2)	88.9 (76.8 to 101)	89.5 (77.7 to 101.3)	85.0 (71.3 to 98.7)
TCR (%)	96.1 (88.7 to 103.5)	61.5 (42.8 to 80.2)	92.3 (82.1 to 102.5)	88.5 (76.2 to 100.8)

Probable IPA (by Bulpa criteria) vs control

He H et al. Crit Care 2012;16>R138

Why Aspergillosis in COPD?

- Chronic smoking → impaired ciliary function → poor clearance of Aspergillus from airways
- Antibiotics → alteration of microbial milieu favouring Aspergillus
- Role of genetic factors??
- STEROIDS

Yii ACA et al. Front Biosc (Schol Ed) 2017;9:127
Samarakoon P et al. Chr Resp Dis 2008;5:19

COPD on steroids main risk

- Autopsy data from ICU deaths
- 222 autopsies done on 489 ICU deaths
- 6 had disseminated aspergillosis
- 5 of them were COPD on steroids

Dimopoulos G et al. J Chemother 2003;15:71

A fatal case of cerebral aspergillosis in a diabetes mellitus patient

Xiaohui Liu[1] · Wanrun Lin[2] · Yongxiang Wang[1] · Zhou Wang[2] · Yifeng Du[1] Neurol Sci (2015) 36:1717–1719

Angioinvasive cerebral aspergillosis presenting as acute ischaemic stroke in a patient with diabetes mellitus

Norlinah MI, Ngow HA, Hamidon BB Singapore Med J 2007; 48(1) : e1

Cerebral Aspergillosis with Multiple Enhancing Nodules in the Right Cerebral Hemisphere in the Immune-Competent Patient

J Korean Neurosurg Soc 53 : 312-315, 2013

Hyperglycemia: risk for complicated infection, incl IFI

TABLE 4
Rate of Infection during Induction Chemotherapy

	Hyperglycemia, Yes (n = 103)	Hyperglycemia, No (n = 175)	P value
Any infection	74 (72%)	98 (56%)	0.009
Fever of unknown origin	44 (43%)	70 (40%)	0.656
Sepsis	17 (17%)	14 (8%)	0.030
Complicated infection	40 (39%)	44 (25%)	0.016

TABLE 5
Rates of Toxicity during Induction Chemotherapy

Toxicity	Hyperglycemia, Yes (n = 103)	Hyperglycemia, No (n = 175)	P value
Mucositis	8 (8%)	14 (8%)	0.945
Neuropathy	5 (5%)	9 (5%)	0.915
Neutrophil recovery, median (days) (range)	18 (11–88)	19 (13–88)	0.911

"Complicated" infxn: severe sepsis, or involving major organ (heart, lungs, kidneys, CNS, soft tissue), or IFI

Weiser MA et al. Cancer 2004;100:1179

ASIAMOLD STUDY

DM – 30.9% (48/155), commonest "underlying condition"

AML – 19.4%

Diabetes as sole underlying condition	Total n = 20
Probable	6
Modified diabetes criteria in sino-orbital	4
Blot eligible[a]	2
Proven	14
Syndrome	
Pulmonary	5
Sinus related	8
Soft tissue-related	1
Lung and sinus-related	3
Others	3

Diabetes cases with/without underlying conditions	Total n = 48
Diabetes only	20
Diabetes with coexisting conditions	28
AML	7
ALL	4
Lymphoma	4
Post-allogeneic HSCT no GVHD	1
Post-allogeneic HSCT with GVHD	2
Solid organ malignancy	2
COPD	3
Chronic liver disease	1
Fulminant liver disease	1
Rheumatologic condition	3
Other conditions on steroids	7

Porpon R et al. Med Mycol 2017

Characteristics	Number (%)
Mean age ± SD, years (range)	47.9±19.4 (17-89)
Gender	
Male	54 (57.4)
Female	40 (42.6)
Underlying conditions[a]	78 (83.0)
Malignancy	38 (40.4)
Hematology	36 (38.3)
Solid	2 (2.1)
Diabetes mellitus	16 (17.0)
Systemic lupus erythematosus	14 (14.7)
Human immunodeficiency virus infection	7 (7.4)
Transplantation	5 (5.3)
Chronic obstructive pulmonary diasese	2 (2.1)
Others[b]	10 (10.5)
Predisposing factors[a]	61 (64.9)
Neutropenia	37 (39.4)
Chemotherapy	32 (34.0)
Corticosteroid	23 (24.5)
Immunosuppressive drugs[c]	14 (14.9)

Kiertiburanakul S et al. J Med Assoc Thai 2007;90:895

DM in a French cohort of IA = 55/303 (18%)*

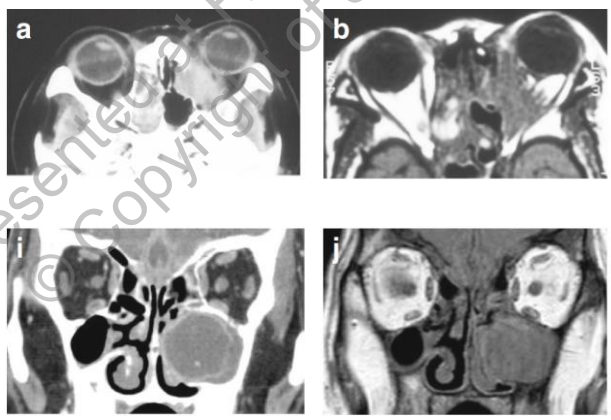
My own reading of that paper

DM was in 53/289 (18.3%)#

18% is higher than the usual rate of DM among pts admitted to their unit

* Herbrecht R et al. Ann NY Acad Sci 2012;1272:23
# Nivoix Y et al. CID 2008;47:1176

Seven cases of localized invasive sino-orbital aspergillosis



All diabetics

Biopsy and biopsy!

Initial diagnoses:

Lymphoma,
Tolosa-Hunt
Tumour
Idiopathic inflammation
Sarcoid
Retrobulbar neuiritis
Ischemic optic neuropathy

Japan J Ophthalmol 2017;61:179

Disseminated Aspergillosis Complicating Hepatic Failure

Thomas J. Walsh, MD, Stanley R. Hamilton, MD

Arch Intern Med 1983;143:1189-1191

50yo woman, halothane hepatitis
D1 to 11 – hi fever, normal CXR, IV Penicillin
D13 – still febrile, CXR new shadows, LFTs worsening, prednisolone started
D26 – RIP – autopsy hyphae in brain, lungs, kidney

9yo boy – hepatic failure ? cause
D5 - po Prednisolone
D20 – hi fever, CXR with LLL infiltrate, (-) blood & sputum cultures, IV Penicillin
D28 – RIP – autopsy – Aspergillus in lung, cerebellum

66yo woman, 2/12 jaundice & lethargy
Worsening bili, PT in ward
D28 – hi fever, CXR new shadows, po Pred
Sputum grew MSSA, *A. fumigatus*
RIP – autopsy – Aspergillus in brain, cerebellum, lungs

All 3 had been on steroids, though duration not prolonged.

Invasive aspergillosis in patients with severe alcoholic hepatitis

94 cases, biopsy proven alc hep
70/94 treated with steroids (Pred 40mg/d X 28d)
IA diagnosed by EORTC, and ICUAsp criteria
(Modified – accepted "non-specific lung infiltrates" on chest imaging)

IA – 15 cases
Diagnosed median 26d from liver bx (0-80)
Proven: 6 (5 diagnosed post-mortem), 1 by brain biopsy
Probable: 8
Possible: 1
13/15 IA cases received steroids

Independent predictors for IA: MELD ≥ 24 (on day 0), ICU admission

Journal of Hepatology **2014** vol. 60 | 267–274

Risk Factors for Invasive Pulmonary Aspergillosis and Hospital Mortality in Acute-On-Chronic Liver Failure Patients: A Retrospective-Cohort Study

Zhejiang U, Hangzhou
1/12/2008 – 1/5/2012

787 pts with ACLF
39 with IPA
48 controls (no pneumonia)

ACLF – defined by APASL guide
IPA -- defined by EORTC guide

	+IPA	-IPA
Age	43	37*
HBV	94%	91%
Hep enceph	61%	4%*
Ascites	82%	32%*
BSAb	89%	62%*
Steroids#	89%	25%*

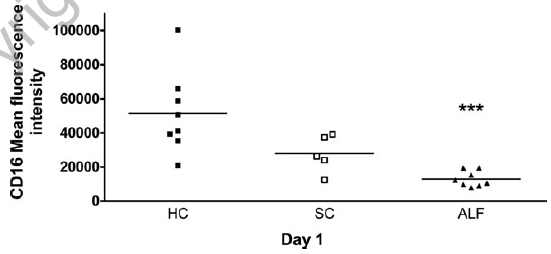
*Stat sig (univariate); BSAb – broad spectr abx
#Dose, duration not defined

Logistic regression: independent risk factors

Age,
Hepatic encephalopathy,
Steroids

Chen J et al. Int J Med Sc 2013;10:1625

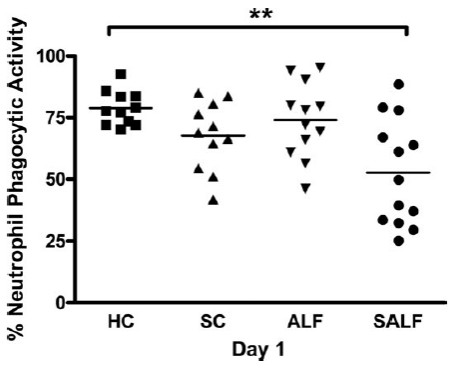
Neutrophil CD16 expression : healthy controls, septic controls & ALF patients



- Presence of CD16 (FcγRIII) likely helps neutrophils bind to an opsonized microbe
- Diffce btw healthy controls and ALF patients is stat sig ($p<0.001$)

Taylor NJ et al. Hepatology 2013;57:1142

Neutrophil phagocytic activity on D1 ICU



NPA in SALF < in HC (p<0.01)

NPA in ALF pts of D1 ICU - likely hasn't had time to fall

↓ in NPA in SALF likely explains resemblance btw sepsis and SALF

HC - healthy control, SC - septic control, ALF - acute liver failure, SALF - subacute liver failure

Taylor NJ et al. Hepatology 2013;57:1142

Cryptococcus neoformans Infection in Patients With Cirrhosis, Including Liver Transplant Candidates

RV of 33 patients (5 from their institution)

Peritonitis	15 (45.4%)
Meningitis	13 (39.0%)
Lung/pleura	6 (18.0%)
Others	3 (9.0%)

Of those who had blood c/s: 67% +

Mean age 57 (21 – 80)
12 (63.6%) no other immunosuppression

Singh N et al. Medicine 2004;83:188

Cryptococcal peritonitis

- Median WBC 340/mm^3 (36 – 48,000)
- 69% of them had <500 wbc in ascitic fluid
- Predominantly polymorphonuclear
- (but 4 patients had predominantly lymphocytic or mononuclear ascitic pleocytosis)
- Mean time to + culture: 6 days
- Role of crypt antigen in ascitic fluid?

Singh N et al. Medicine 2004;83:188

Cryptococcosis in cirrhosis

Overall mortality 81%

Consider cryptococcosis in culture-negative peritonitis

Singh N et al. Medicine 2004;83:188

RESEARCH ARTICLE

Risk Factors for Invasive *Cryptococcus neoformans* Diseases: A Case-Control Study

RV of all admissions to NTUH, 2002 – 2010
Cryptococcal meningitis 101 (266 controls)
Cryptococcemia 47 (188 controls)

Independent risk factors for cryptococcal disease

AIDS	aOR 181 (p<0.001)
Decompensated cirrhosis	aOR 8 (p=0.008)
CMI-suppression (sans CNI)	aOR 7 (p=0.034)

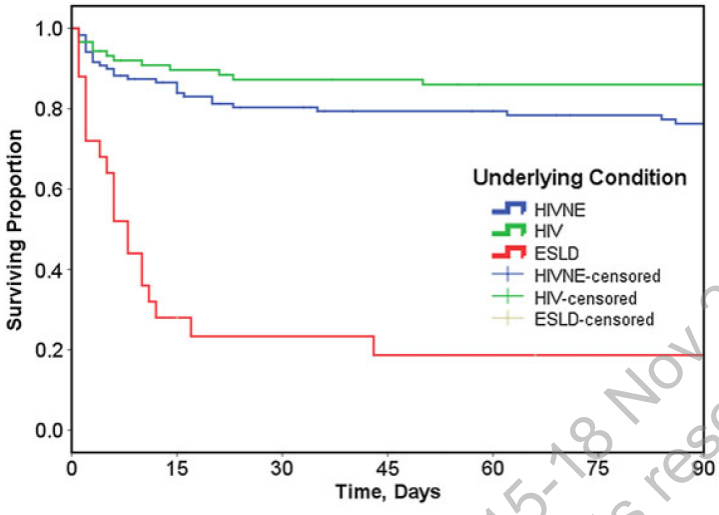
Lin YY et al. PLoS One 2015;10:e0119090

Table 6. Independent risk factors for cryptococcemia.

Variables	Adjusted OR (95% CI)	p-value
AIDS	216.3 (24.2–>999)	<0.001
CMI-suppressive regimens without CAs	7.3 (1.1–57.5)	0.034
Autoimmune diseases	9.3 (1.1–135.7)	0.038
Decompensated liver cirrhosis†	23.8 (3.4–340.9)	<0.001

AIDS: acquired immunodeficiency syndrome. CMI: cell-mediated immunity. CAs: calcineurin inhibitors.
†Decompensated liver cirrhosis: Child-Pugh score of B or C.

Lin YY et al. PLoS One 2015;10:e0119090



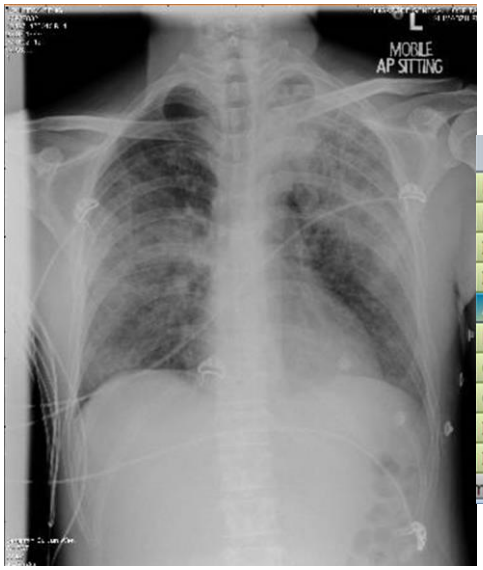
Spec A et al. OFID 2016

42yo man presents with…

1) Fever x4/7
- a/w chills/rigors

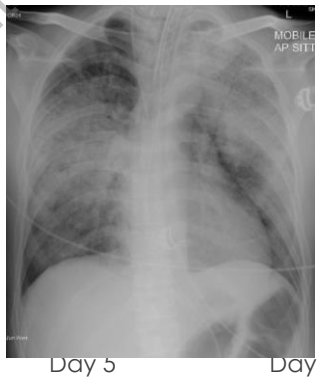
2) Cough x4/7
- Productive of white sputum
- a/w rhinorrhea and pharyngitis

Initial CXR



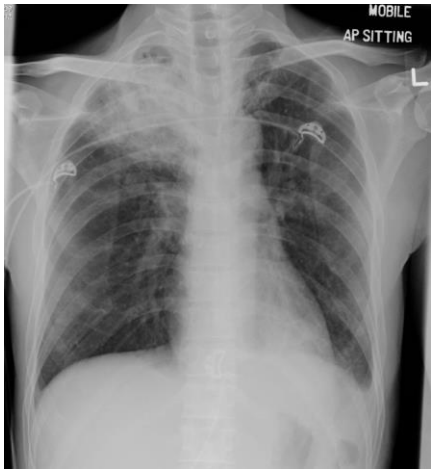
	07:52
Respiratory Syncytial Virus Antigen	
Parainfluenza Pooled Virus Antigen	
Influenza A Virus Antigen	
Influenza B Virus Antigen	
Adenovirus Antigen	
Respiratory Virus Isolation	
Cytomegalovirus Antigen	
Cytomegalovirus Isolation	
Influenza A Virus	* NOT DETEC...
Influenza B Virus	DETECTED
nmune	

72hrs after admission



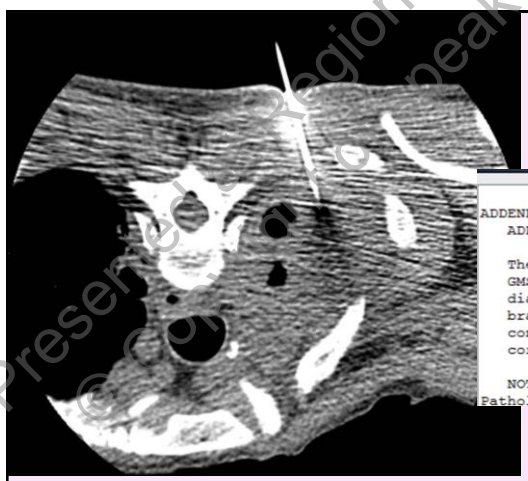
- Day 4 Day 5 Day 10

Develops fever in Rehab…



D15

D17 – on same day, microbiologist says ….

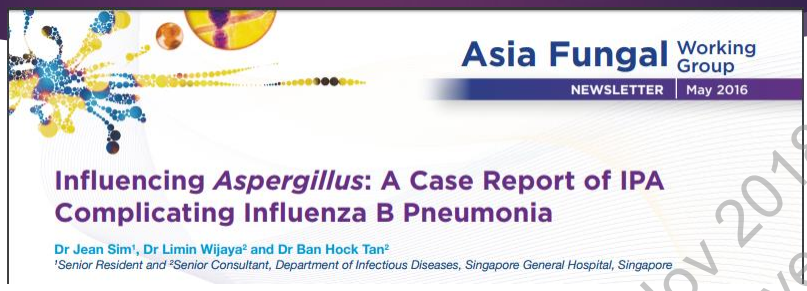


ADDENDUM
ADDENDUM TO HISTOPATHOLOGY REPORT 12:PB80407

The fungal element's morphology is enhanced by the GMS stains. They are filamentous, uniform in diameter and has less than 45 degree acute branching angles. Features are entirely consistent with aspergillus species, please correlate with microbiological findings.

NOTE : Please see below for original report.
Pathologist :

Lung tissue grew *A. niger*



Influencing *Aspergillus*: A Case Report of IPA Complicating Influenza B Pneumonia

Dr Jean Sim[1], Dr Limin Wijaya[2] and Dr Ban Hock Tan[2]
[1]Senior Resident and [2]Senior Consultant, Department of Infectious Diseases, Singapore General Hospital, Singapore

MARCH 8, 1952 BRITISH MEDICAL JOURNAL 523

PULMONARY ASPERGILLOSIS FOLLOWING POST-INFLUENZAL BRONCHOPNEUMONIA TREATED WITH ANTIBIOTICS

BY

J. D. ABBOTT, M.D., Dip.Bact.

H. V. J. FERNANDO, M.B., B.S.

K. GURLING, M.D., M.R.C.P.

Lower respiratory tract respiratory virus infections increase the risk of invasive aspergillosis after a reduced-intensity allogeneic hematopoietic SCT

Independent risk factors for IA

- ✓ Steroids for GVH (HR 2.9, p=0.03)
- ✓ CMV disease (HR 2.8, p=0.03)
- ✓ RV LRTI (HR 4.3, p<0.01)

Bone Marrow Transplantation (2009) 44, 749–756

Case-control study

- 48 ICU patients tested for flu in 2015-6 flu season
- 8 positive for influenza
- 6 of these developed IA (all were ventilator-dependent)
- Underlying influenza: H3N2, B
- None of the 40 ICU patients who were flu-negative developed IA
- Time btw influenza diagnosis & 1st + culture for Aspergillus: 3d (0-8)
- 5 of 6 were lymphopenic
- Only 1 had received steroids (asthma exacerbation)

Crum-Cianflone NF. OFID 2016

Influenza & aspergillosis – link?

- Local damage to mucosa, disruption of ciliary clearance
- Depletion of alveolar macrophages
- Suppression of alveolar macrophage activity
- Shift to TH2 response, eg, ↑ IL-10
- Lymphopenia

Astry CL. J Virol 1984;50:287

Ghoneim HE et al. J Immunol 2013;191:1250

Barthelemy et al. Mucosal Imm 2017;10:460

Could strain of Aspergillus be a factor?

- Mice infected with 'flu A virus
- D6 – intra-tracheal instillation of *S. aureus* (wild type) vs *S. aureus* ΔsaeR/S
  - (SaeR/S is a 2-componenet gene regulatory system that controls transcription of virulence genes needed for neutrophil evasion)
- Infection with 'flu A virus – survival 100%
- Co-infection with *S. aureus* – survival fell to 30%
- Co-infection with *S. aureus* ΔsaeR/S – survival 100%

Borgogna TR et al. J Infect Dis 2018'218:809

Alternative clinical algorithm

Proven Invasive pulmonary aspergillosis

Idem EORTC/MSG criteria

Putative invasive pulmonary aspergillosis (all four criteria must be met)

1. Aspergillus-positive lower respiratory tract specimen culture (=entry criterion)

COPD patient, usually treated with steroids and severe according to GOLD (stage III or IV), with recent exacerbation of dyspnoea[#], suggestive chest imaging[¶] (radiograph or CT scan; <3 months[+]) and one of the following:
1) Positive culture[§] and/or microscopy for Aspergillus from LRT. 2) Positive serum antibody test for *A. fumigatus* (including precipitin

Bulpa P et al. Eur Resp J 2007;30:782

SPUTUM CULTURE

APPEARANCE : blood stained and mucoid

MICROSCOPY :	Epithelial cells	1+
	Polymorphs	1+
	Hyphae seen	2+

Remarks 1+ : Few (1 - 9 cells/lpf)
2+ : Moderate (10-24 cells/lpf)
3+ : Abundant (>=25 cells/lpf)

PRELIMINARY REPORT ON 17/09/15:
Moulds isolated

FINAL REPORT:
ASPERGILLUS FLAVUS

Colonizer

Or

Pathogen?

LRT cultures in COPD vs ICH

- Chinese study of IPA in COPD
- Comparison group – std ICH
- Eligibility criterion: isolation of Aspergillus from lower resp tract
- Criteria: EORTC (!)
- 100% of COPD cases on steroids

In ICU

- Incidence of IPA in COPD pts (on steroids) & with Aspergillus grown = 66%
- Incidence of IPA in ICH & with Aspergillus grown = 91% (p=0.09)

He et al. Chin Med J 2012;125:2973

Non-neutropenic, non-transplant patients with + Aspergillus cultures

- Only criteria applied was Bulpa's
- Aspergillosis (proven/probable) correlated with
  - ICU admission
  - Congestive heart failure
  - Steroids pre-admission
  - COPD exacerbation
  - Cavitation on XR/CT

Barberan J et al. BMC Infect Dis 2012;12:295

How many of the colonized developed Aspergillosis?

- Follow-up from previous study
- Voluntary participation of study sites
- 67 patients followed
- 12 (17.9%) developed aspergillosis
- All 12 had COPD (GOLD IV)

COPD GOLD IV patients with + Aspergillus cultures should be followed up closely for development of IA

Barberan J et al. BMC Infect Dis 2017;17:34

In COPD patient on steroids, isolation of Aspergillus in respiratory secretions very worrying for IPA!!

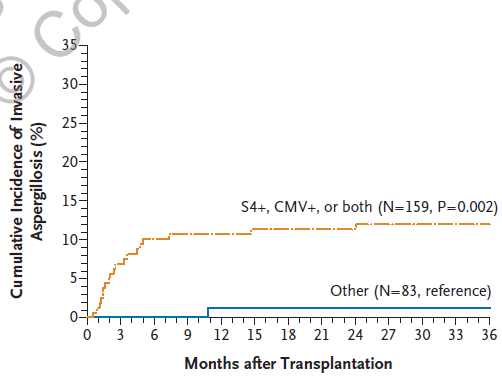
Toll-like Receptor 4 Polymorphisms and Aspergillosis in Stem-Cell Transplantation

Donor haplotype TLR-4 S3	AHR 2.20
Donor haplotype TLR-4 S4	AHR 6.16

N Engl J Med 2008;359:1766-77

- Rate of IA in CMV seroneg (D^-R^-) & S4-neg 1%
- Rate of IA in CMV seropos (D or R+) &/or S4-pos 12%

(HR 11.95, p=0.002)



N Engl J Med 2008;359:1766-77

Different criteria, different cases

- Leeds NHS Trust
- Looked for patients with a + culture for Aspergillus (121)
- Applied 3 sets of criteria
  - EORTC/MSG, Bulpa's, Denning (for CCPA)
- 2 patients under EORTC
- Another 2 patients (out of 62) under Bulpa
- Yet a different 2 patients (under Denning)

Authors: difficulties in applying different criteria may lead to under-diagnosis

Barton RC et al. Eur J Clin Micro Infect Dis 2013

Critique: low yield as criteria may not have been systematically applied
Important to apply the criteria systematically in different pt subsets

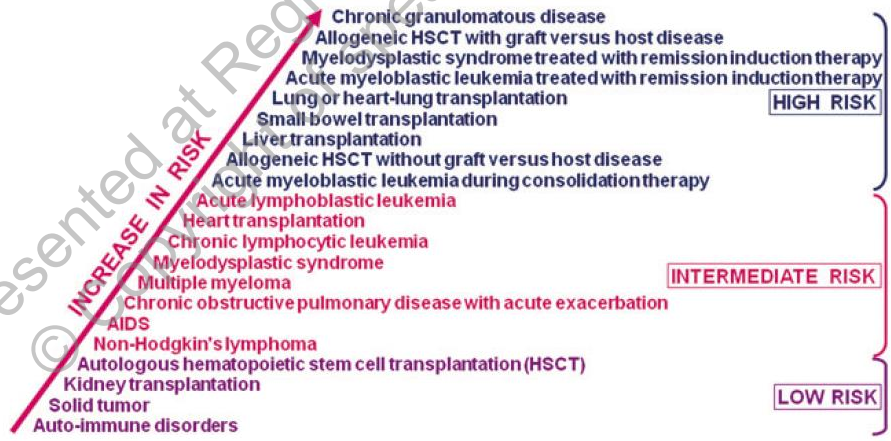


Figure 3. Risk of invasive aspergillosis based on the primary host factor.

strongly suggest that two or more risk factors may precipitate the occurrence of invasive aspergillosis in patients who do not meet the consensus criteria for host factors. This necessitates greater flexi-

Herbrecht R et al. Ann NY Acad Sci 2012;1272:23