

How do I treat Invasive Aspergillosis?

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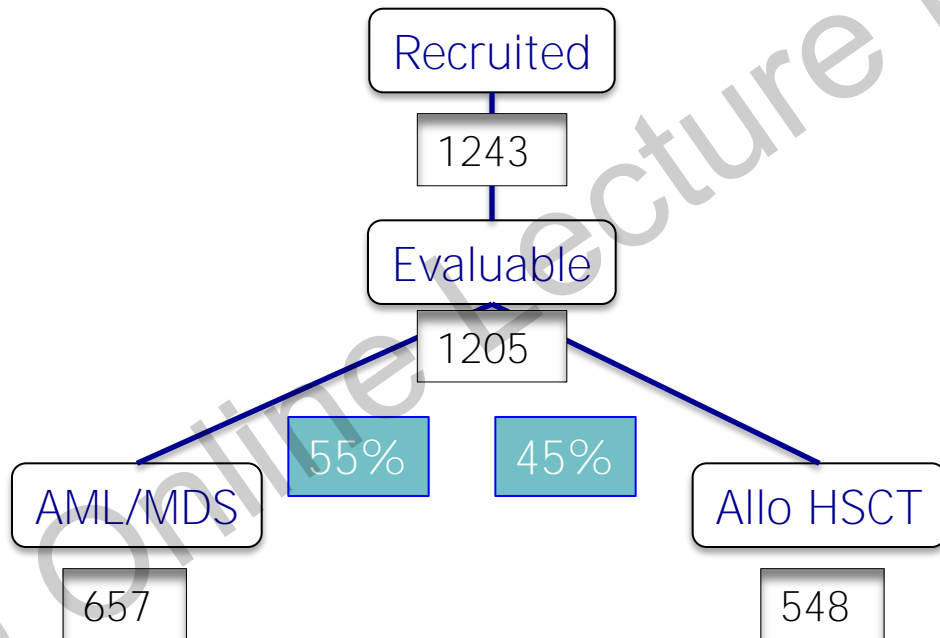


Disclosures

- **Grants**
 - **Gilead, Merck, Sharp & Dohme**
- **Consultant**
 - **Astellas, Gilead, Merck, Sharp & Dohme and Schering-Plough**
- **Speakers' bureau**
 - **Astellas, Gilead, Merck, Sharp & Dohme, Pfizer, Schering-Plough and Zeneus/Cephalon**

Invasive Mold Infections

- **Frequent cause of infectious morbidity in patients with leukemia and allo-HSCT**
- **Display constant epidemiological shifts**
- **Remain difficult to diagnose and to manage**
- **Associated with high case fatality rates**



IMD	N	%	
Proven/Probable	53	8.1 %	18.1 %
Possible	66	10.0 %	

IMD	N	%	
Proven/Probable	26	4.7 %	9.1 %
Possible	24	4.4 %	

... considering possible infections,
 10 to 20 % cumulative frequency in the era of antifungal prophylaxis

Presentation of a Case

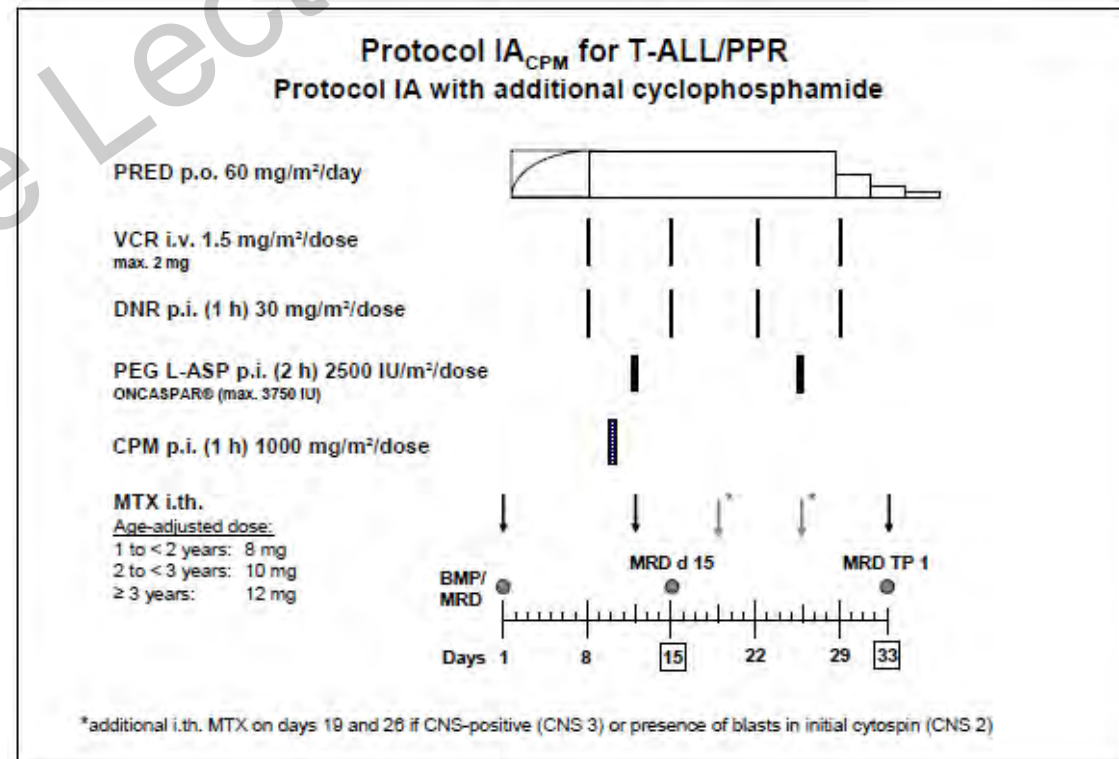
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New cough in an ALL Patient during induction therapy

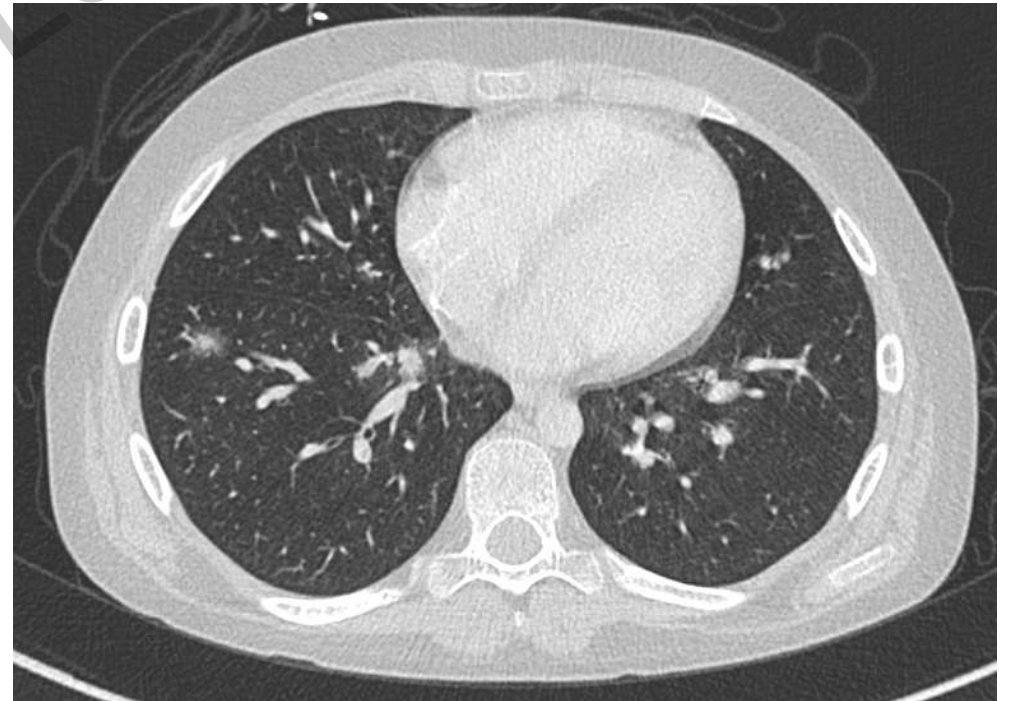
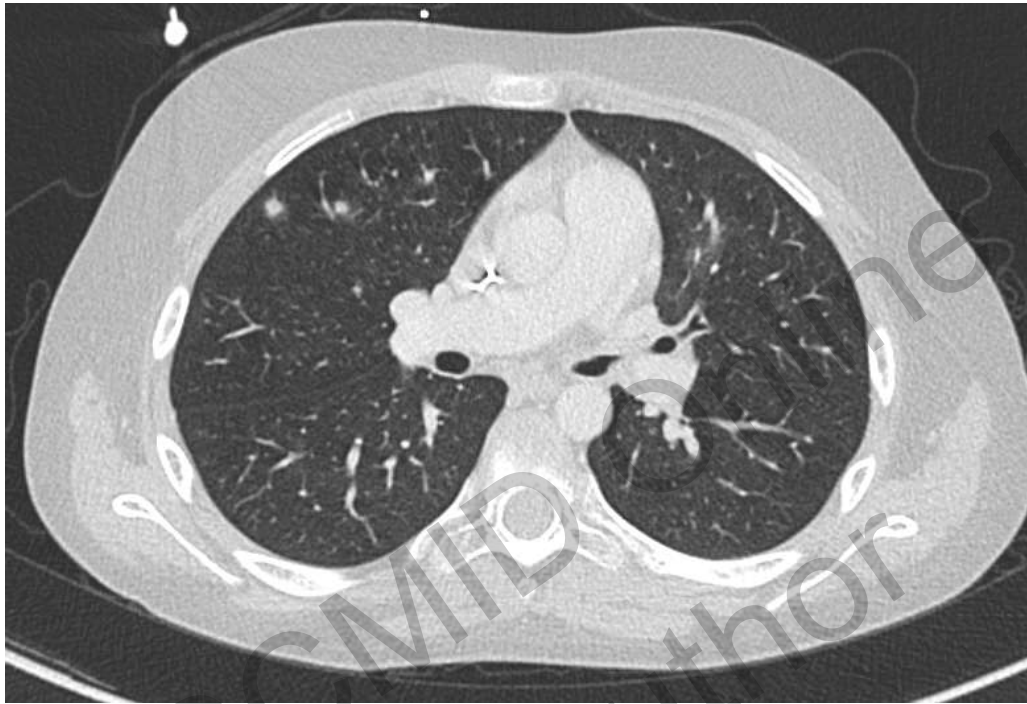
Louis: T-ALL with expression of myeloid markers, CNS neg.

- Polychemotherapy according to AIEOP-BFM ALL 2009 protocol
- Prednisone Poor Response on day 8, M3 marrow on day 15

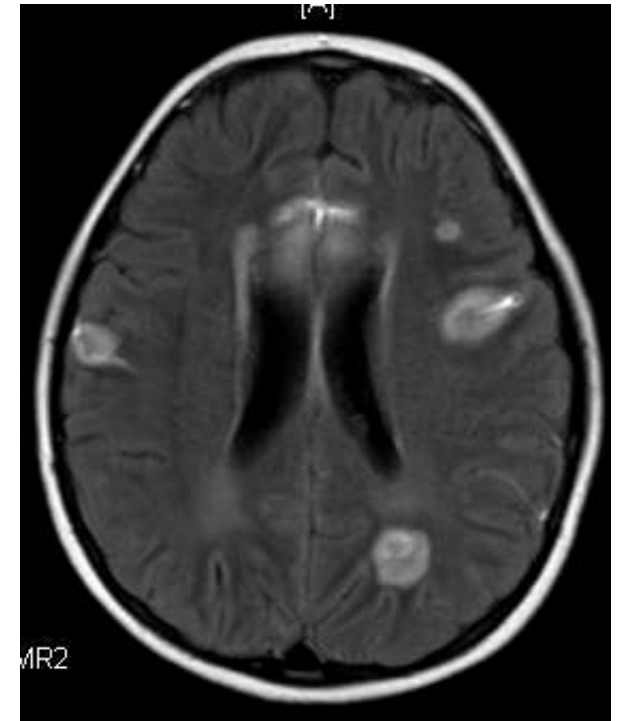
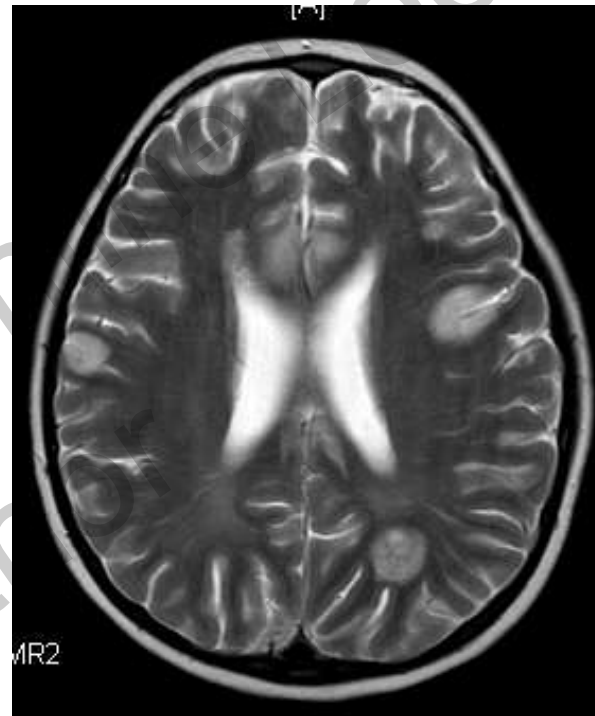
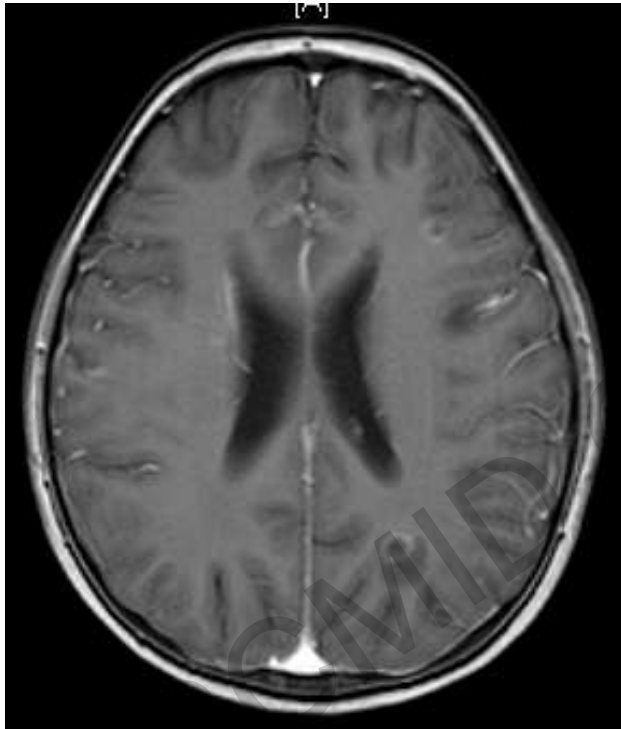
- Now day 30 and after a 4 weeks history of prednisone and an ANC always $<500/\mu\text{L}$
- More sleepy, less responsive, no focal findings



New cough in an ALL patient...



New cough in an ALL patient...



Challenges and Decisions

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Challenges...

- This is an ID emergency, and ***prompt*** initiation of ***adequate*** therapy is critical
- Invasive aspergillosis most likely diagnosis
 - ***voriconazole*** considered best available option
- However, it is Friday night
 - ***no immediate access to invasive procedures***
 - ***no galactomannan results available for the next 72 h***
 - ***no TDM available for the next 72 h***

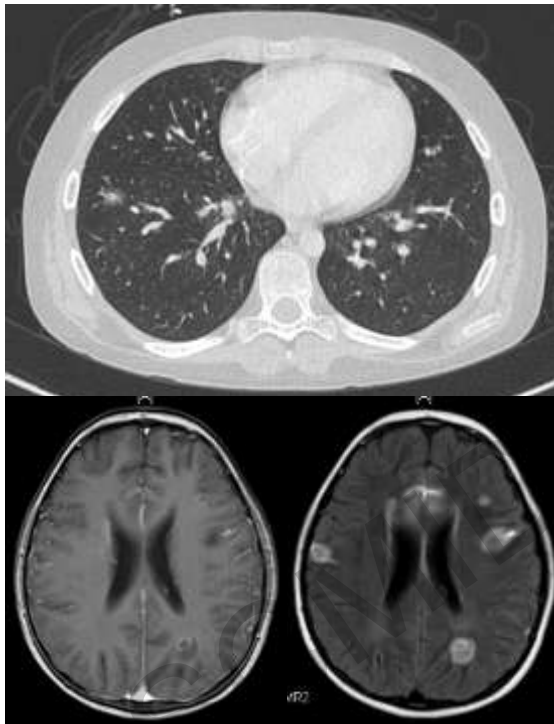
... Management Decisions

- ***Treatment*** needs to be started pre-emptively on the basis of clinical findings, imaging results and likelihood
- ***Microbiological diagnosis:*** All efforts should be made to perform the necessary procedures to identify the causative agent and to allow for resistance testing
 - Bronchoscopy and BAL ✓ *done Saturday in AM*
 - microscopy and culture
 - galactomannan antigen
 - Serial galactomannan in serum ✓ *done during the weekend*

**What is behind
the Quest for Microbiology ?**

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Spectrum of Invasive Mold Infections



≥ 80%

Aspergillus fumigatus
Aspergillus flavus
Aspergillus niger
Aspergillus terreus

≤ 20%

Other hyalohyphomycetes
Phaeohyphomycetes
Zygomycetes

Susceptibility of Invasive Mold Isolates

	AMB	CAS	VCZ	ICZ	PCZ	ISCZ
<i>A.fumigatus</i>	S	S	S	S	S	S
<i>A.flavus</i>	S	S	S	S	S	S
<i>A.niger</i>	S	S	S	S	S	S
<i>A.terreus</i>	I-R	S	S	S	S	S
<i>Zygomycetes</i>	S	R	R	S-I	S-I	S-I
<i>Hyalohyphomyc</i>	I-R	R	I-R	I-R	I-R	I-R
<i>Phaeohyphomyc</i>	S-I	I-R	S-I	S-I	S-I	S-I

Emergence of Azole Resistance in *Aspergillus fumigatus*

- ITZ-resistant isolates found in 32 / 1,219 patients
 - All cases were observed after 1999



Emergence of azole-resistant invasive aspergillosis in HSCT recipients in Germany

J. Steinmann^{1*†}, A. Hamprecht^{2†}, M. J. G. T. Vehreschild^{3,4}, O. A. Cornely³⁻⁵, D. Buchheidt⁶, B. Spiess⁶, M. Koldehoff⁷, J. Buer¹, J. F. Meis^{8,9} and P.-M. Rath¹

- **Epidemiology of azole resistance in IA in two German HSCT centers with a total enrolment of 762 patients between 2012 and 2013**
- Susceptibility testing by Etest / EUCAST for elevated MICs, sequencing of the *cyp51A* gene in ARAF /microsatellite typing to determine genotype
- ***A. fumigatus* was recovered from 27 HSCT recipients**
 - ***Eight patients had azole-resistant IA, and seven were fatal (88%). All except one patient received antifungal prophylaxis (triazoles in 5)***
 - TR34/L98H was most common mutation (5), followed by TR46/Y121F/T289A (n=2). In one resistant isolate no *cyp51A* mutation was detected
 - Genotyping revealed genetic diversity within the isolates and no clustering with resistant isolates from the Netherlands, India and France.

What are our Options for Antifungal Chemotherapy ?

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Invasive Mold Infections: Management Concept

- **Prompt, appropriate antifungal chemotherapy**
- **Stabilization of the infection during neutropenia / compromised host defenses**
- **Immunoreconstitution, if feasible**
- **Surgical intervention, if appropriate**
- **Treatment until the resolution of all symptoms and findings**

Invasive Aspergillosis: First Line Clinical Trial Data

Treatment	CR/PR at 3 mo	Surv. at 3 mo
Voriconazole 12/8 mg/kg	52.8 %	70.8 %
D-AMB 1.0 mg/kg + OLAT	31.6 % *	57.9 % *

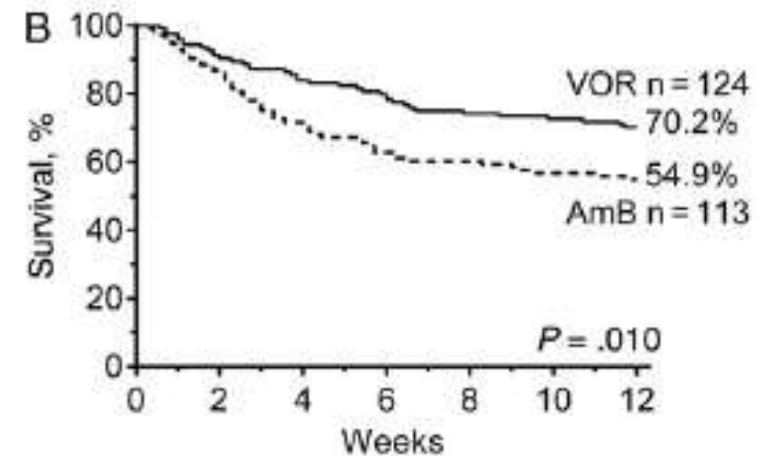
	CR/PR at EOT	Surv. at 3 mo
L-AMB 3 mg/kg	50.0 %	72 %
L-AMB 10 / 3 mg/kg	46.0 %	59 %

- No controlled data on outcome following first-line therapy with CAS and other triazoles

Voriconazole vs. Amphotericin B: Application of 2008 EORTC/MSG Criteria

Probable and Proven Invasive Aspergillosis

Response	VOR (n = 124)	AmB (n = 113)
Response at end of randomized therapy		
Favorable response ^a , No. (%)	63 (50.8)	22 (19.5)
Unfavorable response ^b , No. (%)	61 (49.2)	91 (80.5)
Difference in response rate, % (95% CI)	31.3 (19.1–43.6)	
<i>P</i> value	<.0001	
Response at week 12		
Favorable response ^a , No. (%)	62 (50.0)	29 (25.7)
Unfavorable response ^b , No. (%)	62 (50.0)	84 (74.3)
Difference in response rate, % (95% CI)	24.3 (11.9–36.7)	
<i>P</i> value	.0002	



Isavuconazole vs. Voriconazole for Primary Treatment of Inv. Aspergillosis

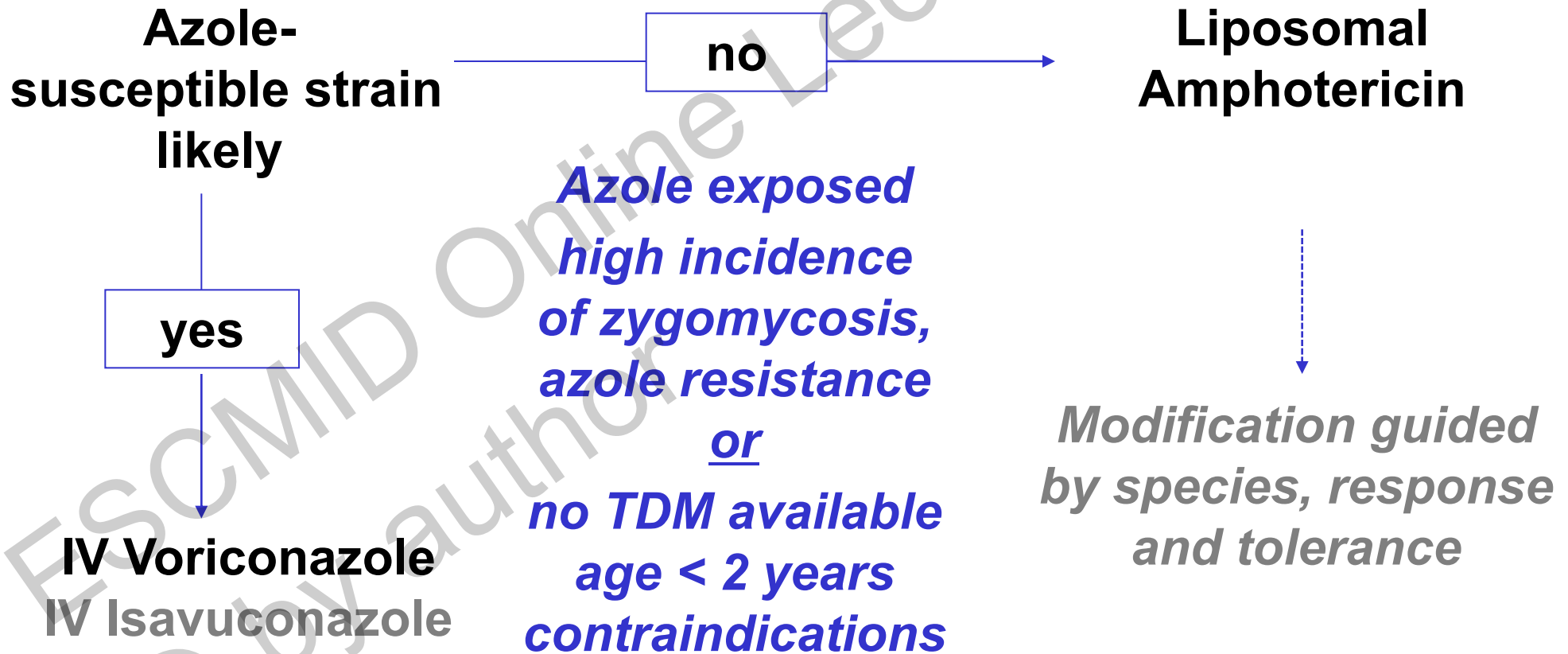
- **Primary Endpoint –All-Cause Mortality Through Day 42:**

	CRESEMBA		Voriconazole		Difference ^a (95% CI)%
	N	All-cause Mortality n (%)	N	All-cause Mortality n (%)	
ITT	258	48 (18.6)	258	52 (20.2)	-1.0 (-8.0, 5.9)
Proven or Probable Invasive Aspergillosis	123	23 (18.7)	108	24 (22.2)	-2.7 (-13.6, 8.2)

^a Adjusted treatment difference (CRESEMBA-voriconazole) by Cochran-Mantel-Haenszel method stratified by the randomization factors.

- **Overall treatment success for proven/probable IA at EOT 43/123 (35.0%) vs. 42/108 (38.9%) (-4.0 (-16.3, 8.4), n.s.)**
- **Study drug related AEs: 42.4 vs. 59.8%**
- **AEs leading to discontinuation: 14.4 vs. 22.8%**

Initial Treatment Algorithm



Voriconazole for CNS Aspergillosis

- Historical data indicate >95% mortality with AMB
- Retrospective analysis of 81 pts. with proven/probable CNS aspergillosis treated on clinical trials / compass.use
 - 35% CR/PR (r, 16-54%)
 - 31% survival (median observation: 390 d)

VCZ considered 'best available therapy' for CNS IA

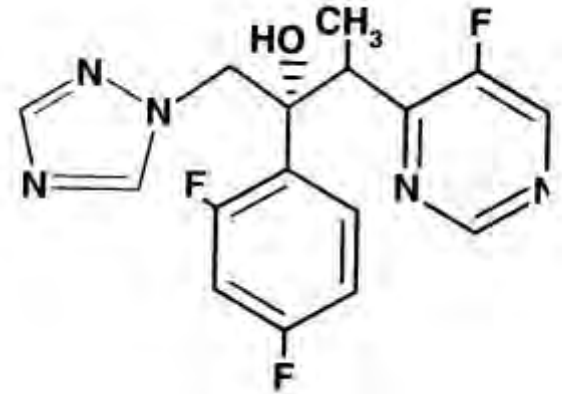


! Uncontrolled data / selection bias

! Neurosurgery associated with survival (40 vs.15%)

Voriconazole - Pharmacology

- ***Non-linear pharmacokinetics***
- ***Complex hepatic metabolization***
 - **Substrate/inhibitor of CYP2C9, 3A4, 2C19**
 - ***Genetic polymorphisms of CYP2C19***
 - ***Other, not fully elucidated variables***
- ***Number of relevant pharmacokinetic interactions***
 - ➔ ***High variability in exposure***

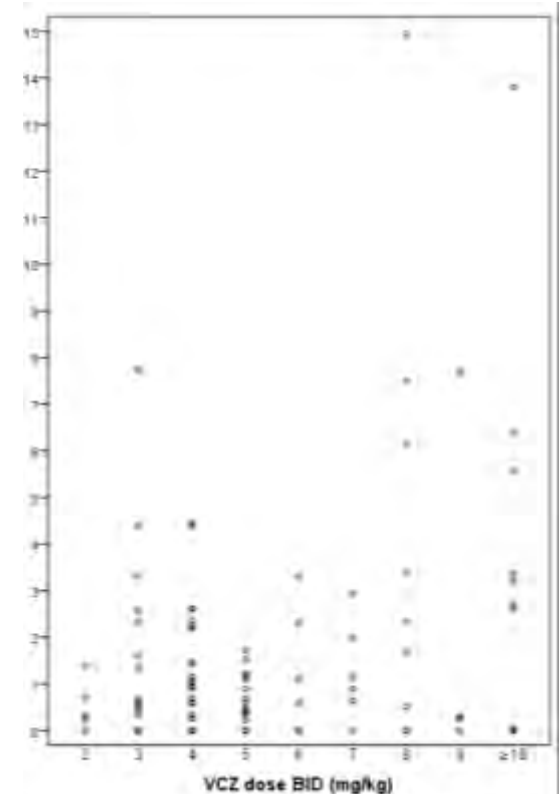


VCZ TDM in Immunocompromised Pediatric Patients

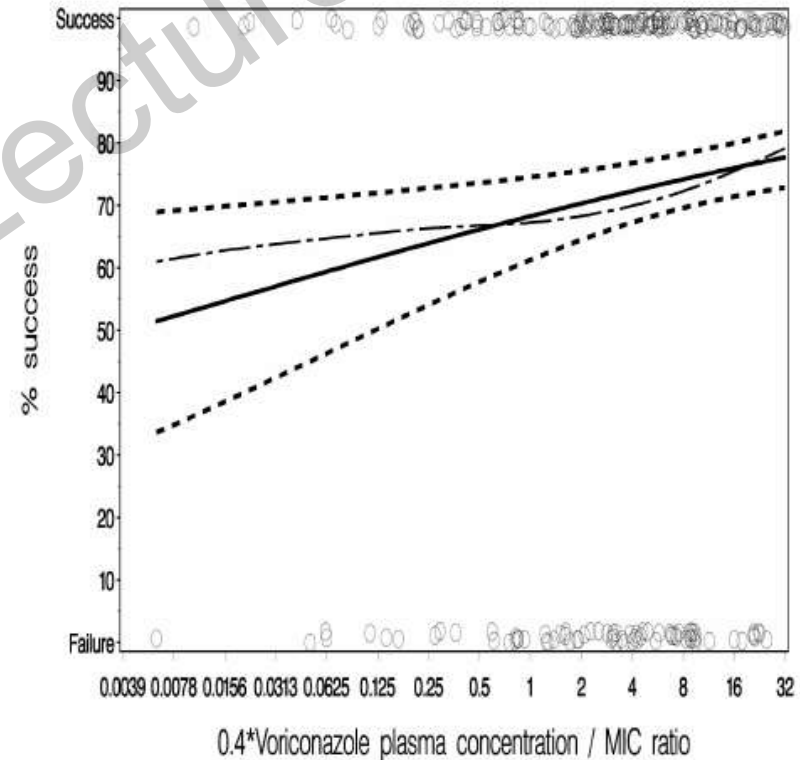
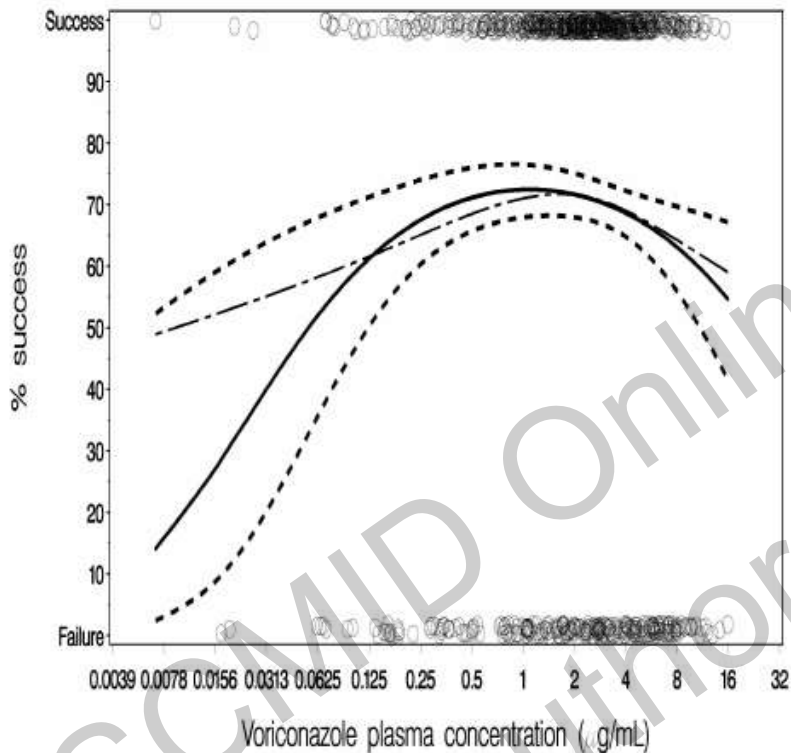
74 pts (0.2-18y; mean: 10.2y) / 101 courses of VCZ IV (4) and (15)/or (82) PO at median of 4.8 mg/kg BID (r, 2.2-17.4) for a median of 40 days (r, 6-1002)

Voriconazole trough [mg/L]	No. (%) of samples
< 0.2	56 (22.3)
0.2 – 0.5	50 (19.9)
> 0.5 – 1.0	39 (15.5)
> 1.0 – 2.0	36 (14.3)
> 2.0 – 5.0	50 (19.9)
> 5.0	20 (8.0)

- *some patients have no or low VCZ concentrations*
- *also: high inter-individual variability in exposure*



Relationship between VCZ Concentrations and Response



- Non-linear relationship with response ($p < 0.003$) with the probability lower at both extremes

- Higher free ratios associated with progressively higher probability of response

A Rationale for Combination Therapy?

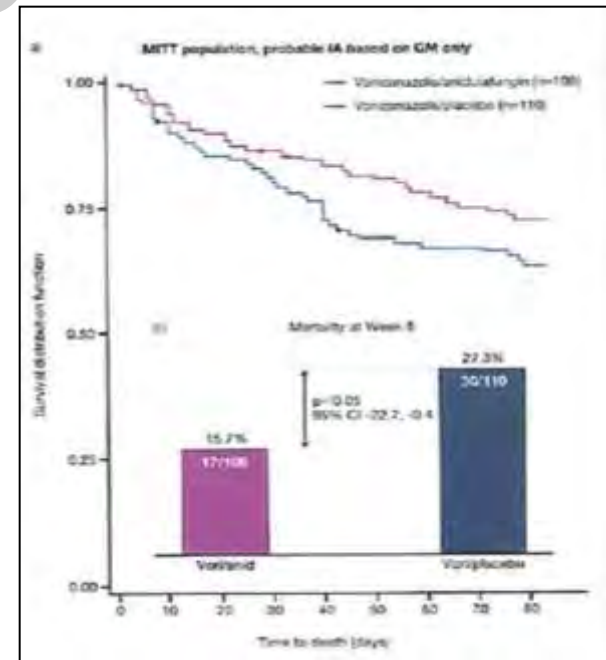
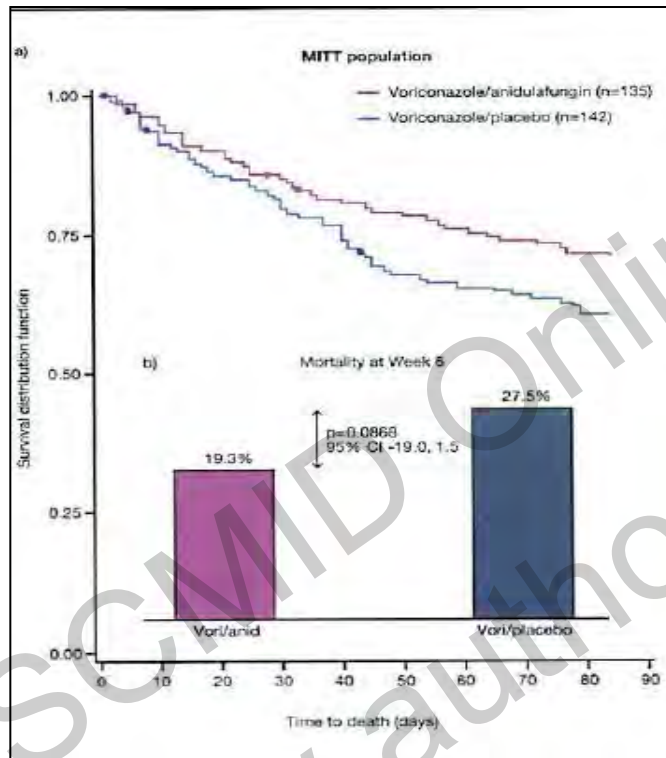
Pharmacokinetic interactions

- Indirect or direct interactions affecting drug concentrations at the target site:
 - amount of drug
 - rate of accumulation
 - ratio of concentrations

Pharmacodynamic interactions

- spectrum
- synergism or antagonism
- resistance
- toxicity

Voriconazole plus Anidulafungin for Primary Treatment of Inv. Aspergillosis



**What was the Further
Course in our Patient?**

... Further Clinical Course

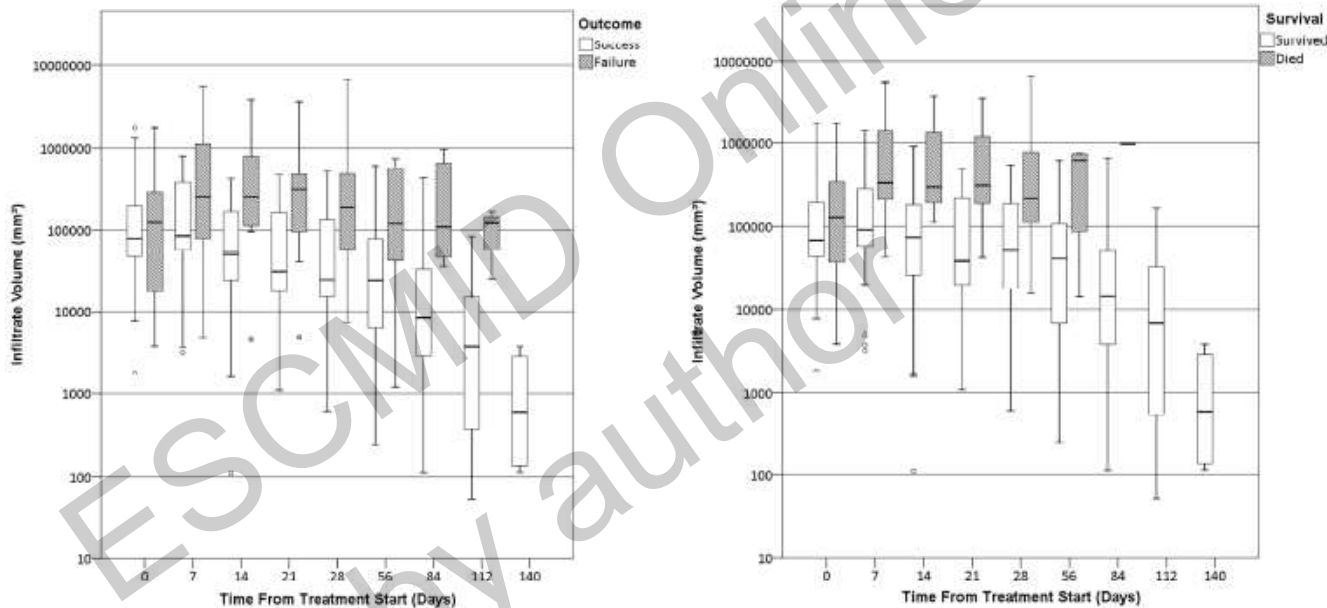
- **Treatment** was started with the combination of voriconazole plus caspofungin
 - TDM revealed high exposure in the context of evolving chemotherapy-related severe hepatic dysfunction (*bilirubine* > 15mg/dL)
 - Switch to liposomal amphotericin B plus caspofungin
- **Microbiological diagnosis**
 - *A. fumigatus*, azole susceptible, in BAL material
 - High galactomannan indices in BAL and serum
 - **Probable invas. pulmonary and cerebral aspergillosis**

How to Monitor Responses to Treatment ?

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Prediction of Outcome in Invasive Pulmonary Aspergillosis

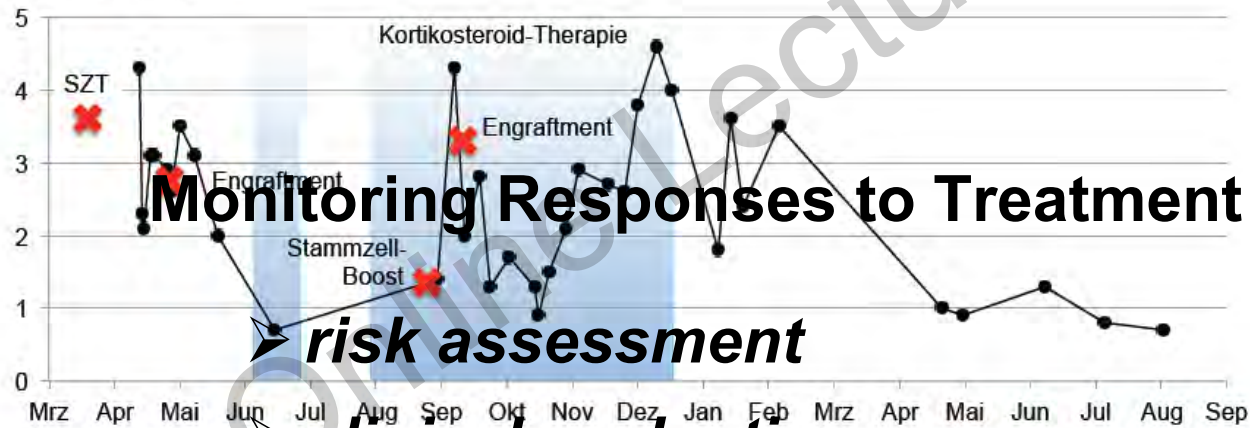
- 190 CT scans and 309 follow-up records from 40/46 pts from a clinical trial on escalating doses of caspofungin for treatment of IPA were re-evaluated and compared with available biomarkers



- Lesion volume at d 7 and trend between d 7 and d 14 were strong predictors of death (OR20, OR15) and treatment failure (OR 5, OR 40)
- Predictive value exceeded other biomarkers (WBC, ANC, GAL)

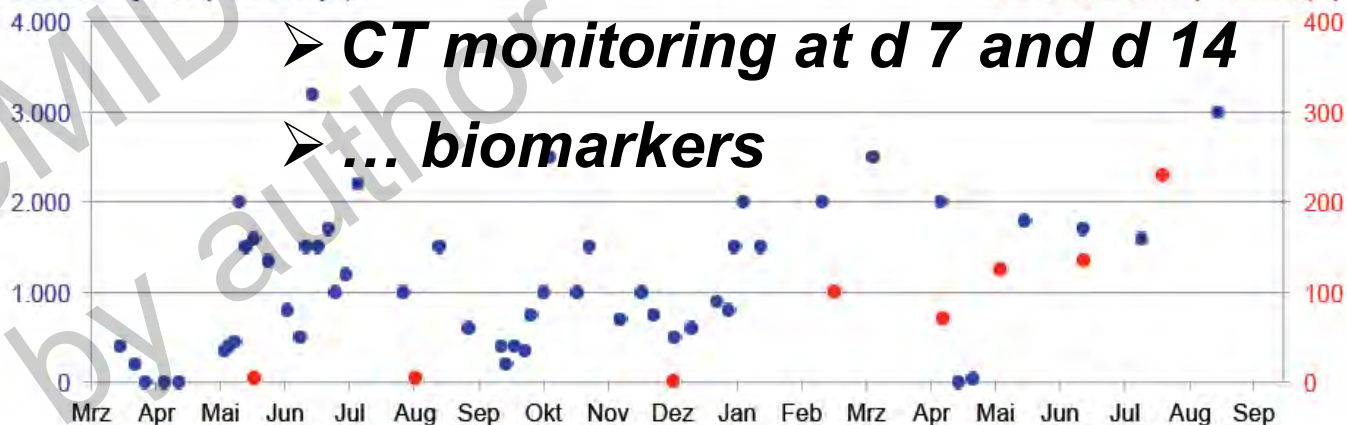
Serum-Galactomannan: Monitoring of Treatment Response

Galaktomannan



Granulozyten (Anzahl/ μ l)

T-Helferzellen (Anzahl/ μ l)



Further Management Issues

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General Management Issues

- ***Adjunctive surgery:*** skin and soft tissue infections; impeding arrosion of pulmonary arteries; operable CNS or lung lesions
- ***D/c of steroids*** in immunosuppressed pts
- ***Neutropenic patients***
 - **Colony-stimulating factor (G-CSF)**
 - Granulocyte transfusions - ???

Granulocyte Transfusions: Outcomes and Complications

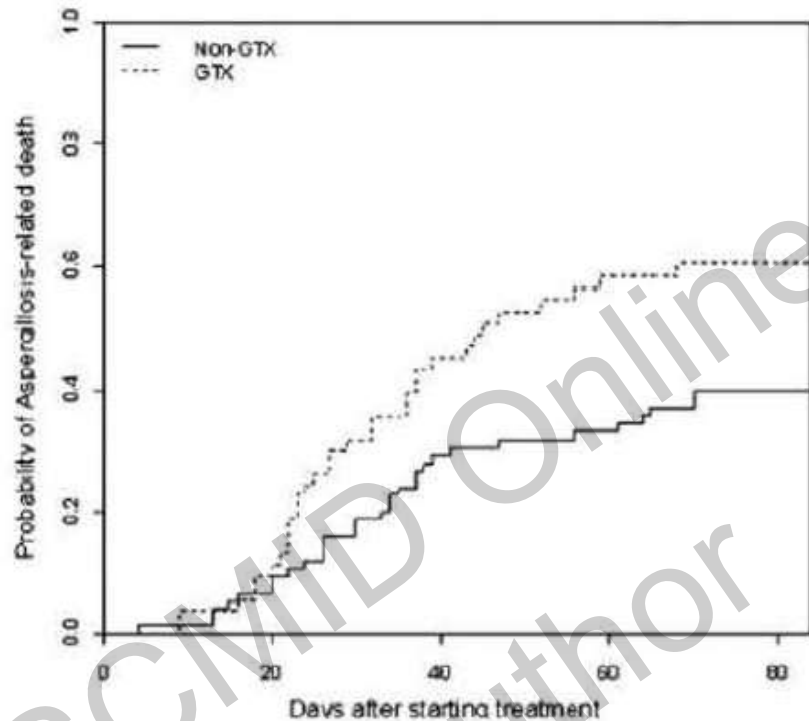


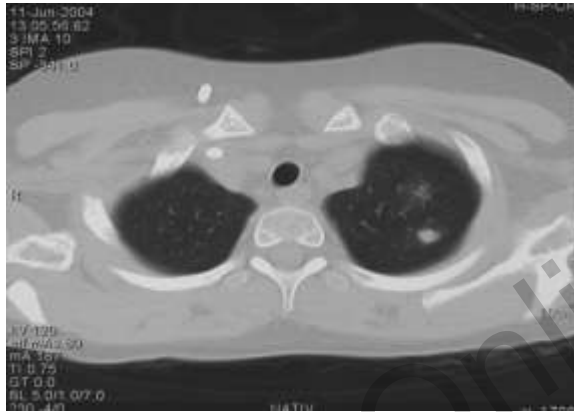
Figure 1. Cumulative incidence curves of IA-related deaths for prolonged neutropenic hematologic malignancy (HM) patients with aspergillosis who received GTXs and those who did not (non-GTX) by a competing risk analysis, using death due to other causes as a competing event ($P = 0.018$) ($n = 128$).

Table 3. Multivariate competing risk model for aspergillosis-related mortality, using death due to other causes as a competing event ($n = 128$)

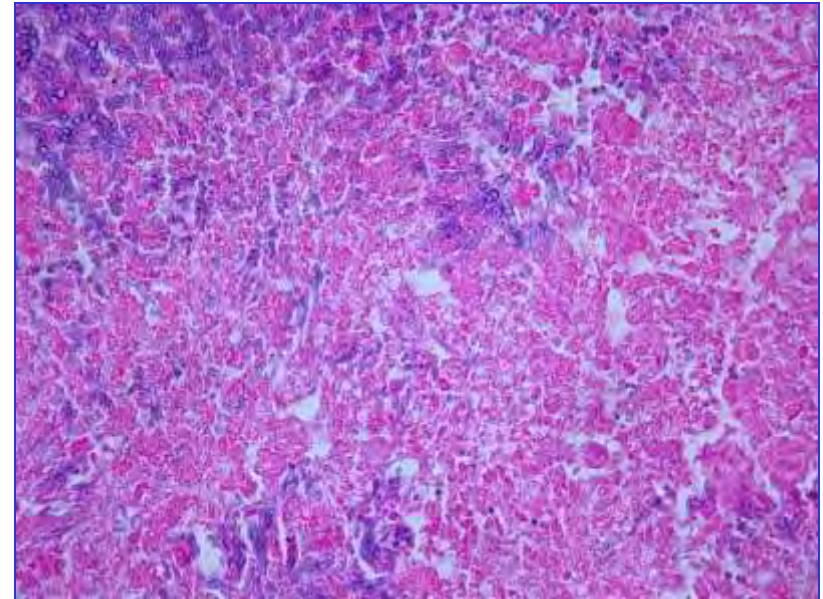
Variables	N	Hazard ratio	95% confidence interval	P
Persistent neutropenia				0.001
Yes	71	2.6	1.5, 4.7	
No	57	1.0		
Shortness of breath at baseline				0.003
Yes	55	2.2	1.3, 3.8	
No	73	1.0		
Intensive care unit (ICU) stay				<0.0001
Yes	57	3.0	1.8, 5.1	
No	71	1.0		
Azole-containing regimen in primary or salvage antifungal therapy				<0.0001
Yes	61	0.3	0.2, 0.5	
No	67	1.0		
Received GTX				0.011
Yes	53	2.0	1.2, 3.3	
No	75	1.0		

Treatment Duration

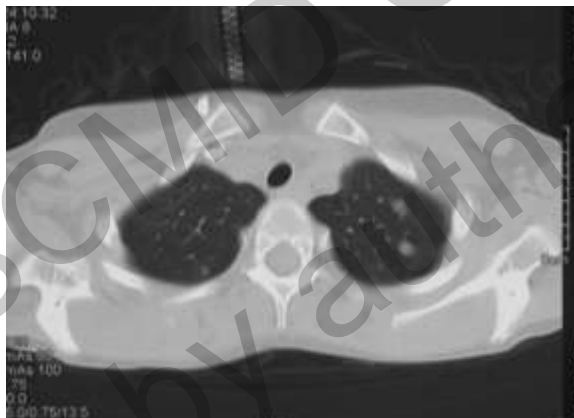
+ 13:



+338: Thoracoscopic lung biopsy



+ 330:



- CX negative
- PCR: *A.fumigatus*

Thank you for your Attention!

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