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Fungal infections during the treatment of childhood cancer

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Fungal infections during the treatment of childhood cancer

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Conflict of Interest

Speakers bureau:	Astellas, Gilead Sciences, Merck/MSD, Pfizer, Sanofi-Aventis
Advisory board:	Astellas, Basilea, Gilead Sciences, Merck/MSD, Mundipharma, PSI, Roche
Research grant:	Gilead Sciences

Learning Objective

- Invasive fungal infection in pediatric hematology/HCT
  - Clinical significance / risk groups and risk factors
  - Antifungal compounds
  - Diagnostics
  - Antifungal strategies
    - Prophylaxis
    - Empirical /pre-emptive antifungal therapy
    - Therapy of established infection

Invasive aspergillosis: Clinical significance

Retrospective cohort study: Identification of 666 pediatric cases of invasive aspergillosis among 152,231 immunocompromised children

Immunocompromised childen	with IA	without IA	*P*
Median length of hospital stay	16 days (IQR 3-38)	3 days (IQR 2-6)	<.001
Median per-patient hospital charges (IQR)	$49,309 ($7975-$189,579)	$9035 ($4774-$19,656)	<.01

Zaoutis et al. *Pediatrics* 2006

Invasive aspergillosis: Mortality

TABLE 2 In-Hospital Mortality Rate by Underlying Condition

Underlying Condition[a]	Mortality Rate, %		RR (95% CI)	*P*[b]
	Patients With IA ($N = 666$)	Patients Without IA ($N = 151\,537$)		
Malignancy	21	1	13.5 (10.9–16.8)	<.001
Solid tumor	18	1	14.0 (6.8–28.6)	<.001
Bone	0	0.6		NA
CNS	69	2	21.6 (9.1–51.0)	<.001
Other	0	0.7		NA
Leukemia	21	2	11.0 (8.5–14.2)	<.001
ALL	21	1	14.9 (10.2–21.7)	<.001
AML	20	3	5.0 (3.3–7.4)	<.001
Lymphoma	29	2	13.5 (6.7–27.1)	<.001
Other malignancy (NOS)	19	2	9.5 (5.3–17.0)	<.001
Hematologic disorder (aplastic anemia)	22	3.4	5.3 (3.7–7.5)	<.001
Immunodeficiency[c]	6	2.3	2.4 (1.1–5.2)	.2
Solid-organ transplant	33	6	4.7 (0.9–23.6)	NA
BMT	44	8	3.8 (2.6–5.6)	<.001
Allogeneic	45	11	3.3 (2.2–4.8)	<.001
GVHD	44	10	3.4 (2.2–5.3)	<.001
Non-GVHD	52	13	3.0 (1.4–6.1)	<.001
Autologous	66	3		NA

→ invasive aspergillosis significantly increases in-hospital mortality in immuno-compromised children

Zaoutis et al. *Pediatrics* 2006

Local epidemiology

Availability / value of diagnostic tests

Population at risk
(e.g. clinical, genetics)

Availability of antifungal compounds

Antifungal strategy

Tx Strategy	Prophylaxis	Empiric Tx	Pre-emptive Tx	Specific Tx
Signs or symptoms		Fever refractory to antibiotics	Fever refractory to antibiotics Antigen positive Pulm. infiltrates	Positive culture and/or histology
				
Invasive mycosis*	No	Possible	Probable	Proven

* in clinical practice, not EORTC/MSG criteria!

Adapted from Lehrnbecher T, et al. *Mycoses* 2008;52:107-17

IFD in Pediatric Hem/Onc and HCT

Pediatric AML (AML–CCG 2961)

Sung et al. *Blood.* 2007

	Induction (N=492)		Consolidation (N=407)		Intensification (N=248)	
	N	**%**	**N**	**%**	**N**	**%**
Fungus	**88**	**18**	**86**	**21**	**34**	**14**
Candida albicans	21	4	5	1	2	1
Other *Candida* spp	30	6	20	5	7	3
Aspergillus spp	20	4	42	10	7	3
Fusarium	2	0	3	1	2	1
Mucor	1	0	1	0	2	1

Pediatric allo HCT:

- retrospective single-center study of 209 children (2004-2012): incidence of IFD 12%
  - patients who developed IFD had a significantly increased risk of TRM (OR 3.773, *P*=.004)

Hol et al *BMT* 2014

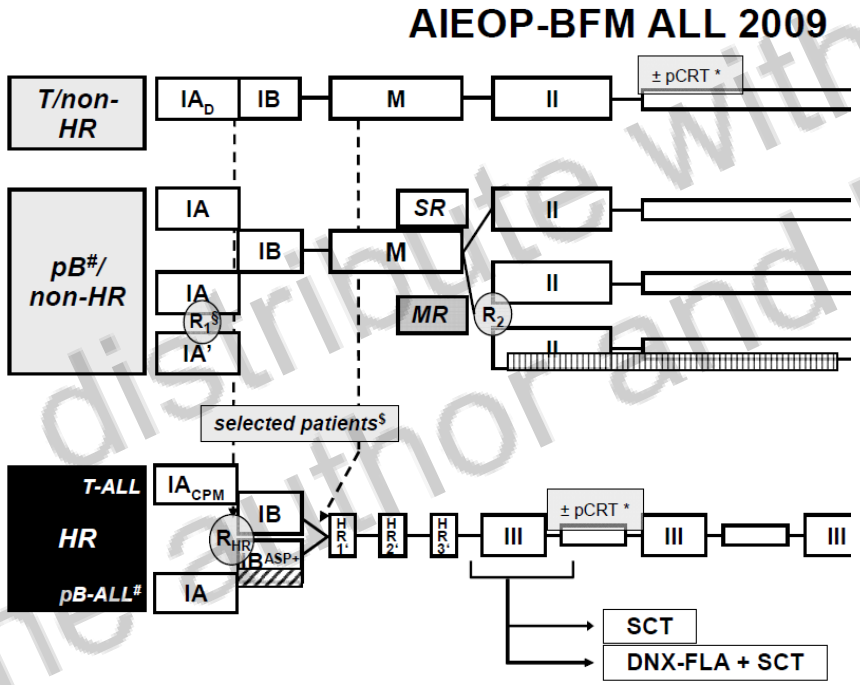
IFD in pediatric ALL

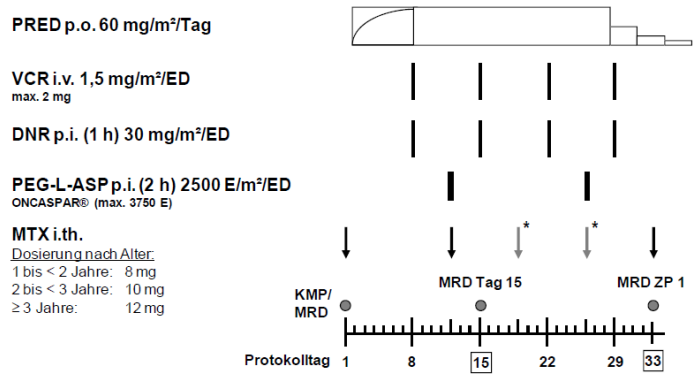
Study patients total 6130

- Girls 2594 (42.3%)
- Boys 3536 (57.7%)

- SR 2040 (33.3%)
- MR 2685 (43.8%)
- HR 1405 (22.9%)

- No IFD 5749 (93.8%)
- Possible IFD 148 (2.4%)
- Proven/probable IFD 233 (3.8%)





Unpublished data

	All	No		Possible		Prov./prob.	
	N	N	%	N	%	N	%
Risk group (final)							
SR	2040	1949	95.5	39	1.9	52	2.5
MR	2685	2551	95.0	49	1.8	85	3.2
HR	1405	1249	88.9	60	4.3	96	6.8
FCM day 15<0.1%	2108	1996	94.7	47	2.2	65	3.1
FCM day 15<10%	3054	2902	95.0	60	2.0	92	3.0
FCM day 15>=10%	780	677	86.8	40	5.1	63	8.1
Age							
Age <10 Years	4633	4427	95.6	79	1.7	127	2.7
Age 10-14 Y.	994	896	90.1	42	4.2	56	5.6
Age >=15 Y.	503	426	84.7	27	5.4	50	9.9

Unpublished data

Stratification of Risk of IFDs in Pediatric Cancer / HCT Patients

Risk stratum	Patient population
High risk (≥ 10 %)	-acute myeloblastic leukemia -recurrent acute leukemia's -allogeneic HCT -high-risk acute lymphoblastic leukemia*
Low risk (≤5 %) **	-acute lymphoblastic leukemia * -non-*Hodgkin* lymphoma's -autologous HCT
Sporadic occurrence **	-pediatric solid tumors -brain tumors -*Hodgkin's* lymphoma

* depending on the protocol and additional risk factors (e.g., steroids, prolonged granulocytopenia), risk for IFD may be near or exceeding 10 %

** consider that low and sporadic risk is not equal to no risk

Fisher et al. J Pediatric Infect Dis Soc 2018

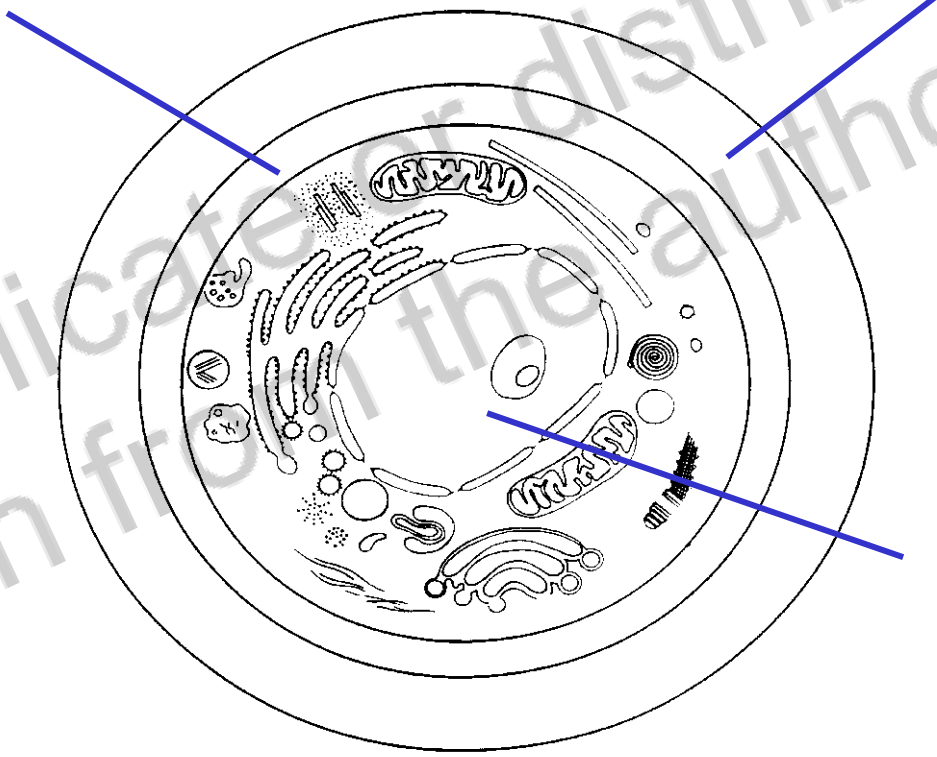
Fisher et al, *JPIDS* 208; Warris et al, *CMI* 2019; Lehrnbecher et al *JCO* 2020; Groll et al, *Lancet Oncol* 2021

Antifungal compounds and pediatric approval

Cell membrane

- **Polyenes**
  - > DAMB
  - > LAMB
  - > ABLC
  - > ABCD

- **Triazoles**
  - > Fluconazole
  - > Itraconazole *
  - > Voriconazole
  - > Posaconazole *
  - > Isavuconazole *



Cell wall

- **Echinocandins**
  - > Caspofungin
  - > Micafungin
  - > Anidulafungin

Nuclein acid synthesis

- > Flucytosine

* *not approved in pediatric patients*

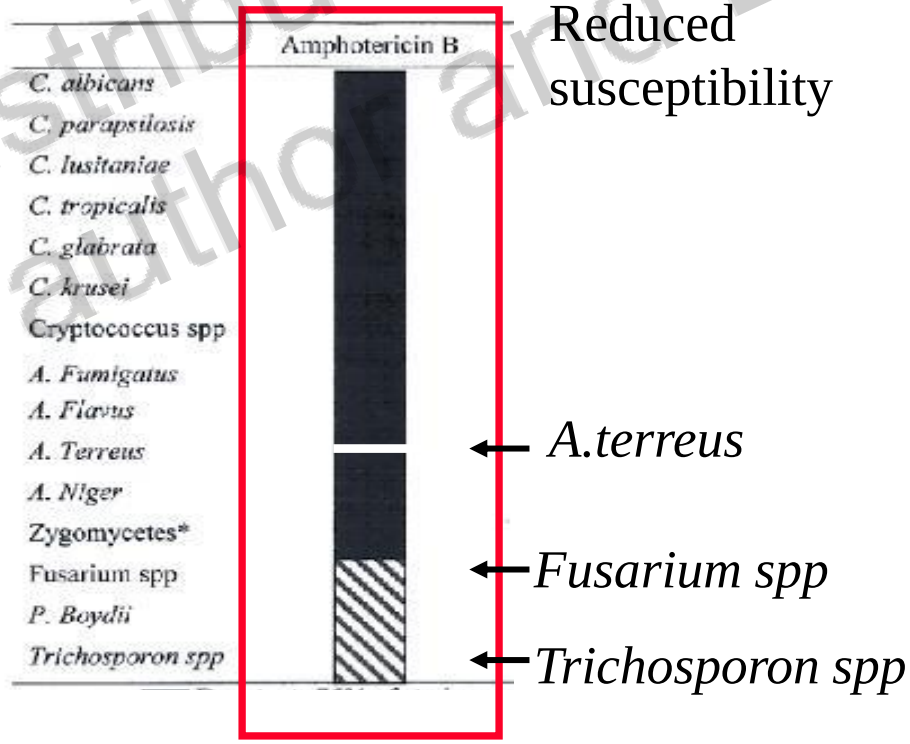
Groll & Tragiannidis 2009

Liposomal Amphotericin B

- Approved for children of all ages
- Only i.v. formulation
- Broad activity

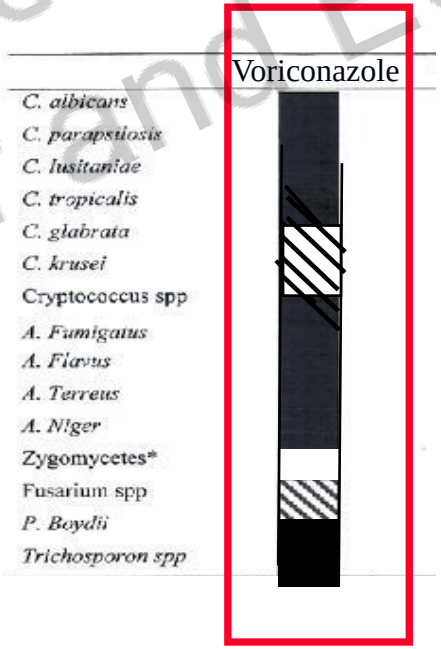
- Liposomal amphotericin B with similar activity as conventional amphotericin B, but with better tolerability

- Problem: nephrotoxicity, loss of potassium



Broad-spectrum triazoles

- Voriconazole
  - approved ≥ 2 years; i.v. + oral
  - CNS penetration excellent
- Posaconazole
  - approved ≥ 18 years (US: ≥ 13 years)
  - Solution: blood level insufficient in children*, better slow release tablet and i.v.**
  - Activity similar to voriconazole, but includes also mucormycetes



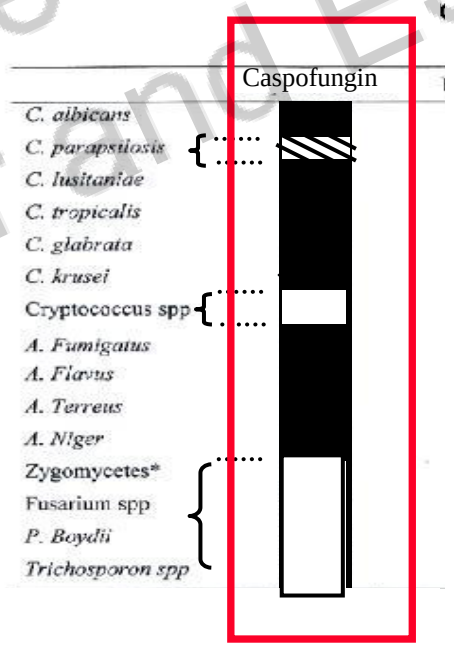
- Triazoles:
  - Multiple drug-drug interactions, e.g. with vincristin, cyclosporin…
  - Therapeutic drug monitoring strongly recommended

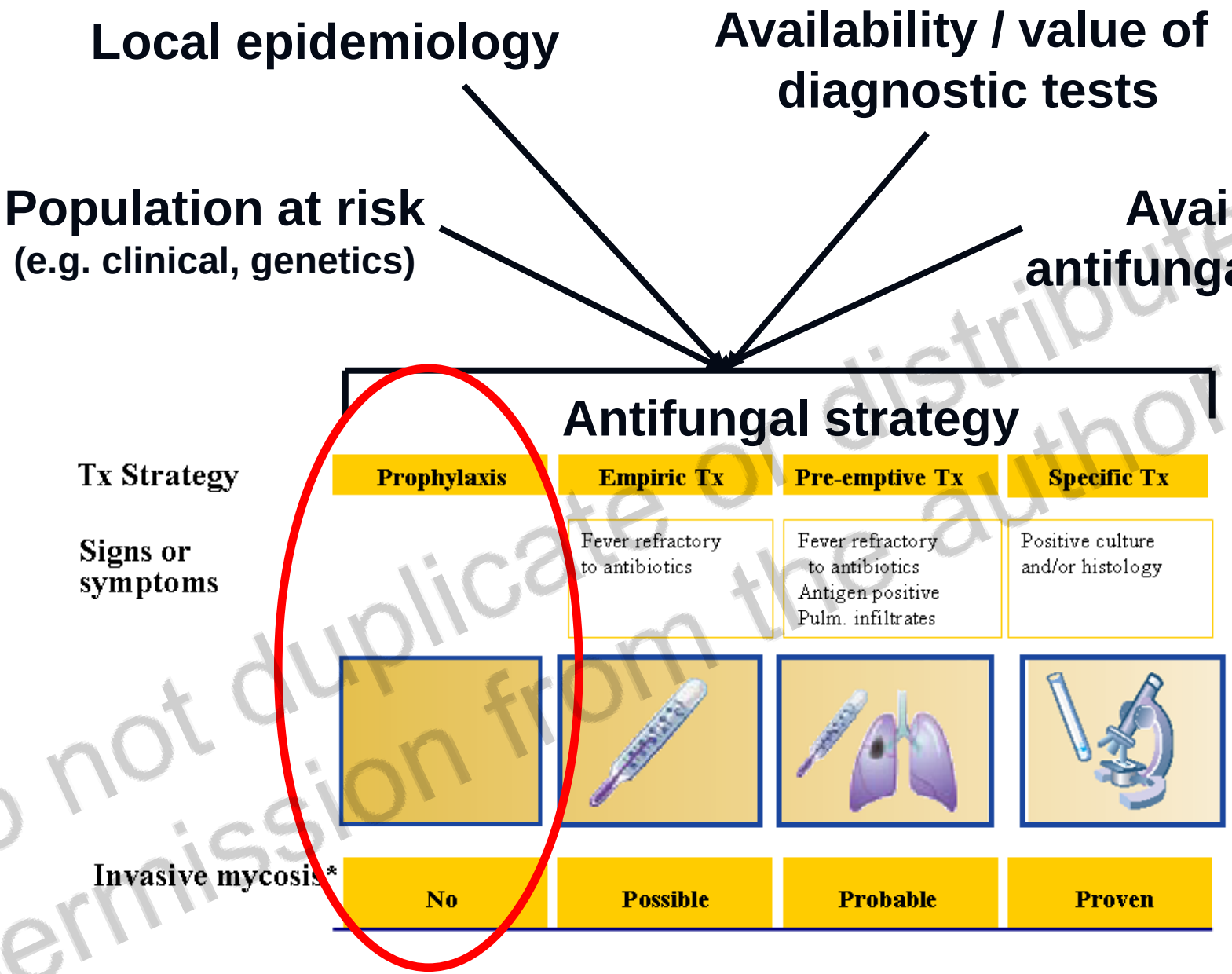
** Arrieta et al PLoS One 2019; **Groll et al Int J Antimicrob Agents 2020*

Echinocandins

Echinocandins:

- Caspofungin, micafungin, anidulafungin
- Approved for children of all ages
- Only i.v. formulation
- All with similar activity
- Excellent tolerability
- No major CNS penetration





* in clinical practice, not EORTC/MSG criteria!

Adapted from Lehrnbecher T, et al. *Mycoses* 2008;52:107-17

Antifungal prophylaxis – whom to prophylax?

Primary antifungal prophylaxis is strongly recommended for paediatric patients at high risk (≥10% estimated natural incidence) of invasive fungal disease	..	A	IIt	Includes patients with acute myeloid leukaemia, recurrent leukaemia, high-risk acute lymphoblastic leukaemia, and those undergoing allogeneic HCT in the pre-engraftment and in the post-engraftment phase until immune reconstitution, or in situations of augmented immunosuppressive treatment in the context of graft-versus-host disease; augmented immunosuppression refers to the use of additional immunosuppressive interventions to control overt graft-

Groll et al.ECIL-8 Guidelines *Lancet Oncol* 2021

Antifungal prophylaxis – which compound?

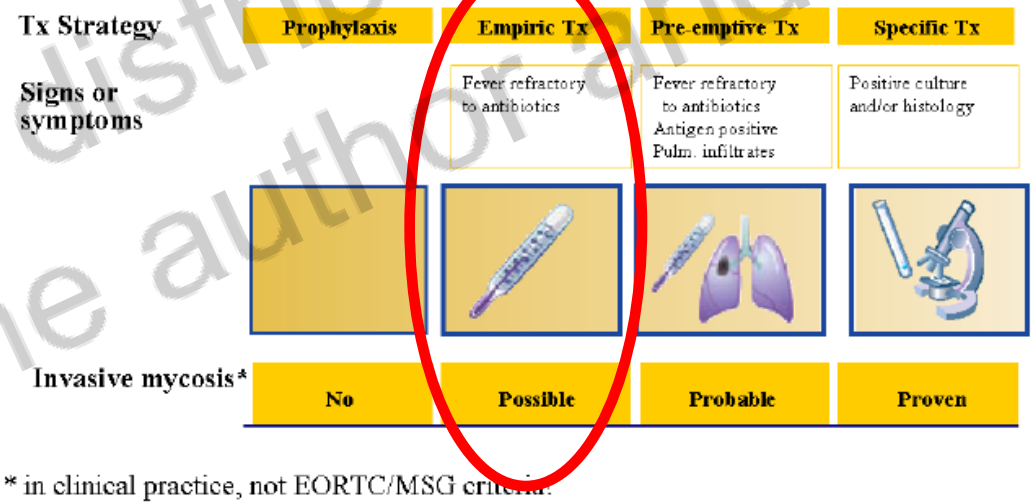
Posaconazole	Patients aged 13 years or older:	A	IIt
Itraconazole	Patients aged 2 years or older:	B	IIt
Liposomal amphotericin B	1 mg/kg every other day intravenously	B	IIt
Liposomal amphotericin B	2·5 mg/kg twice per week intravenously	B	II
Voriconazole	Patients aged 2–12 years, or aged	B	IIt
Micafungin	1 mg/kg per day (max 50 mg) once daily intravenously	C	I
Micafungin	4 mg/kg twice weekly	C	II
Caspofungin	50 mg/m² per day (70 mg/m²	NA	NA

Groll et al.ECIL-8 Guidelines *Lancet Oncol* 2021

Empirical antifungal therapy: background

- Empirical antifungal therapy: Longstanding ‘standard of care’ in patients with:
  - ANC ≤500/µl ≥10 days and
  - Persistent fever >3-5 days or recurrent fever despite broad-spectrum antibiotics

    - Targeted prevention in highest-risk situations
    - Early treatment of occult infections



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Adapted from Lehrnbecher T, et al. *Mycoses* 2008; 52: 107-17

Empirical Antifungal Therapy: Pediatric Data

- 4 prospective randomized trials in children
  - *Prentice et al* 1997
    - D-AmB vs L-AmB (1mg/kg) vs L-AmB (3 mg/kg)
    - n=204, >60% children with leukemia
  - *Sanders et al* 2000
    - D-AmB vs ABCD*
    - n=49, >60% children with leukemia/HSCT
  - *Maertens et al* 2010
    - L-AmB vs Caspo (50 mg/m^2 after loading day 1)
    - n=82, >70% children with leukemia/HSCT
  - *Caselli et al* (2012)
    - L-AmB vs Caspo in 56 high risk children
    - L-AmB vs Caspo vs no treatment in 47 low risk children

*Ampho B colloidal dispension is not licensed for this indication in children

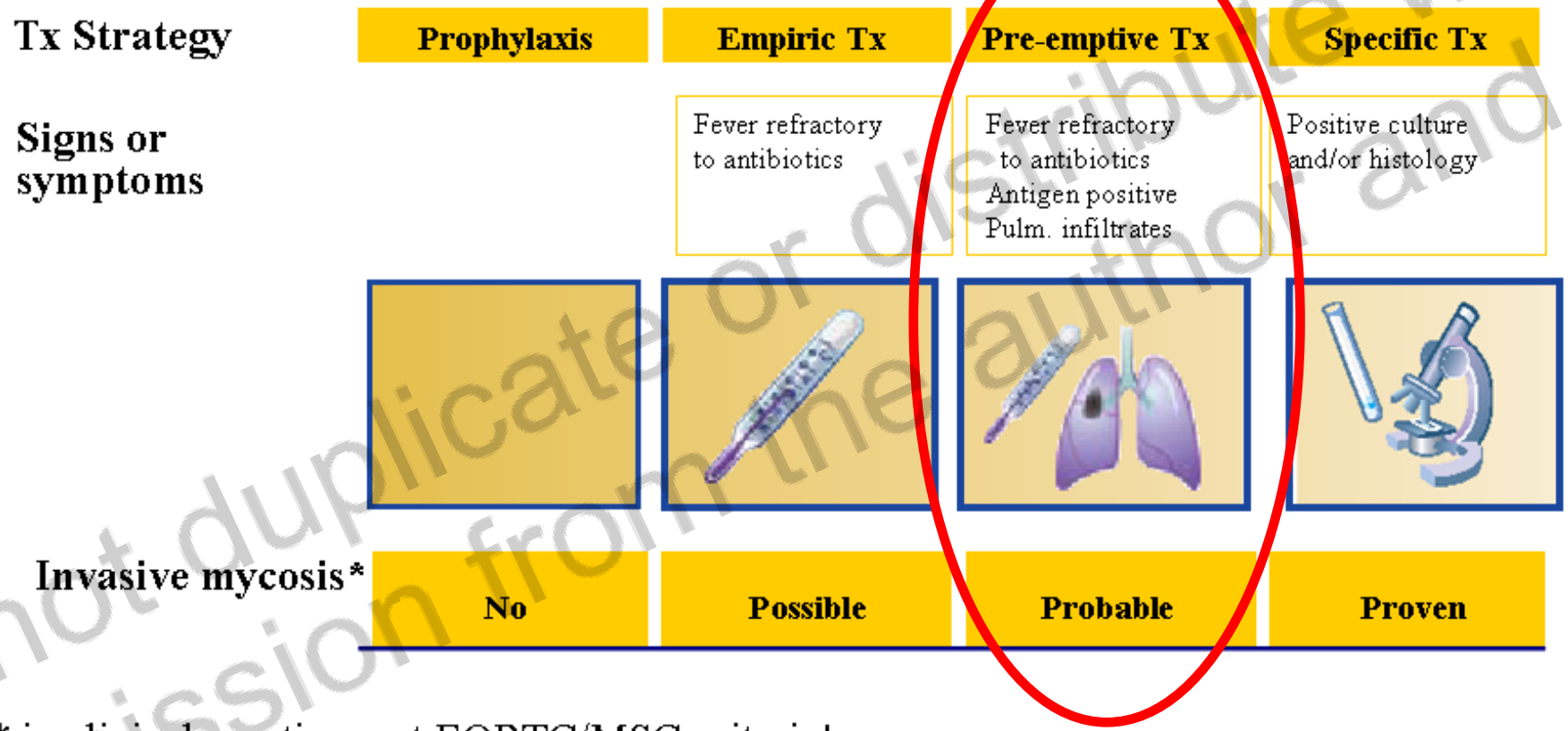
Prentice 1997; Sanders 2000; Maertens 2010; Caselli 2012

Empiric Therapy in Paediatric Patients

Population	Intention	Intervention	SoR	QoE	Comments
High risk for IFD	Management of persistent (>96 hours) febrile neutropenia without obvious cause and treatment of 'occult' IFI	Caspofungin	A	I	Similar safety and efficacy in larger adult clinical trials Both L-AmB as Caspofungin are approved for this indication in children If patients receive mold-active antifungal prophylaxis, switching to a different class of mold-active antifungal is recommended
		Liposomal AmB	A	I	
		AmB colloidal dispersion	D	II	
		AmB deoxycholate	D	II	

Lehrnbecher et al. *J Clin Oncol*. 2017, Warris et al.*CMI* 2019; Groll et al. *Lancet Oncol* 2021

Pre-emptive Treatment



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Adapted from Lehrnbecher T, et al. *Mycoses* 2008; 52: 107-17

Pre-emptive Antifungal Therapy: Children

- One randomized study in children including a total of 149 children
- Except of days of antifungals, no major difference between empirical and pre-emptive arm

	Intervention		
	empirical, $N = 73$	pre-emptive, $N = 76$	P
Primary endpoint			
overall mortality at day 30, *n* (%)	6 (8)	4 (5)	0.47
Secondary endpoints			
IFD-related mortality at day 30, *n* (%)	2 (3)	2 (3)	0.97
days of fever, median (IQR)	9 (7–13)	9 (6–14)	0.76
days of hospitalization, median (IQR)	19 (14–23)	17 (13–22)	0.15
days of antifungal, median (IQR)	11 (7–16)	6 (3–13)	<0.001
developing IFD, *n* (%)	9 (12)	9 (12)	0.92
antifungal start required, *n* (%)		32 (42)	
antifungal modification required, *n* (%)	15 (21)	12 (16)	0.45
need for ICU, *n* (%)	18 (25)	15 (20)	0.47

- Preconditions for pre-emptive therapy:
  - Galactomannan assay with quick turn-around (e.g., daily)
  - CT scan available daily

Santolaya ME et al. *J Antimicrob Chemotherapy.* 2018;73:2860-66

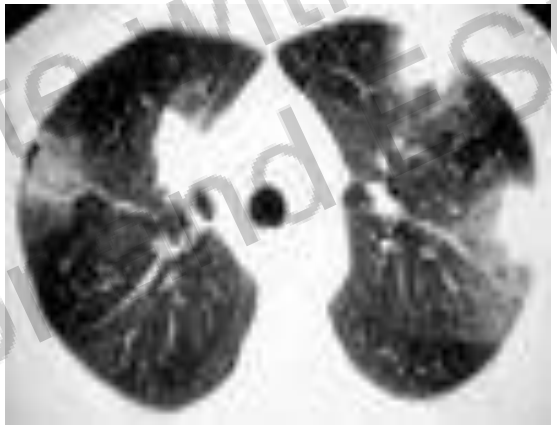
Biomarker: galactomannan

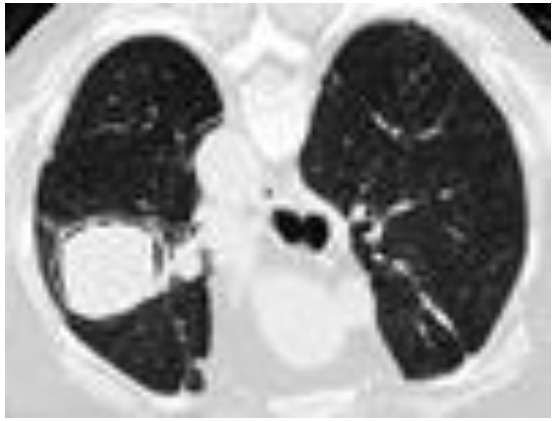
- Cell wall antigen of *Aspergillus* spp
- Test with high negative, but low positive predictive value
- Causes of false-positivity include cross-reaction from an existing non-*Aspergillus* fungal infection, the intravenous administration of some ß-lactam antibiotics, various blood products
- False-negative results often in patients receiving mold-active prophyaxis
- Assessment possible in blood, broncho-alveolar lavage (BAL), and cerebrospinal fluid (CNS)
- Diagnostic use for children with prolonged FN and/or abnormalities in chest CT (A-II)

Lehrnbecher et al. *CID* 2016; Groll et al ECIL-8 Guidelines, *Lancet Oncol* 2021

Imaging: Pulmonary CT scan in adults

- In adults, systematic CT scans allow earlier diagnosis of invasive pulmonary aspergillosis, which is associated with improved prognosis
- Pulmonary nodules (in particular, nodules with halo sign, air crescent sign and cavitation) are typical CT findings for fungal pneumonia in adults
- Appearance of these findings depends on time of imaging and are not specific for fungal infections
- Data of „typical CT findings“ in children scarce and contradicting*

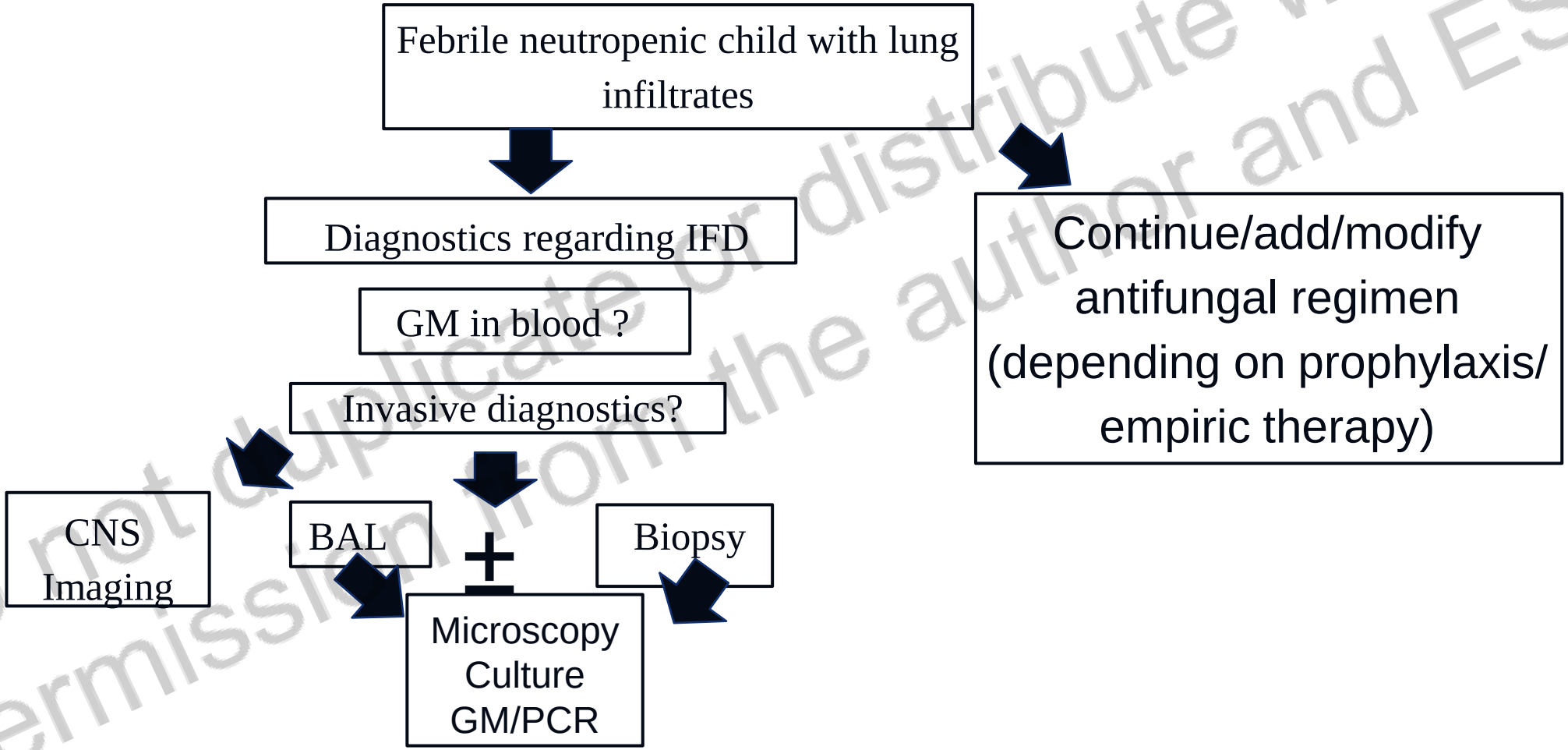




*Burgos et al 2008; Han et al 2015

Caillot et al. J Clin Oncol. 1997;15:139-47; Heussel et al. J. Clin Oncol 1:796–805

Potential algorithm in febrile neutropenic children with lung infiltrates



Groll et al ECIL-8 Guidelines, *Lancet Oncol* 2021

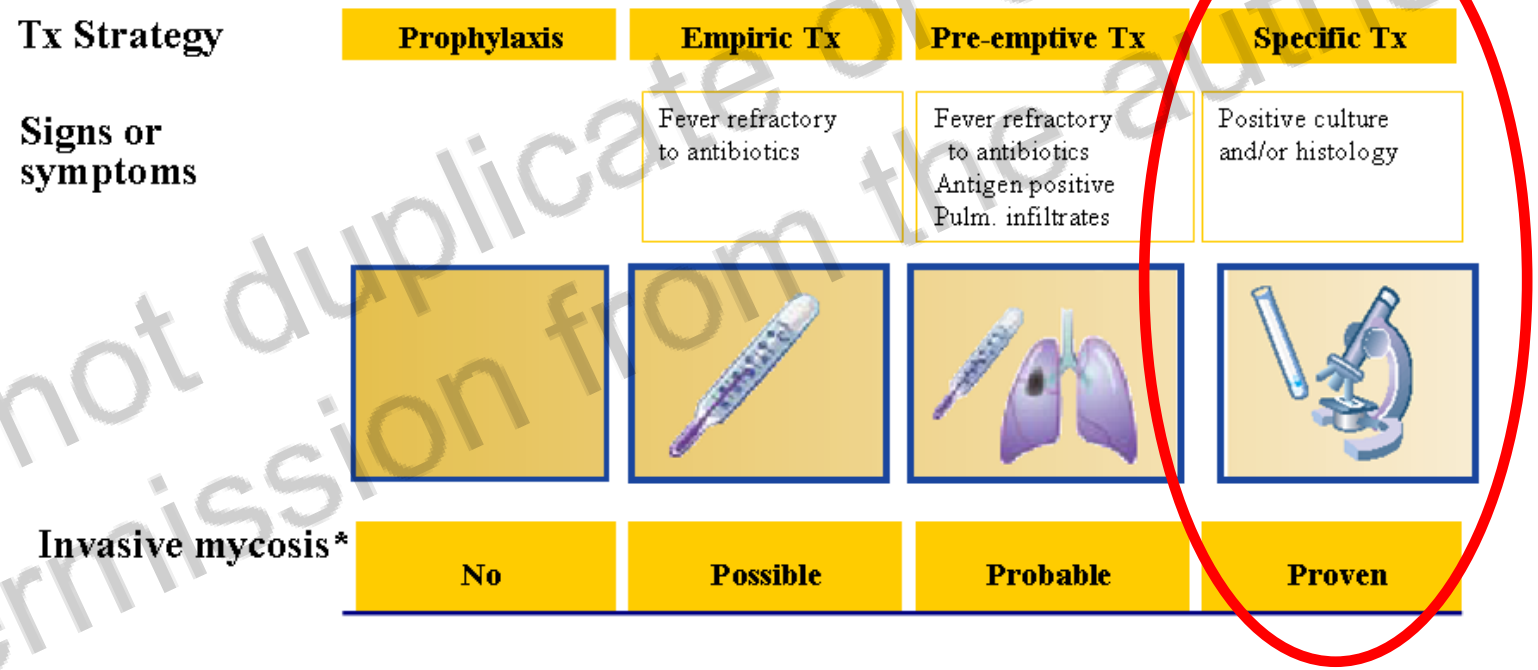
Local epidemiology

Availability / value of diagnostic tests

Population at risk
(e.g. clinical, genetics)

Availability of antifungal compounds

Antifungal strategy



* in clinical practice, not EORTC/MSG criteria!

Adapted from Lehrnbecher T, et al. *Mycoses* 2008;52:107-17

Invasive Candidiasis in Neutropenic Patients

Invasive candidiasis			
Caspofungin	Single dose 50 mg/m² per day (70 mg/m² on day 1) intravenously	A	IIt
Liposomal amphotericin B	Single dose 3 mg/kg per day intravenously	A	IIt
Micafungin	Single dose 2–4 mg/kg per day intravenously (100–200 mg for patients weighing 50 kg or more)	A	IIt
Voriconazole	Patients aged 2–12 years, or aged 12–14 years and weighing less than 50 kg: 8 mg/kg (9 mg/kg on day 1) twice a day intravenously or 9 mg/kg twice a day orally; patients aged 12–14 years and weighing 50 kg or more, or aged 15 years and older: 4 mg/kg (6 mg/kg on day 1) twice a day intravenously or 200 mg twice a day orally	B	IIt
Fluconazole	Single dose 12 mg/kg (maximum 800 mg) per day intravenously	D	IIt

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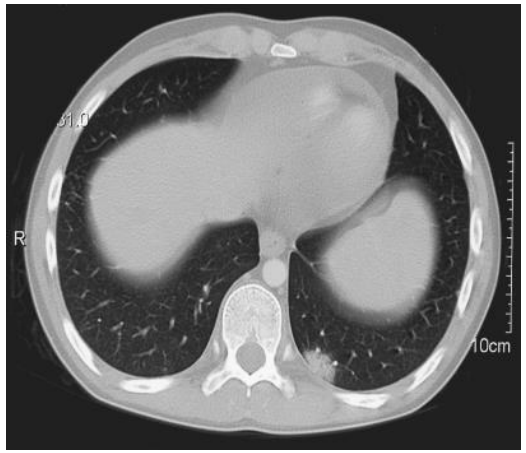
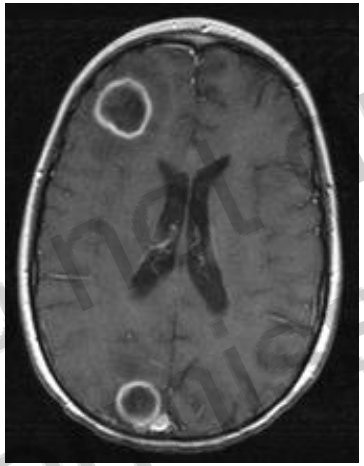
Invasive Aspergillosis

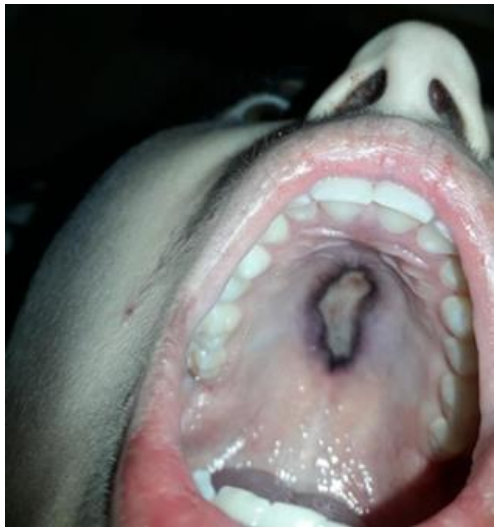


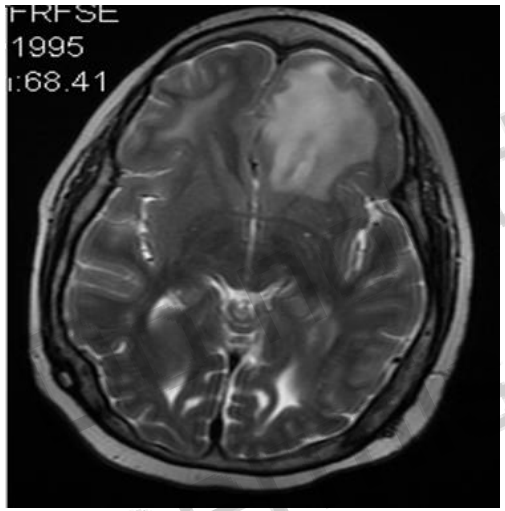


Invasive aspergillosis			
Voriconazole	Patients aged 2–12 years, or aged 12–14 years and weighing less than 50 kg: 8 mg/kg (9 mg/kg on day 1) twice a day intravenously or 9 mg/kg twice a day orally; patients aged 12–14 years and weighing 50 kg or more, or aged 15 years and older: 4 mg/kg (6 mg/kg on day 1) twice a day intravenously or 200 mg twice a day orally	A	IIt
Liposomal amphotericin B	Single dose 3 mg/kg per day intravenously	B	IIt
Amphotericin B lipid complex	Single dose 5 mg/kg per day intravenously	C	II
Combination therapy (voriconazole or liposomal amphotericin B plus echinocandin)	..	C	IIt
Isavuconazole	10 mg/kg (maximum 372 mg) isavuconazonium sulfate intravenously once daily (every 8 h on days 1–2)	A†	IIt†

Groll et al.ECIL-8 Guidelines *Lancet Oncol* 2021

Mucormycosis





Mucormycosis			
Liposomal amphotericin B	Single dose 5–10 mg/kg per day intravenously	A	IIt
Amphotericin B lipid complex	Single dose 5·0–7·5 mg/kg per day intravenously	B	II
Combination therapy (lipid amphotericin B formulation plus caspofungin or posaconazole)	..	C	III

Groll et al.ECIL-8 Guidelines *Lancet Oncol* 2021

Take home messages

- IFD associated with significant morbidity and mortality
- Diagnostics – GM and CT, consider BAL / biopsy
- Prevention:
  - Problematic: heterogenous group of children with ALL – identification of patients who benefit from prophylaxis
  - Antifungal compound?
- Empirical antifungal therapy
  - In most sites standard of care
  - L-AmB and caspofungin with AI recommendation
- Pre-emptive antifungal
  - Little data in children
  - Pre-condition: rapid availability of GM and CT-scan (pediatric specific performance)
- Specific Therapy - Pediatric specific guidelines

Thank you!!

Discussion