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Ασπεργίλλωση σε αιματολογικούς ασθενείς

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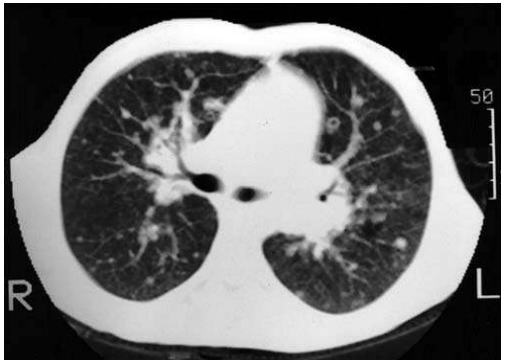
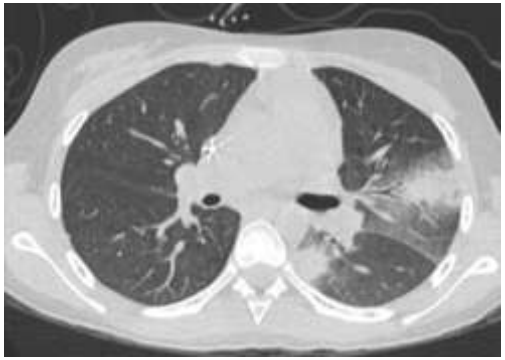
- Independent Contractor (research grants) of significant value from Pfizer, Gilead, Merck, Sanofi, Astellas, Astra-Zeneca, Cubist
- Scientific Advisor (Review Panel or Advisory Committee) of Schering, Gilead, Astellas, Pfizer, Merck
- Speaker's Bureau of Gilead, Pfizer, Merck, Aventis, Astellas, GSK

1.5-yr old boy with ALL, fever and an opacity in his lung

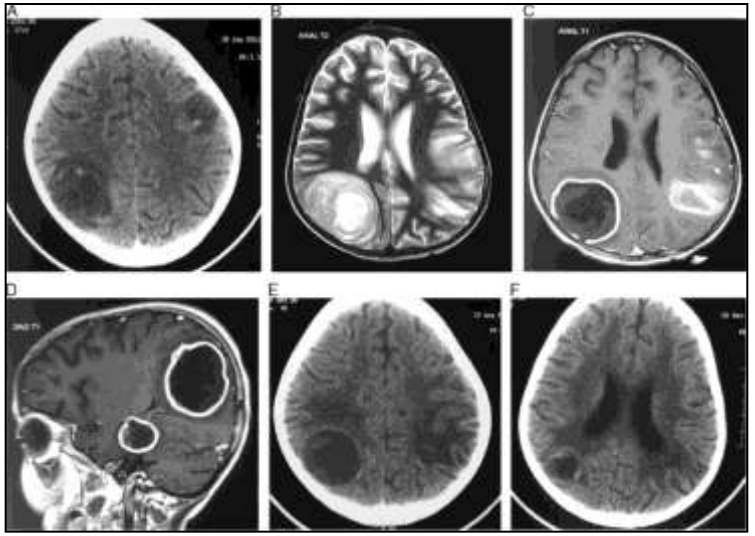
- Has had multiple episodes of fever+neutropenia treated with broad spectrum antibiotics





6-mo old infant with ALL and IA involving CNS

- Receiving caspofungin for persistent febrile neutropenia
- Galactomannan very high in both serum and CSF



Invasive aspergillosis in pediatric hematological patients

- Epidemiology – risk factors, outcome
- Diagnosis
- Treatment - guidelines

Risk factors for IA in children

- **Acquired immunodeficiencies**
  - Treatment for cancer
  - Bone marrow failure syndromes
  - Allogeneic HSCT
  - Solid organ transplantation
- **Primary immunodeficiencies**
  - Defects of phagocytic host defenses
- **Immunosuppressive therapies**
- **Chronic airway diseases (i.e. CF)**
- Low-birthweight - prematurity
- Advanced HIV infection
- Acute illnesses or trauma

Tragiannidis et al. CID. 2011

IA in Children With Acute Leukemia

	Rubio et al[14]	Kaya et al[20]	Burgos et al[15]	Zaoutis et al[5]	Crassard et al[16]	Groll et al[19]	Abbasi et al[17]	This Study
No.	20	09	139	666	24	13	66	34
Age (y)	< 20	< 16	< 18	< 20	< 16	≤ 22	≤ 22	< 18
Population	Hematolog disorders	Acute leukemia	Benign malignant, BMT	Benign malignant, BMT	Hematolog disorders, BMT	Acute leukemia	Hematolog disorders, BMT	Acute leukemia
Incidence (%)	1.96	8.4	—	AML = 3.7 ALL = 0.6	AML = 5.3 ALL 1.5	Total = 6.8 AML = 27 ALL = 2	—	Total = 9.5 AML = 13 ALL = 9
Risk factors	N, S, Ch	N, S	Immunosup, aBMT	Malignancy, BMT		N	Malignancy, N, S	N, S, Hg
Diagnosis of IA	Proven or probable	Proven, probable and possible	Proven or probable		Proven or probable	Proven or probable	Proven	Proven or probable
Antifungal	LAB = 85% Comb = 15%	LAB = 100% LAB→ vori(44%) itra(12%)	LAB/ AB = 89% Vori = 49%		AB = 100% (± itra/ 5FC/LAB)	AB = 92% + 5FC = 5%		AB = 24% AB→vori 50% Vori = 26%
Outcome AFS (%)	45	90	47.5	82	37.5	64	15	85

→indicates step down to; 5FC, 5 flucytosine; AB, amphotericin B deoxycholate; aBMT, allogenic bone marrow transplant; AFS, aspergillus-free survival; Ch, chemotherapy; comb, combination therapy; Hematalog, hematological; H, hyperglycemia; Immunosup, immunosuppressive therapy; itra, itraconazole; LAB, liposomal amphotericin B; N, neutropenia; S, steroid; vori, voriconazole.

Jain & Kapoor. J Pediatr Hematol Oncol. 37(1):e1-e5, 2015

IA remains a killer despite decreased mortality among children with leukemia

- Infectious complications in children treated according to **AML-BFM 2004 vs. AML-BFM 93**
- 405 pts (median age 8.4 yrs) experienced 1326 infections.
- 240 Gram (+) and 90 Gram (-) isolates were recovered from the blood.
- Invasive fungal infection in 3% of the pts
- As compared with **AML-BFM 93** with lower dose intensity, infection-related morbidity was slightly higher in AML-BFM 2004 (3.3 vs. 2.8 infs/pt)
- However, infection-related mortality significantly decreased in AML-BFM 2004 (from 5.4% previously to 1.5%; P = 0.003)
- 3 children died of Gram (-) bacteremia and 3 died of invasive aspergillosis

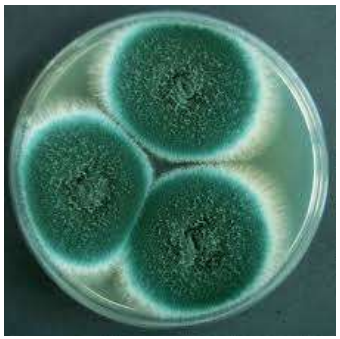
Bochennek et al. Blood Cancer J (2016) 6, e382

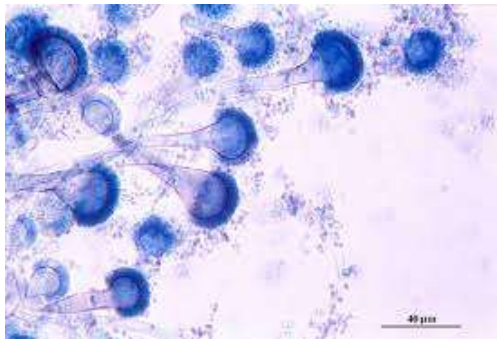
Diagnosis of IA

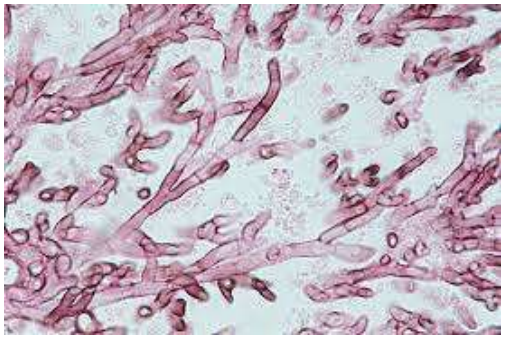
Diagnostic Markers

Standard diagnostic markers in pediatric patients do not differ from adults

- Cultures, microscopy, histology, etc



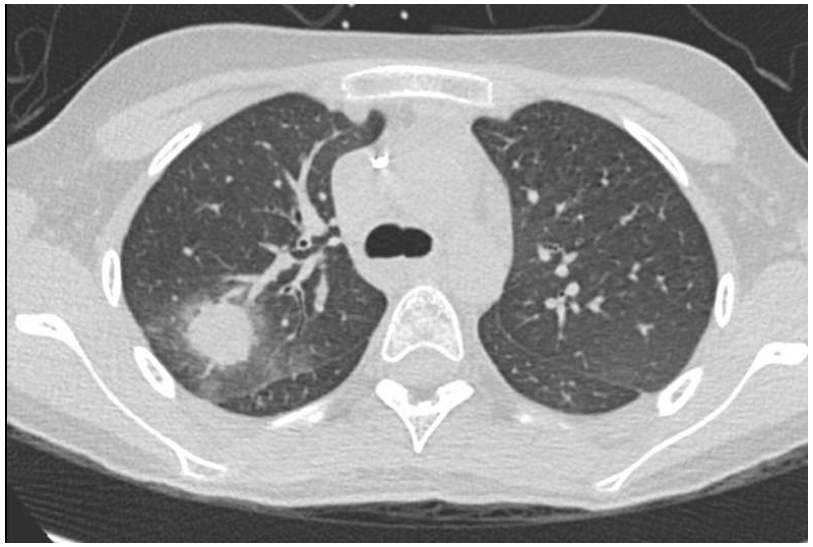




Differences on newer diagnostic markers, CT imaging

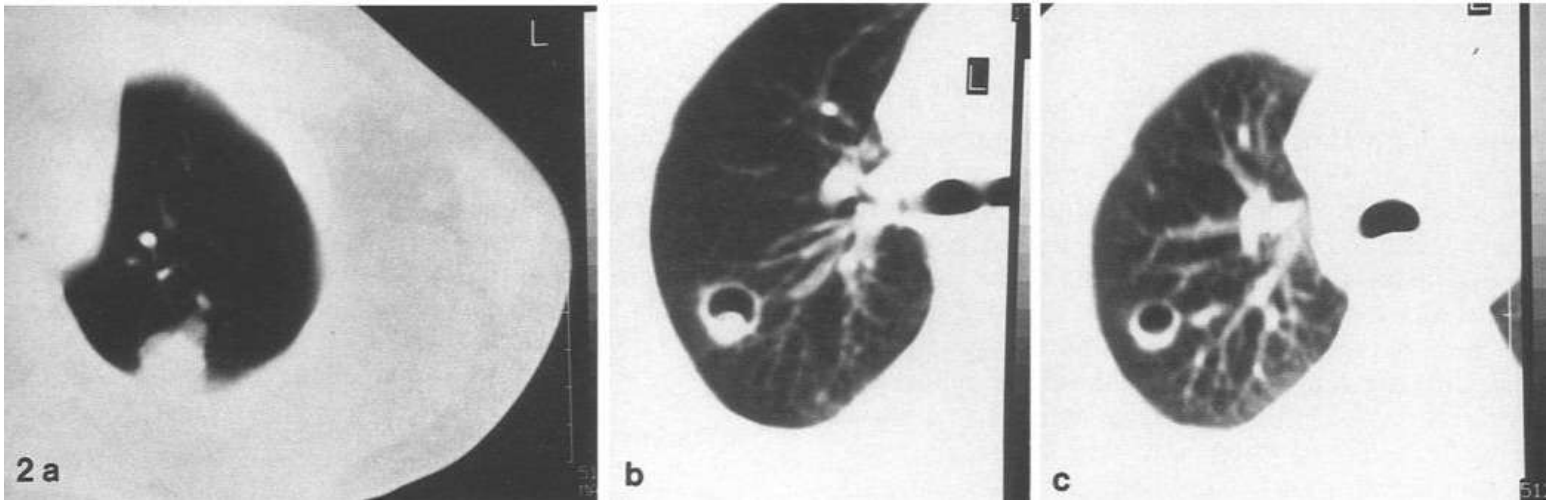
- Imaging studies as mandated by clinical findings
- Antigen markers (GM & BDG assays)
- PCR

IPA in adults



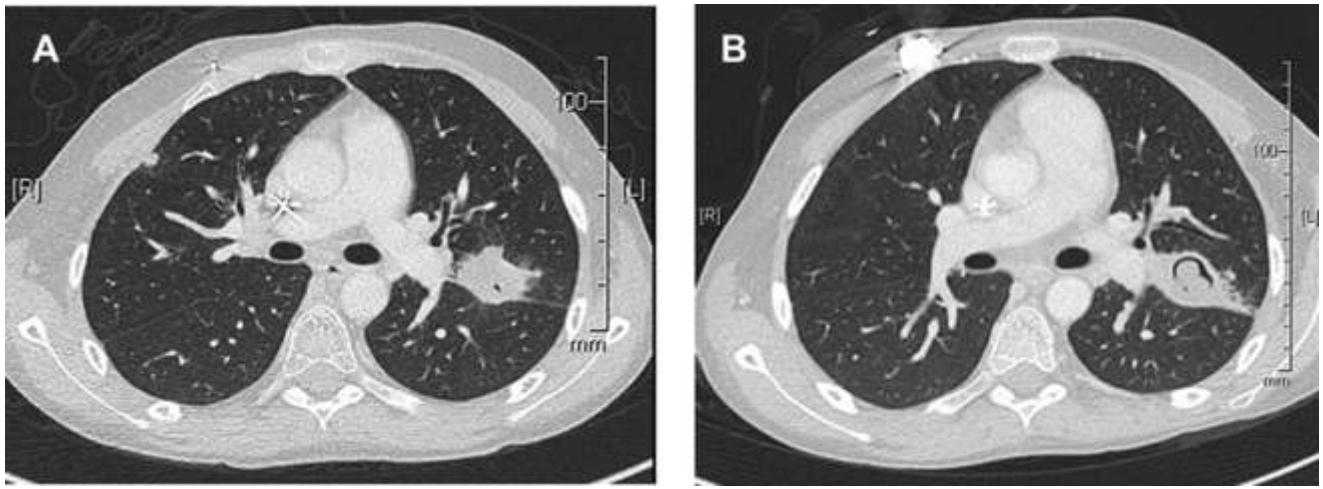
Peripheral nodules with halo sign

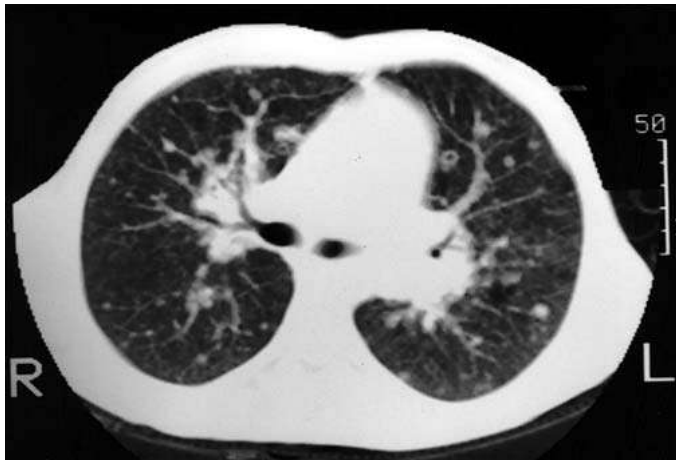
Crescent or meniscus sign



IPA in children

The majority of children non-specific findings





Atypical nodules, no “halo sign’ frequently, “crescent sign” rarely

Tragiannidis et al CID 2011
Thomas et al Pediatr Radiol 2003

Table 2. Types of Radiographic Findings in 110 Pediatric Patients With Probable or Proven Invasive Pulmonary Aspergillosis

Radiographic Finding	Frequency, %
Nodules	34.6
Cavity	14.4
Halo sign	6.4
Air crescent sign	1.6
Wedge-shaped lesions	1.1
Other infiltrates or lesions	42.0

Tragiannidis et al. Clin Infect Dis 2011
Burgos et al. Pediatrics 2008

Biomarkers of IA in children

Beta-D glucan (Fungitell®) assay

- Not specific for *Aspergillus*
- Not validated in pediatric or neonatal populations
- Higher baseline levels in healthy children and therefore unknown cut-off

Galactomannan

- Works in pediatric patients with similar operating characteristics in the same underlying populations and yields similar rates of false-positivity (unlike previous reports)

Serum galactomannan in children

Table 5. Pooled Sensitivity and Specificity for the Biomarkers Galactomannan, β-D-Glucan, and Polymerase Chain Reaction–Based Assays in Children and Adults

	Pediatrics		Adults	
Biomarker	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %
Galactomannan				
Screening (n = 5)	68 (51–81)	91 (86–94)		
Diagnostic test (n = 5)	89 (79–95)	85 (51–97)		
Total	81 (69–89)	88 (75–95)	82 (73–90) [39]	81 (72–90) [39]
β-D-glucan (n = 2)	NA	NA	76.8 (67.1–84.3) [40]	85.3 (79.6–89.7) [40]
PCR				
Screening (n = 1)	NA	NA		
Diagnostic test (n = 6)	76 (62–86)	58 (42–72)		
Total			80.5 (73–86.3) [41]	78.5 (67.8–86.4) [41]

Lehrnbecher et al. / CID 2016; 63: 1340–8

Serum galactomannan in children w ALL

- 141 children treated for ALL 2006-2015 reviewed retrospectively
- Cases of proven and probable IA according to EORTC/MSG criteria
- Proven and probable IA 3.5% (5/141)
- Positive serum GM 5.5% (179/3264 serum samples)
- Of the cases detected
  - 21.7% positive
  - 52.1% false-positive
  - 26.1% ‘undetermined”
- Increase of true-positives through multiple consecutive positive tests
- **Conclusion**: Serum GM may be detected before the clinical signs of IA, but its sensitivity and specificity are variable. False-positivity is a significant disadvantage, and **consecutive positives must be taken into account in the case of clinical and imaging findings of IA**.

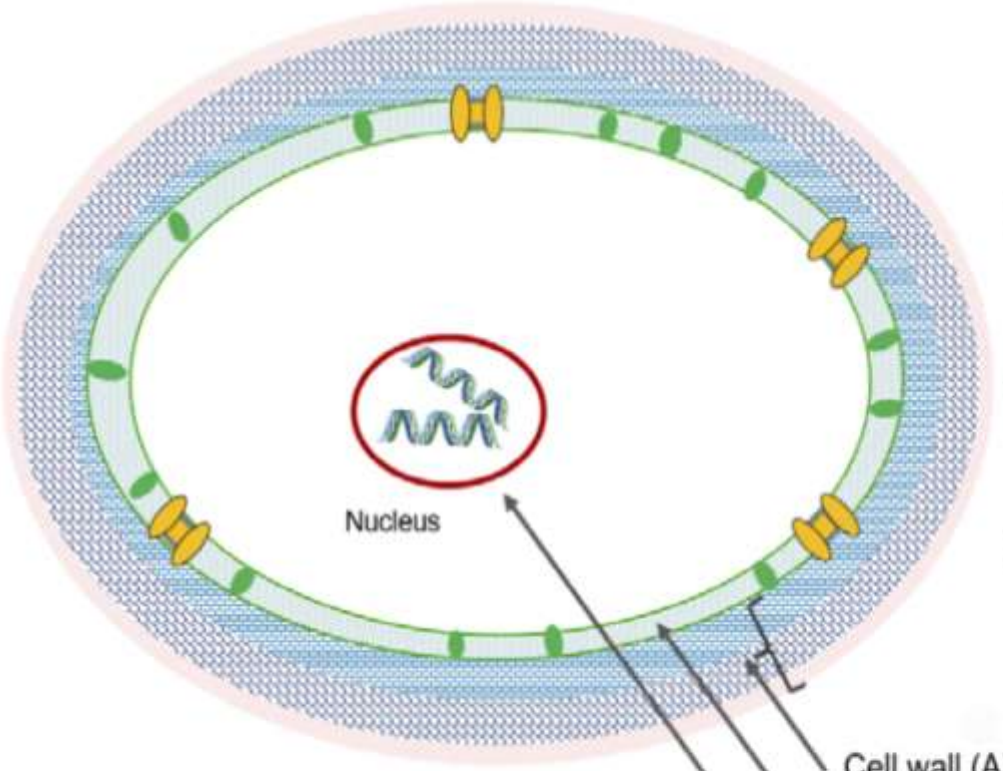
Avcu G et al. Intern J Infect Dis 54 (2017) 8–12

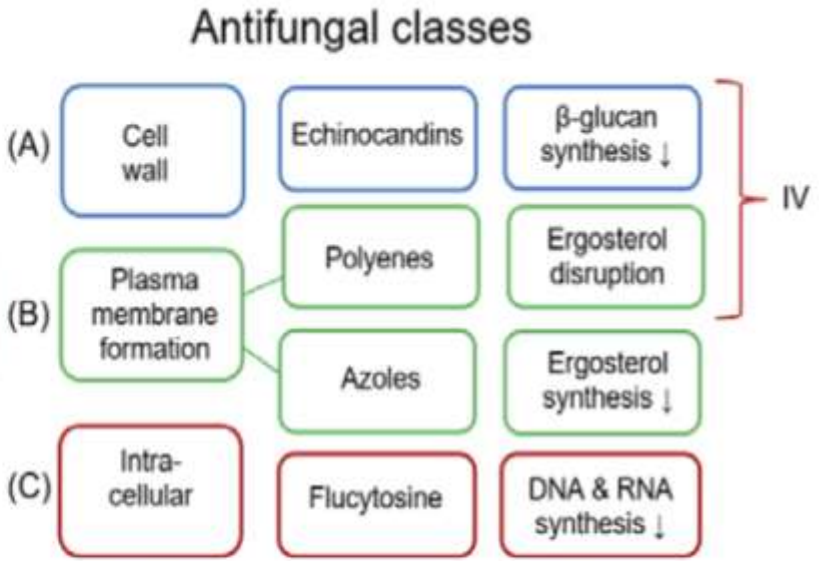
General principles of therapy

As in adults, cornerstones for successful management of invasive aspergillosis in children include

- **prompt initiation of appropriate antifungal therapy**
- **reversal of the patient's underlying deficiency in host defenses if exists and is feasible, and**
- **in select circumstances, surgical interventions**

Antifungal agents





Guidelines for the management of IA in children

(ECIL) **Groll AH et al. The Lancet Oncology 2014;15:e327-40**

(IDSA) **Patterson TF et al. Clin Infect Dis. 2016 63(4):e1-e60**

(ESCMID-ECMM-ERS) **Ullmann A et al. Clin Microbiol Infect 2018 24: e1ee38**

Antifungal agents for therapy of IA in pediatric pts

Agent	Dose	Level of evidence	Comments
First line			
Voriconazole	If ≤ 14 years of age and weight ≤ 50 kg: 8 mg/kg/12 h (D1: 9 mg/kg) IV or 9 mg/kg/12 h PO If ≥ 15 years of age and/or and weight ≥ 50 kg: 4 mg/kg/12 h (D1: 6 mg/kg) IV or 200 mg/12 h PO	A-I	Monitoring of recommended plasmatic trough level (target 1.0–5.0 mg/l) Preferred treatment in case of central nervous system involvement Discuss another therapeutic class in case of IA occurring while treated azoles
Liposomal amphotericin B	3 mg/kg/24 h IV	B-I	
Amphotericin B lipid complex	5 mg/kg/24 h IV	B-I	
In combination with echinocandin + polyene or triazole		C-III	
Second line			
Voriconazole	Idem first line	A-I	Not approved if < 2 years of age Option to choose as 2nd line for voriconazole naive patients Monitoring of recommended plasmatic trough level (target: 1.0–5.0 mg/l)
Liposomal amphotericin B	Idem first line	B-I	Preferred treatment in case of failure of or intolerance to voriconazole
Caspofungin	50 mg/m^2/24 h IV (D1: 70 mg/m^2)	A-II	
Amphotericin B lipid complex	Idem first line	B-II	
In combination with echinocandin + polyene or triazole		C-II	
Itraconazole	If ≥ 2 years of age: 2.5 mg/kg/12 h PO	–	Monitoring of recommended plasmatic trough level (target: ≥ 0.5 mg/l)
Posaconazole	If ≥ 13 years of age: 800 mg/day in 2 or 4 intakes PO	–	Monitoring of recommended plasmatic trough level (target: ≥ 0.7–1.5 mg/l)
Micafungin	2–4 mg/kg/24 h IV (100–200 mg/24 h if weight ≥ 50 kg)	–	

P. Frange et al. / Médecine et maladies infectieuses 45 (2015) 189

Antifungal prophylaxis

- High-risk populations with incidence rates of ~10% or higher
  - acute leukemia, bone marrow failure syndromes, allogeneic HSCT
  - particularly when immunosuppression is augmented for GVHD
  - primary immunodeficiency, ie CGD
- Posaconazole is not approved for <13 years
- Voriconazole is not approved for <2years

IDSA 2016 Guidelines for *Aspergillus*

- Treatment of aspergillosis in children uses the same recommended therapies as in adult patients
- However, the dosing is different and for some antifungals it is unknown

(strong recommendation; high-quality evidence)

Patterson TF et al. Clin Infect Dis. 2016 63(4):e1-e60

Age-dependent therapy

Patients ≥2 years old

•Options for first-line treatment of invasive aspergillosis: voriconazole or liposomal amphotericin B

Patients <2 years old

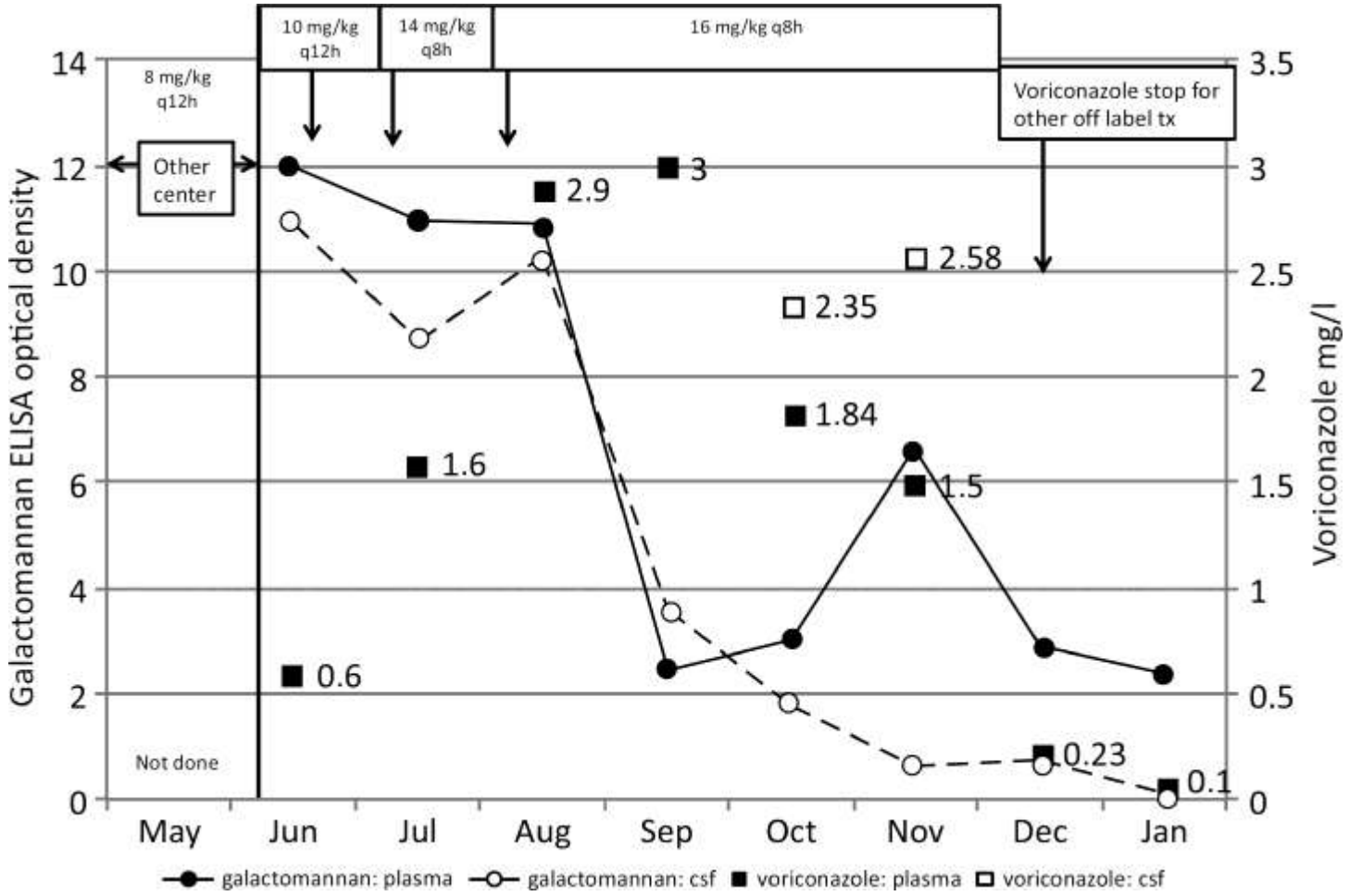
•The only option with an existing pediatric dosage and safety profile: liposomal amphotericin B

Voriconazole in children

- Therapeutic drug monitoring (TDM) strongly recommended in children due to the much higher rates of drug elimination and potential for underdosing **(AII)**
- Repeated monitoring until steady-state level is confirmed, if there are changes in the patient clinical condition, concomitant medications, or suspected toxicity

ESCMID-ECMM-ERS Guidelines 2018

Voriconazole levels in a young child w IA involving CNS



Palmisani et al. J Chemother. 2017 Feb; 29(1): 42-44

Isavuconazole for children

- Phase 1, open, multicentre, non-comparator pharmacokinetics and safety study of iv and oral isavuconazole in pediatric patients
- 60 children aged 1-18 years with haematological malignancies
- IV loading of isavuconazole with 1 dose q8h on days 1 and 2, followed by iv maintenance dose qd to max treatment of 28 days
- Aim: Safety, PK
- Started Oct 2017 - US centers

ClinicalTrials.gov. June 2018

Azole-resistant *Aspergillus*

No cases have been reported in Greece. However, there is no reason why not to see such cases.

Verweij et al. Clin Infect Dis. 2016; 62: 362–368

In conclusion …

- Standard diagnostic methods equally applicable in adults and children
- Imaging - CT scan: Useful tool; however, more non-specific markers than in adults
- Galactomannan: Can be used in children with caution
- Beta-D-glucan: Needs more research in children
- Molecular markers – PCR: Helpful in diagnosis of IA

In conclusion …

- Antifungal agents – not all appropriately studied, formulated for infants & children
- TDM is necessary during azole use in children

Thus,

- Diagnosis in young children is more challenging due to less helpful laboratory findings
- Early antifungal drug therapy with continuous drug monitoring absolutely necessary

ΔΙΟΡΓΑΝΩΣΗ

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