Histoplasmosis in children

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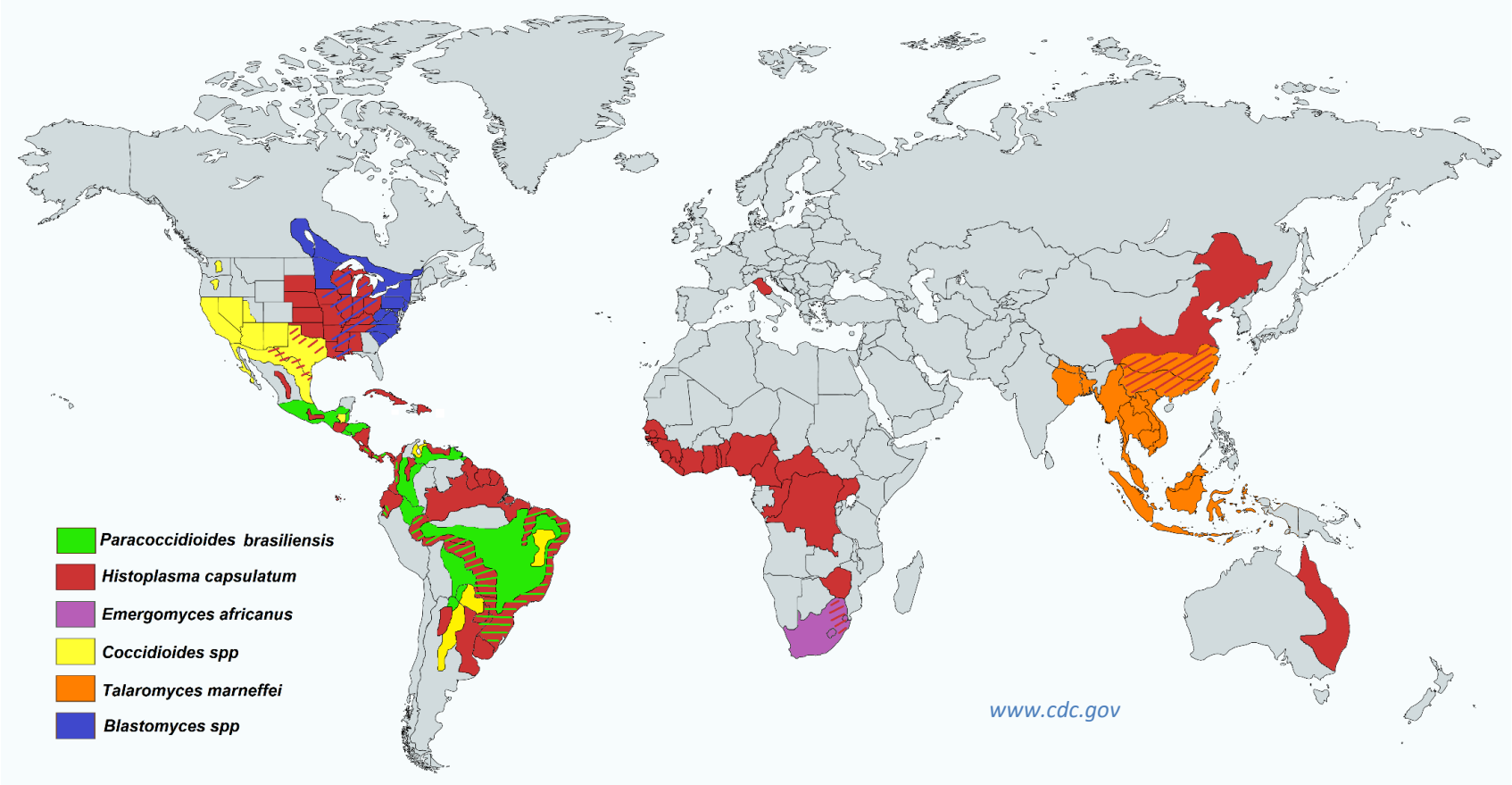
Histoplasma capsulatum
More widespread than previously thought

- Traditional histoplasmosis geographic areas
  Eastern United States (Ohio and Mississippi, and River valleys)
  Most of Latin America

- Histoplasmosis in India
  A histoplasmin skin-test positivity rate of 12.3% was reported in northern India between the 1950s and 1970s. *H. capsulatum* was isolated from the soil of the Gangetic plains
- Histoplasmosis in China
  Histoplasmin survey – 1006 healthy individuals or patients with lung diseases
  Prevalence: 6%-35%, according to the province
  Proved disease – From 300 histo cases, 75% were considered autochthonous
  Most (82%) from the Yangtze river valley
- Autochthonous cases from African countries, Thailand, Myanmar, Philippines, Australia and…

Antinori S, Am. J. Trop. Med. Hyg. 2014,

Global distribution of the Endemic Systemic Mycoses



Case Presentation

- 04 y/o girl presented with a 06 mo. history of an ulcerated lesion on the face
- She lived with her family in small farm. The mother referred contact with domestic animals: chicken, cows, pigs
- Initial clinical diagnosis = mucosal leishmaniasis
- Proved histoplasmosis was documented by histology and culture
- She was successfully treated with itraconazole
- Died at the age of 13 y/o from pneumonia related to Autosomal Dominant Hyper – IgE Syndrome (HIES)

Primary immunodeficiencies underlying Histoplasmosis

PID
Hyper-IgE Syndrome (HIES)
GATA2 deficiency (AD-MonoMAC)
STAT1 GOF (AD-CMC)
CD40L deficiency (XL-HIGM)
IL12Rβ1 deficiency (AR-MSMD)
IFNγR1 deficiency (AD/AR-MSMD)

{ (HIES) is a rare autosomal-dominant (AD) immune defect associated with lung, skin, and other infections, usually due to bacteria or selected fungi. Lung infections and hemoptysis are the major cause of mortality and morbidity.

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Empirically treated With D-Ampho B

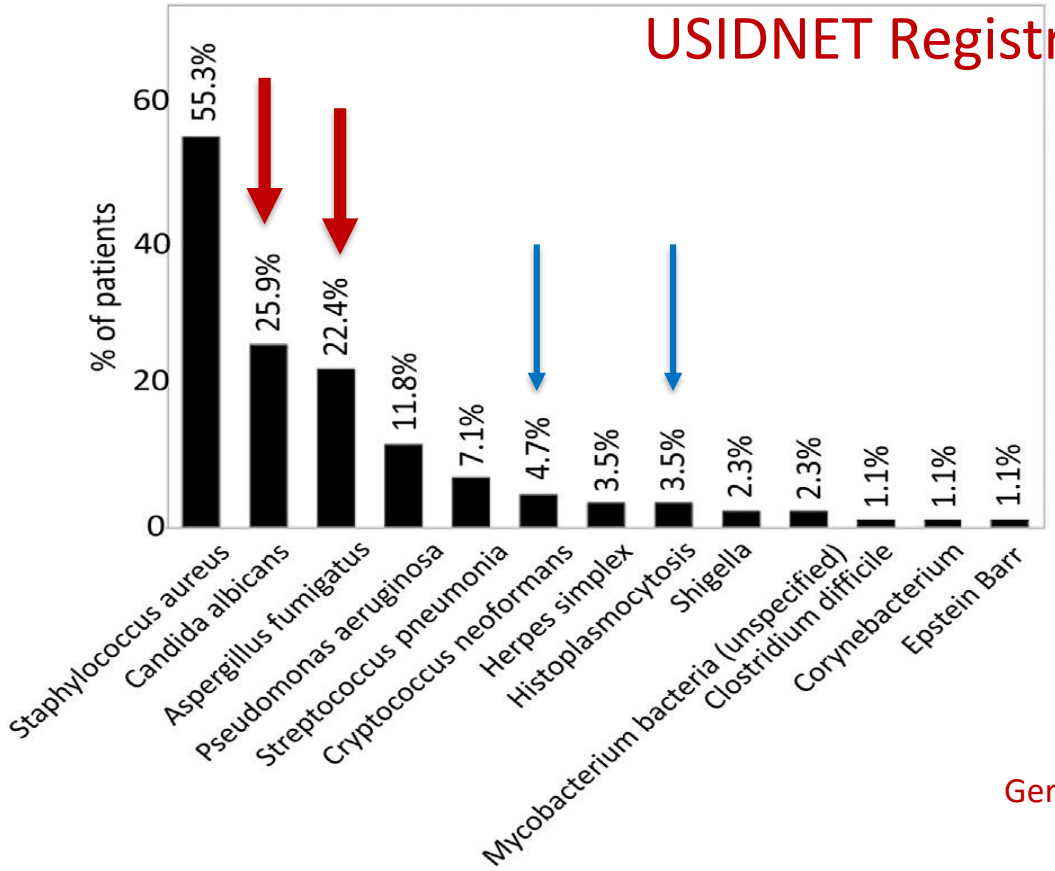
Staphylo or Histo Pneumatocele?

The patient died

Clinical and radiological aspects at 13 y/o

Corvilan et al. J Clin Imunnol, 2018

Infectious organisms associated to HIES
US Immune - Deficiency Network
USIDNET Registry



Data from 85 patients (0-18 y/o)
Collected between 2001 and 2016

Estimated burden of HIES
1:1,000,000

Gernez et al J Clin Alerg Clin Immunol Prat 2017

Clinical manifestations on children with histoplasmosis

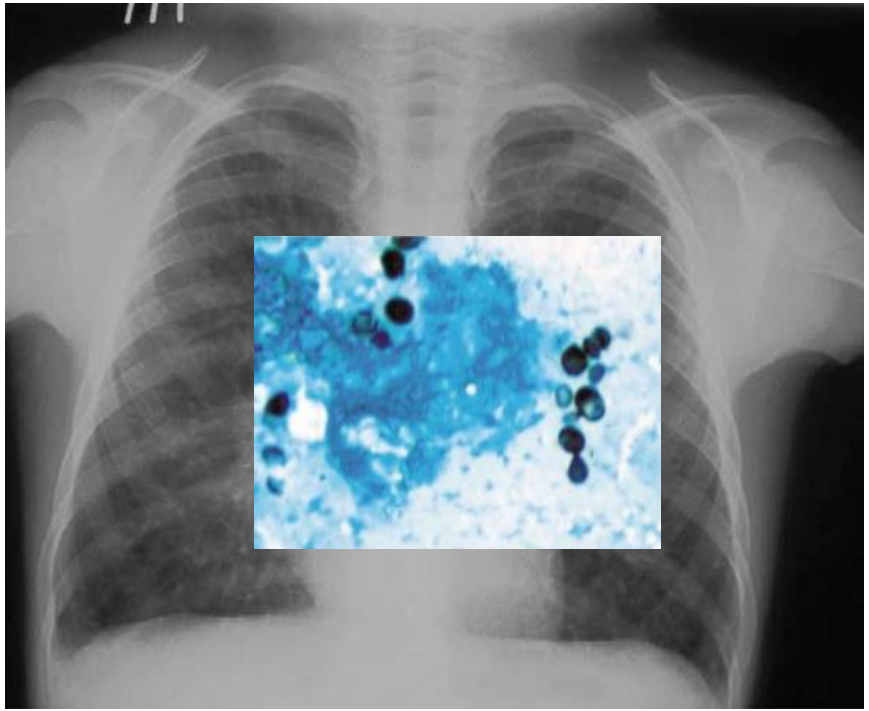
- Depend on the pathogen and host factors

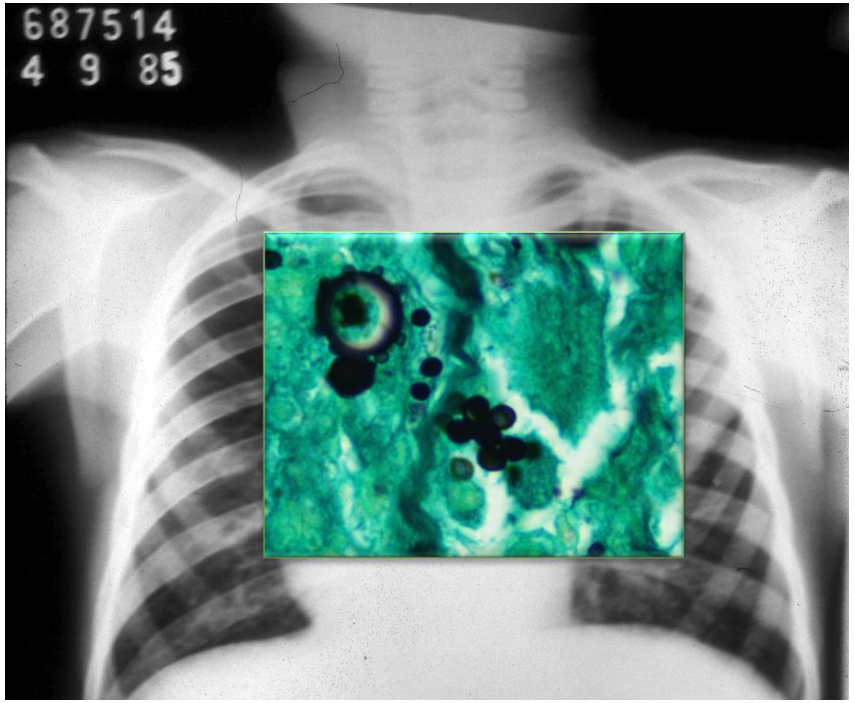
  The fungus – Inoculum size, strain virulence, etc
  The host – extremes of age (infants), malnutrition and immunocompromising conditions that may lead to severe disease
  AIDS, Malignancies, HSCT, SOT, Anti TNFs, Steroids, PID etc.

- Asymptomatic infection is the most type of infection

- Most of the published data on pediatric histoplasmosis are from outbreaks and case reports

Kids chest radiographies





Characteristic	Entire Cohort (n = 73)	Non-ICCs (n = 57)	ICCs[a] (n = 16)	P[b]
Age (median [IQR]) (years)	13 (10–16)	13 (9–16)	13.5 (10–18)	.4
Sex, male (n [%])	41 (56)	35 (61)	6 (38)	.15
Ethnicity (n [%])				
Non-Hispanic/non-Latino	61 (84)	46 (81)	15 (94)	
Hispanic/Latino	1 (1)	1 (2)	0 (0)	
Not reported	11 (15)	10 (17)	1 (6)	
Exposure history (n [%])				
Multiple	18 (25)	15 (26)	3 (19)	
Farm or barn	6 (8)	4 (7)	2 (13)	
Bird	3 (4)	2 (4)	1 (6)	
Soil or construction	3 (4)	2 (4)	1 (6)	
Bat or cave	2 (3)	1 (2)	1 (6)	
None or not reported	41 (56)	33 (57)	8 (50)	
Hospitalized (n [%])	45 (62)	32 (54)	13 (81)	.09
Duration of hospitalization (median [IQR]) (days)	5 (2–11)	3.5 (2–8)	11 (6–20)	.001

Retrospective chort study in USA

Estimated burde73 patients with
proved (n=13)
or probable (n = 56)
Histoplasmosis
Age 3-18 y/o (mean=13 y/o)
Immunocompromised – 16

Unifocal/pulmonary = 71%
Disseminate = 21%

Ouellette et al. JPIDS, 2018

Diagnostic Evaluation in 73 Children With Histoplasmosis

Testing	Entire Cohort N	Entire Cohort No. (%) of Positive Tests or Median (IQR) Value	Non-ICCs N	Non-ICCs No. (%) of Positive Tests or Median (IQR) Value	ICCs N	ICCs No. (%) of Positive Tests or Median (IQR) Value	P[a]
Culture							
Sputum	21	1 (5)	16	1 (6)	5	0 (0)	1
BAL fluid	8	1 (13)	4	0 (0)	4	1 (25)	1
Tissue[b]	20	0 (0)	13	0 (0)	7	0 (0)	1
Histopathology							
Tissue[b]	24	15 (63)	17	10 (59)	7	5 (71)	.7
BAL fluid	8	1 (13)	4	0 (0)	4	1 (25)	1
Bone marrow	1	1 (100)	0	0 (0)	1	1 (100)	1
Urine antigen	53	15 (28)	40	7 (18)	13	8 (62)	.004[c]
Concentration (ng/mL)		5.4 (3.8–6.5)		4.5 (0.6–5.4)		6.4 (4.3–10.7)	.03[c]
Pulmonary histoplasmosis	36	7 (19)	31	5 (16)	5	2 (40)	.2
Disseminated histoplasmosis	17	8 (47)	9	2 (22)	8	6 (75)	.057
Blood antigen	48	20 (42)	35	11 (31)	13	9 (69)	.02[c]
Concentration (ng/mL)		1.3 (0.5–7.4)		0.66 (0.5–1.5)		7.5 (1.3–15.7)	.02[c]
Pulmonary histoplasmosis	29	11 (38)	25	9 (36)	4	2 (50)	.6
Disseminated histoplasmosis	19	9 (47)	10	2 (20)	9	7 (78)	.02[c]
Antibody (complement fixation titer)	68	59 (87)	53	47 (87)	15	12 (80)	.4
≥1:32		50 (74)		40 (76)		10 (67)	.5
1:8–1:16		9 (13)		7 (13)		2 (13)	1
<1:8		9 (13)		6 (11)		3 (20)	.4
Pulmonary histoplasmosis	48	43 (90)	41	38 (93)	7	5 (71)	.14
Disseminated histoplasmosis	20	16 (80)	12	9 (75)	8	7 (88)	.6
Antibody (immunodiffusion)[d]	68	48 (71)	53	40 (75)	15	8 (53)	.12
Pulmonary histoplasmosis	48	34 (71)	41	32 (78)	7	2 (29)	.02[c]
Disseminated histoplasmosis	20	14 (70)	12	8 (75)	8	6 (75)	1

Ouellette et al. JPIDS, 2018

Clinical Characteristics of 73 Children with Proven or Probable HISTO

Disease severity (n [%])	Entire Cohort (n = 73)	Non-ICCs (n = 57)	ICCs[a] (n = 16)	P[b]
Severe	15 (21)	11 (19)	4 (25)	
Moderate	33 (45)	24 (42)	9 (56)	
Mild	25 (34)	22 (39)	3 (19)	
Clinical syndromes (n [%])				
Pulmonary	52 (71)	45 (79)	7 (44)	.01[c]
Proven	9 (12)	7 (12)	2 (13)	
Probable	43 (59)	38 (67)	5 (31)	
Disseminated	21 (29)	12 (21)	9 (56)	.01[c]
Proven	8 (11)	4 (7)	4 (25)	
Probable	13 (18)	8 (14)	5 (31)	
Signs and symptoms (n [%])[d]				
Cough	43 (59)	34 (60)	9 (56)	1
Fever	35 (48)	25 (47)	10 (63)	.3
Fatigue	26 (36)	20 (35)	6 (38)	1
Shortness of breath	25 (34)	18 (32)	7 (44)	.4
Chest pain	20 (27)	18 (32)	2 (13)	.2
Weight loss	18 (25)	13 (23)	5 (32)	.5
Lymphadenopathy	11 (15)	9 (16)	2 (13)	1
Rash[e]	4 (5)	3 (5)	1 (6)	1
Rales	3 (4)	3 (5)	0 (0)	1
Splenomegaly	3 (4)	1 (2)	2 (13)	.12
Hepatomegaly	2 (3)	1 (2)	1 (6)	.4
Hepatosplenomegaly	1 (1)	1 (2)	0 (0)	1

Immunocompromised kids
09 under anti TNFs
05 – with malignancies 5 patients with
No AIDS patients

Forty-nine (67%) patients received antifungal therapy for HISTO

Itraconazole
L-ampho B

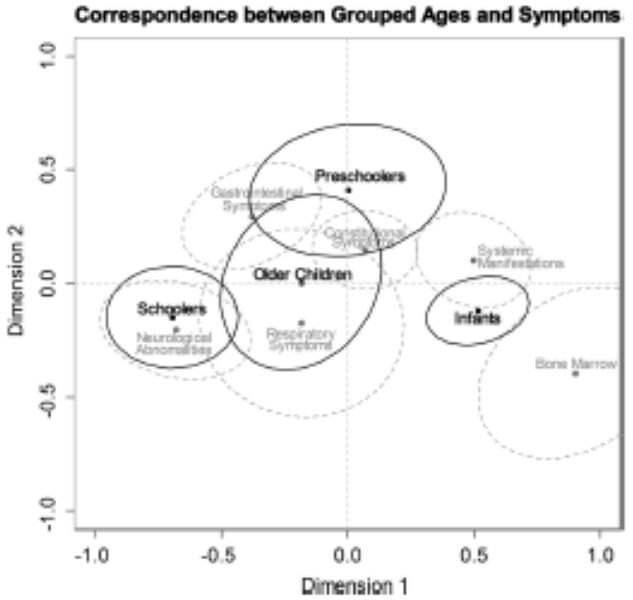
Ouellette et al. JPIDS, 2018

Medical Mycology, 2016, 54, 677–683
doi: 10.1093/mmy/myw020
Advance Access Publication Date: 26 April 2016
Original Article

Original Article

Childhood histoplasmosis in Colom and laboratory observations of 45 p

Luisa F. López[1,†], Yorlady Valencia[1,†], Ángela M. Tobón Oscar Velásquez[3], Cristian D. Santa[4], Diego H. Cácere Ángela Restrepo[1] and Luz E. Cano[1,5,*]



Correlations among clinical syndromes and age

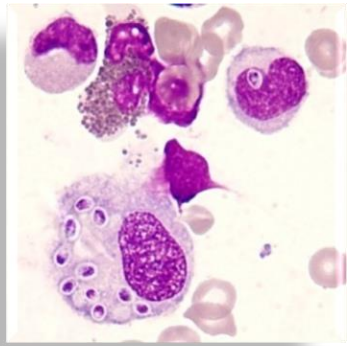
Lopez et al, Med Mycol, 2016

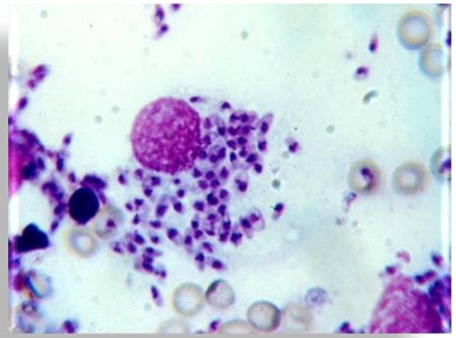
10 Síndromes clínicas que confundem se com Histoplasmose sis

- Infeções pulmonares agudas ou crônicas
- Síndrome febril consuptiva
- Hepatoesplenomegalia febril
- Febre de origem desconhecida em AIDS ou receptors de TOS
- Febre prolongada em usuarios de corticoesteróides ou imunobiológicos
- Meningite crônica
- Doença de Addison
- Úlceras orais crônicas
- Endocardite crônica
- Celulite e outras lesões cutâneas em imunodeprimidos
- Diarréia crônica e sangramento intestinal

Kauffman CA Clin Chest Med 30: 217–225, 2009; Agudelo CA et al Am J Trop Med Hyg 87(6):1094-8, 2012
Ozdalga E et al J Gen Intern Med 27(9):1219, 2012; Yang et al. BMC Infectious Diseases 2013, 13:143
Severo et al Rev Inst Med trop S Paulo set-out 1997; Assi MA et al Medicine 86(3): 162-169, 2007

Microbiologic Differential diagnosis of Histoplasmosis





As leveduras de *H. capsulatum* são pequenas e intracelulares. Podem ser confundidas com varios agentes intracelulares: Toxoplasma, Trypanosoma, Pneumocystis, Candida, Leishmania, etc

Conclusions

Histoplasma capsulatum may affect children in the Americas

Mostly of the infected pediatric patients are asymptomatic

Disseminated histoplasmosis can be associated to several underlaying conditions, including HIV

Most of the histoplasmosis pediatric data are extrapolated from adult patients

Therapy of pediatric patients is also extrapolated from adults

But we know that children are not small adults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