VIRAL HEPATITIS PREVENTION BOARD MEETING

HEPATITIS C IN CHILDREN

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On Behalf of the Gastroenterology Section of the Portuguese Society of Pediatrics

Lisbon, 18th-19th November 2010

Hepatitis C in children - Epidemiology

- Chronic Hepatitis C in children: “A rare disease ?”

True prevalence unknown

- Seroprevalence* (global/ pediatric): **USA: 1.8%**
  0.2% < 12 ys
  0.4% 12-19 ys

Portugal: 1.5%*
children ?? (0.1%....)

- natural history unknown
- pathogenesis insufficiently understood
- infraclinic expression....

** seroprevalence: Alter MJ et al N Eng J Med 1999*
*** www.apef.com, Marinho R et al, J Gastrenterol Hepatol 2001*

Hepatitis C in children - natural history

Multicenter study (retrospective/ prospective data)*
1990-2005 (15 ys)

Italy National Observatory: Childhood Hepatitis C Infection

N= 504 assymptomatic children
no associated disease

Perinatal transmission:	**56.2%**
Parenteral transmission:	31.3%
Undetermined transmission:	12.5 %

1992 (blood screening)
> 90% cases : Vertical transmission, no-comorbilities

**Bortolotti F. Gastroenterology 2008, Vergani M, Arch Dis Child 2005*

Hepatitis C Virus genotypic profile in children

Multicenter retrospective study, Italy (1990-2002) n= 373 children ARN VHC +

No HIV or VHB co-infection, no co-morbilities

Genotype	**1a**	**1b**	**2**	**3**	**4**	**others**
	20%	**41%**	17%	14.5%	5%	2.5%
Age dd(m)	64	**81**	92	34	23	-
Birth <1990	18%	**49%**	21%	5%	3.5%	3.5%
Birth > 1990	21%	**33%**	13%	23.5%	7%	2%

Genotypes 1b , 3 e 4 : transfusions / IV maternal drug abuse

Genotypo 2: percutaneous exposure

quasispecies diversity - age increase

Bortolotti F, Gut 2005

Gerotto M, Infection,2006

Hepatitis C in children - Epidemiology

- Pregnancy seroprevalence (USA, Europe)*: **1-2%**
  UK: 0.1-0.8%
  Portugal: ???

- **Rate of Perinatal Transmission**: 4-10%**

  0 - 1% if no maternal viremia

  5 % if intrapartum (+) RNA
  - high viral load, chronic liver disease

  7.5% - 40% if HIV co-infection (<< risk if HAART)

**American Academy of Pediatrics, Pediatrics 1998*

***Azzari C, Int J ImmunoPat. Pharmacol 2007, Indolfi G, J Med Virol 2009 Mast E,J Infect Dis 2005, England K, Lancet INfect Dis 2006*

Hepatitis C at pediatric age
Epidemiology in Portugal

PERINATAL TRANSMISSION OF HEPATITIS C VIRUS

S. BACALHAU et al, Acta Med Port. 2010; 23(3):391-398

Santo André Hospital, Leiria 2002-2006 (follow-up protocol > 2002)

- **Aims:** To characterize the population of children born to HCV(+)mothers,
  - identify risk factors for perinatal HCV transmission
  - to improve the approach to HCV screening

- **Methods**:
  - retrospective study enrolling children born to HCV(+) mothers
    > Jan 2002 - Dec 2006
  - transversal analysis to repeat anti-HCV in cases that didn't meet current recommendations for HCV screening and in those without any HCV screening.

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PERINATAL TRANSMISSION OF HEPATITIS C VIRUS

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Santo André Hospital, Leiria 2002-2006

- **Results**:

  total 12985 births / 5 years

  59 children born to HCV(+) mothers ≈ medium prevalence rate: **0,45%.**

  Perinatal HCV transmission rate was 2,9%.

  high rate of **inadequate pregnancy surveillance, prematurity and low birth weight**, mainly in children born to **addicted mothers (54% drug abuse; 20% co-infection) (VS control)**

  1 child with HCV infection without any risk factor for perinatal transmission

  50% children anti-HCV(+) at age 9 months, became (-) at 18months

Hepatitis C in children - Epidemiology

- **When does mother to child transmission of hepatitis C virus occur?**

- *Mok J et al, European Paediatric Hepatitis C Virus Network, Arch Dis Fetal NEonatal Ed 2005Rate of Perinatal Transmission**: 4-7%*
- *Prospective cohort study*

- *54 mother/children pairs tested < 3rd day life*

- *Intrauterine (child ARN + < 3 th day)* ***30%***

- *Peripartum (lateintrauterine/ intrapartum): 50%*
  child ARN + > 3th day and at 4 wks

- ***Postnatally?... Low… (breastfeeding??)***

Influence of genotype??.....

Hepatitis C in children - Epidemiology

- **No preventive strategy for mother-child transmission**

Transmission risk is proportional to viral maternal load (last trimester)

No association: type of delivery, IV drug abuse (HIV -)

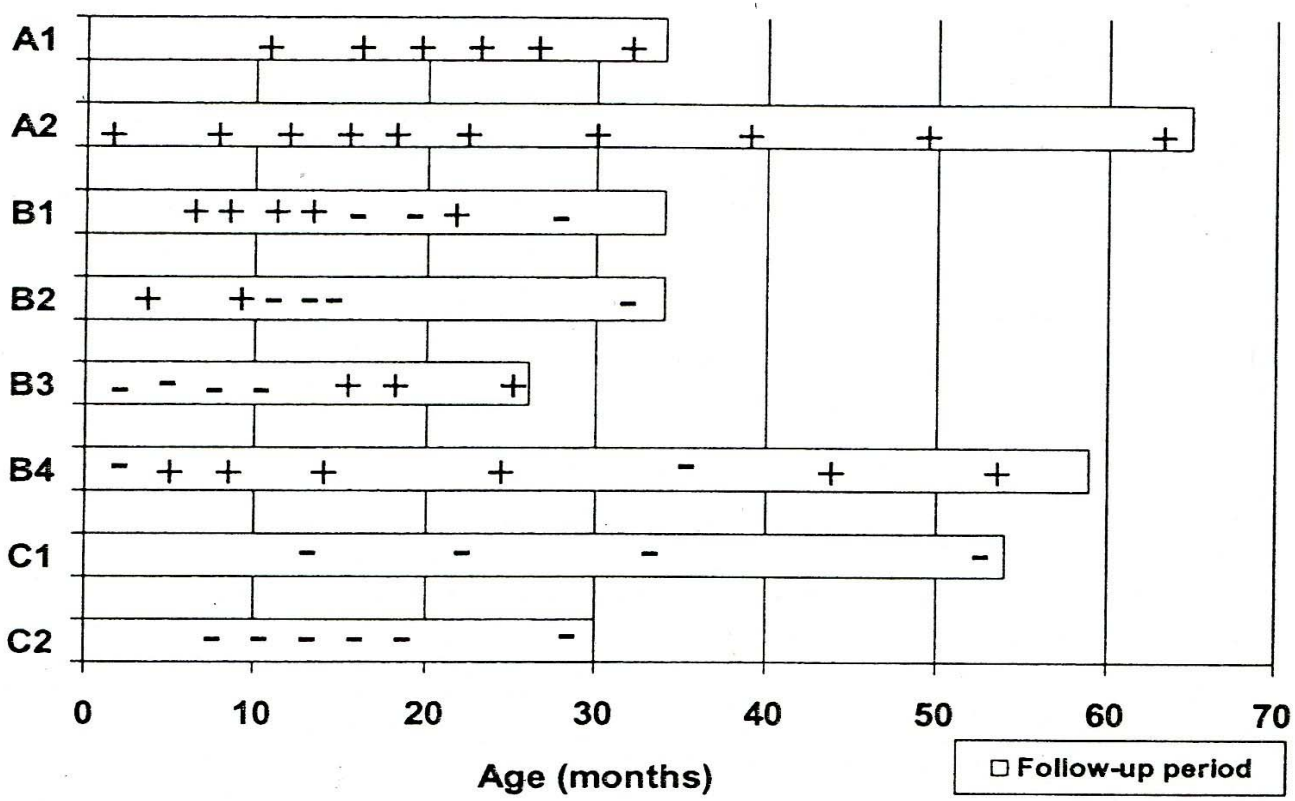
Breast feeding transmission assumed as rare (HIV -)

**American Academy of Pediatrics, Pediatrics 1998*

***Azzari C, Int J ImmunoPat. Pharmacol 2007, Indolfi G, J Med Virol 2009 Mast E,J Infect Dis 2005, England K, Lancet INfect Dis 2006*

Hepatitis C in children - natural history

Children from anti-HCV (+) mothers



Tovo P, European Paediatric Hapatitis C Network. J Infect Dis 2000

Hepatitis C in children - natural history

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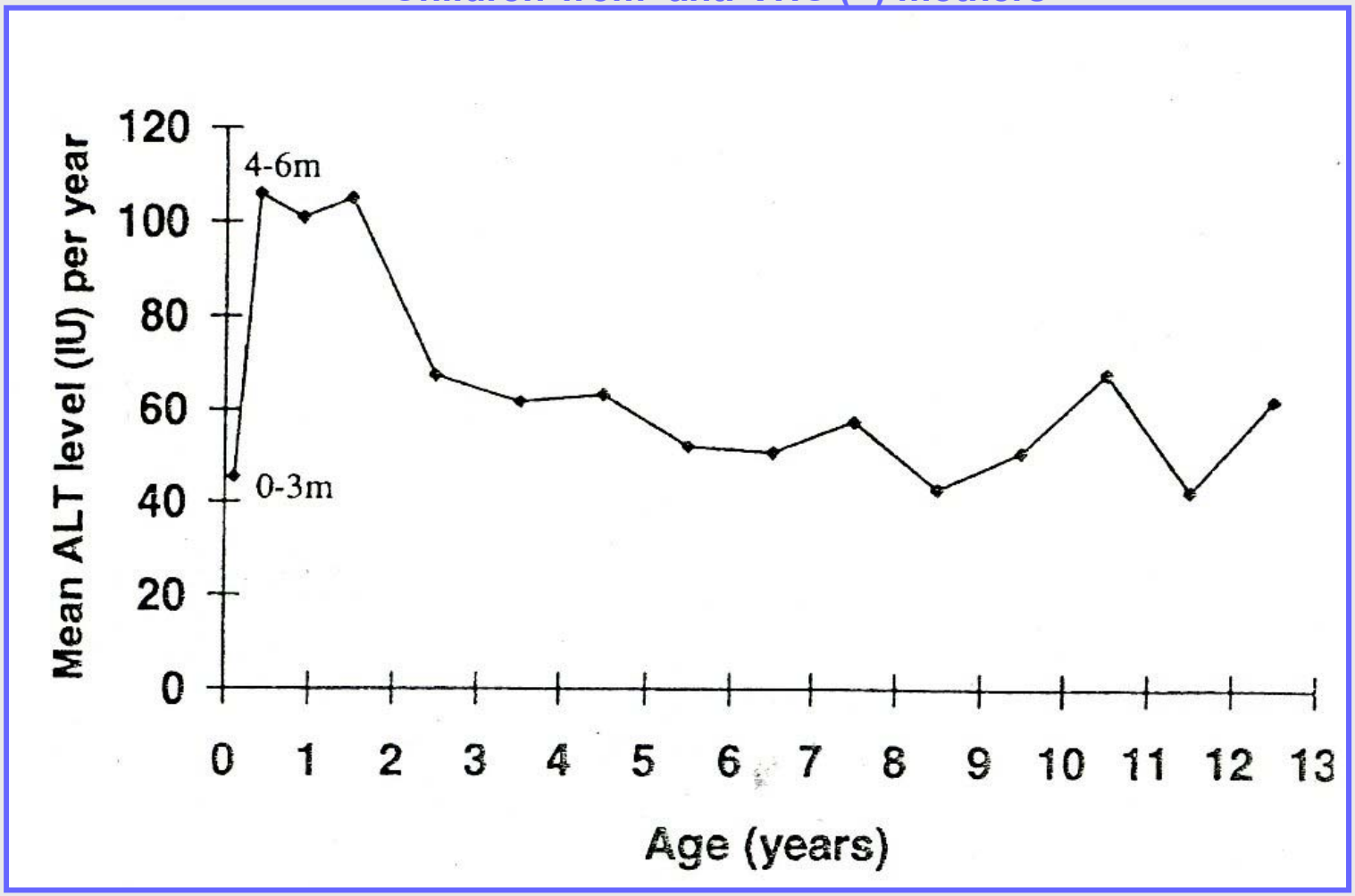


Tovo P, European Paediatric Hapatitis C Network. J Infect Dis 2000

Hepatitis C in children - Epidemiology

Vertical Transmission - Diagnosis

- **Age 2 months**: **RNA (+)** on 2 occasions > 3 months apart

and /or

- **Anti-HCV antibodies(+) > age 18 months**

Hepatitis C in children - Epidemiology

Mother-child transmission

Current Recommendations for screening (anti-HCV)*

- **Pregnancy**

1. No formal recommendation for systematic screening
   (not available effective intervention; ribavirine TT contra-indication)

2. Recommended (high risk settings):

   - present/ past history of drug abuse
   - transfusions/ transplant/ hemodialysis
   - sexual risk behavior
   - HIV infection
   - persistently high AST /ALT

* www.apef.com, Zein NN, J Pediatr 1997, Hay JE, Viral Hep Ver 2000, CDC, MMWR 1991

Hepatitis C in children - Epidemiology

Mother-child transmission
Current Recommendations for screening (anti-HCV)*

- **Infant Screening**
  if mother anti-HCV (+):

  - 1st screening: > 18 months; ELISA > Western BLOT
  - late seroconversions 18-24 months;
  - high false positivity rate before 18 months, no false negative rate

  anti-HCV (+) → confirmation by RNA (PCR) 2x
  (6 months apart, fluctuation of viremia)

  anti-HCV (-): not infected

  - breast feeding recommended, excep if HIV- co-infection (contraindication)

* **www.apef.com,** Zein NN, J Pediatr 1997, Hay JE, Viral Hep Ver 2000, CDC, MMWR 1991

Hepatitis C in children – natural course

RNA HCV (+): 94.6% (477/ 504)

24.7% (118/477): INF-α standard: **27.9% SVR**

75.3 % (359/477) no TT

Indetectable viremia: 7.5% (27)

Persistent **Viremia: 92.0%** (332)

Decompensated cirrhosis: 1.8% (6)

Spontaneous eradication : rare

Terminal Liver disease : in a small subset

perinatal exposure (age related-risk),

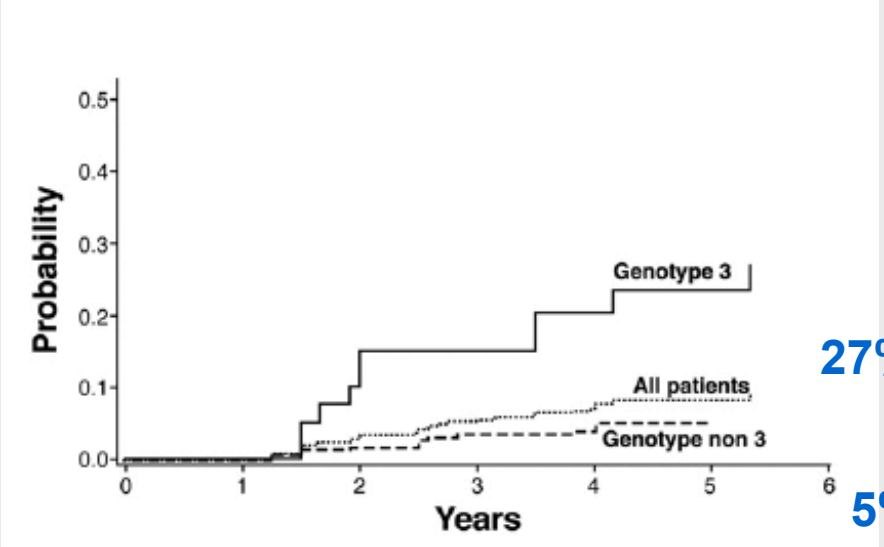
maternal drug abuse

genotype 1a

Bortolotti F. Gastroenterology 2008

Natural history VHC – vertical transmission

Influence of genotype



27%

5%

Bortolotti F et al
Gastroenterology 2008

Possible eradication within the first 3-5 ys / rare < 3 years

Hepatitis C - Treatment at pediatric age

IN FAVOUR

Slight disease / initial stage
comorbility rare

Familial compliance
No social stigmata
< neurocognitive sequela
< direct / indirect costs

AGAINST

assymptomatic disease
slow rate of progression
few cases with advanced disease

suboptimal tretament
treatment cost
adverse effects
new drugs on pipeline ….

Hepatite C crónica na criança - histologia hepática

Bortolotti F et al
Gastroenterology 2008

1990-2005
12 centros Italia
Sem outra patologia

CIRROSE VHC Descompensada
6 / 332= 1.8%
idade: 2 a 15 anos
TH: n=2

McDiarmid SA et al
SPLIT registry
Pediatr Transplant 2004

Cirrose VHC : 0.8 %
8/ 1092 TH en EEUU 1995-2002

Jara P
Hl La Paz
Madrid

Cirrose VHC: 0.2 %
1/ 491 TH 1986-2008

Hepatitis C in children - Treatment
IFN alpha 2b + ribavirine

1998-2001
29 centers Europe, Israel, Canada

Farmacocinetics: RBV + IFN alpha

IFN α-2b: 3 MU/m^2 (3x/week) > Exposure child vs adult

RBV: optimal dosage -15 mg/kg (vs 8 -12 mg/kg)

Gonzalez-Peralta et al
International Pediatric Hepatitis C Group
Hepatology 2005

Hepatitis C treatment in children

Alpha Interferon:SVR 36% (50% G2/3 vs 10% G1) (*4 studies*)

Peg-interferon alpha 2a: **SVR 38%** (G1) (*1 study*)

Interferon alpha + ribavirine: SVR 46% (*1 multicenter study*)

Pharmacocinetics ; FDA approval (2003)

Peginterferon a2b + ribavirine: SVR 55% (2 pylot studies)

International study; ***FDA approval (2008)***

PEDS-C: PEGIFN a2b vs PEGIFN + Ribavirine *(1 study)*

Internacional randomized, placebo controlled study (ongoing)

Antiviral (telaprevir/boceprevir)+Peg+Ribavirine (not evaluated)

PegIFN + RBV at pediatric age
2 pilot studies

Jara P et al
Pediatr Infect Dis J 2008

30 children
pegIFN alpha2b 1 µg/kg/week
+ RBV 15 mg/kg/d

Wirth S et al
Hepatology 2005

61 children
pegIFN alpha2b 1.5 µg/kg/week
+ RBV 15 mg/kg/d

Results

SVR	*Genotype 1*	*Genotype 2/3*
Spain	*46.6%*	*100%*
Germany	*47.8%*	*100%*

Chronic hepatitis C at pediatric age
Current treatment consensus

- **Start treatment: > 3 ys / before adolescence**
- Exclusion of co-morbilities / other etiologies
- Liver biopsy not required (…)

- **PEG-IFN(1-1.5 ug/Kg/ week) + Ribavirine (1.5 mg/Kg/d)**
- **Aim: SVR (viremia negativation at 24th week post-TT)**
- **Duration:**
  - **genotype 2/3: 6 months**
  - **genotype 1 / others: 12 months**
- **Stop: no ARN VHC decrease at 12th week post-TT**

- Monitoring (growth.) , biochemical, viral load
- **Pre TT pregnancy test**
- hepatitis B and hepatitis A immunization

Hepatitis C at pediatric age
Epidemiology in Portugal

CHRONIC HCV INFECTION AT TERTIARY CENTERS

Pediatric Gastrenterology Units / Pediatric Departments (NHS)

Retrospectively collected data (> 1993 – 2008): 16 years period

Exclusion criteria:

- period before universal donor screening (<1992)
- current age: < 2 ys, ≥ 16 ys

Number of patients (no gender predominance):

HS. João, Porto	: 9 cases
H. Maria Pia, Porto	: 8 cases
H. S. Marcos, Braga	: 2 cases
H. Pediátrico Coimbra	: 2 cases
H. Garcia Orta, Almada	: 4 cases
HD. Estefânia, Lisboa	: 6 cases
H. Santa Maria, Lisboa	:17 cases

TOTAL : 48 cases

Hepatitis C at pediatric age
Epidemiology in Portugal

CHRONIC HCV INFECTION AT TERTIARY CENTERS

Pediatric Gastrenterology Units / Pediatric Departments (NHS)

Retrospectively collected data (> 1993 – 2008):16 years

TOTAL: **48 cases**

"Cumulative prevalence": 2.7 cases/ year

Underestimation……

Hepatitis C at pediatric age
Epidemiology in Portugal

CHRONIC HCV INFECTION AT TERTIARY CENTERS

Pediatric Gastrenterology Units / Pediatric Departments (NHS)

Number "newborns" 2008: 10.4/ 1000 inhabitants
104.000 / 10 million inhabitants

If estimated pregnancy seroprevalence 0.2%: 200 anti VHC (+) / 100.000 pregnancies

If estimated vertical transmission 2% : 4 anti-VHC(+) children/ 200 infected mothers

" Expected number children anti-VHC (+) / 2008: 4 cases" (underestimation?...)

Hepatitis C at pediatric age
Epidemiology in Portugal

CHRONIC HCV INFECTION AT TERTIARY CENTERS

route of infection:

- vertical: 47/48 cases
- sexual : 1 case
- 2 siblings

Ethnic background: Caucasian
- 39/40: Portugal
- 1/40 Ucrania

Mean age: 9.2 ys (range 2-17 ys)

no gender predominance

HIV-HCV co-infection: 2 cases Mother HIV-VHC: 6 cases

Parental IV drug abuse: 16/ 40 (not reported: 32 cases)

Other comorbilities: none

Hepatitis C at pediatric age
Epidemiology in Portugal

CHRONIC HCV INFECTION AT TERTIARY CENTERS

Genotypes:

ND: 25

1 : 70% reported cases

1a: 10

1b: 6

3 a: 3

4: 4 (4 cd: 3 4 ab: 1)

Spontaneous negativation: 4/ 48 cases **(10%)**
(at ages 5, 6, 7,7 ys)

Treatment

12 / 48 cases (6 under TT)

Outcome

Viremia Negativation > 24th TTw (SVR): 4/12 (30%)

Decrease viral load : 8/12

Hepatitis C at pediatric age
Conclusions

- **Predominance of vertical transmission**
- **Spontaneous eradication is rare but possible**
- **Treatment efficacy (IFN + Ribavirine) ~ adult**
- **Influence of genotype in natural course and treatment response**
- **No vacination! Disease control depends on**:
  - control of transmission routes
  - treatment of infected patients

Chronic hepatitis C at pediatric age: persisting questions….

- Ideal treatment timing? Individual basis....
- Indications for pre.tt liver biopsy?
- Optimal treatment schema ? Is ribavirine necessary ?
- Predictive factors of response to treatment?
- Duration of ARN VHC indetectable after treatment negativation? (longterm outcome impact of treatment)
- Special cases (co-infection HCV/HIV, HCV/HBV,liver transplant)….
- New drugs/ new treatment regimens …..early treatment in pregnancy??

Chronic hepatitis C at pediatric age: a change in natural course ?..... or a disease in extinction?.....

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