NEONATAL VIRAL HEPATITIS

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DEFINITION

- Liver cell necrosis ± cholestasis
- Onset during first month of life
  - Viral most common
  - Metabolic
  - Toxic
  - (endocrine)
- Mild severity to fulminant hepatitis
- Transplacental or horizontal route of transmission

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NEONATAL VIRAL HEPATITIS
Clinical features

- Generalized or liver specific ?
  - Encephalopathy or encephalitis ?
  - Pneumonia ?
  - MOF ?
- Jaundice – cholestasis or hepatitis only ?
- Liver failure ?
- Muscle disease excluded ?
- Metabolic excluded ?
- Fever ?
- Maternal flu like illness ?
  - Pre-natal ? Which trimester ?
  - Peri-natal ?

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NEONATAL VIRAL HEPATITIS

- **Hepatotropic viruses:**
  - **HAV, HBV, HCV (?)**
- **Transplacental infections:**
  - **Toxo**
  - **Rubella**
  - **CMV**
  - **Herpes**
  - **Syphilis**
  - **HIV**
- **Opportunistic: adeno, entero (cocsackie, echo), PB19, HSV VI (?)**
- **HLH: hemophagocytic lympho histiocytosis**

HEPATITIS A VIRUS

Age (Years)	11551 Cases (%)	Case-Fatality Rate (Per 1000)
0 - 5	5.3	1.50
5 - 14	19.6	0.04
15 - 29	43.0	0.57
30 - 49	23.3	2.50
Over 49	8.8	27.0

HEPATITIS B VIRUS

- **Not neonatal – around 8 -12 weeks**
- **Mild to no hepatitis in children from HBeAG + mothers**
- **Severe to fulminant hepatitis in children from HBsAG +, HBeAg – mothers**
  - **Pre core mutant ?**
  - **Unmasking of viral Ag when maternal Ab drop ?**
- **Role of nucleoside analogue in situations at risk ?**

HEPATITIS B VIRUS

- Fulminant infant hepatitis B in Taiwan
- 1975-1984 period 5.36 per 100,000 infants.
- 1985 -1998 period 1.71 per 100,000 infants.
- Ratio of average mortality : 0.32 ($p<0.001$)
- ➔Benefit of mass vaccination

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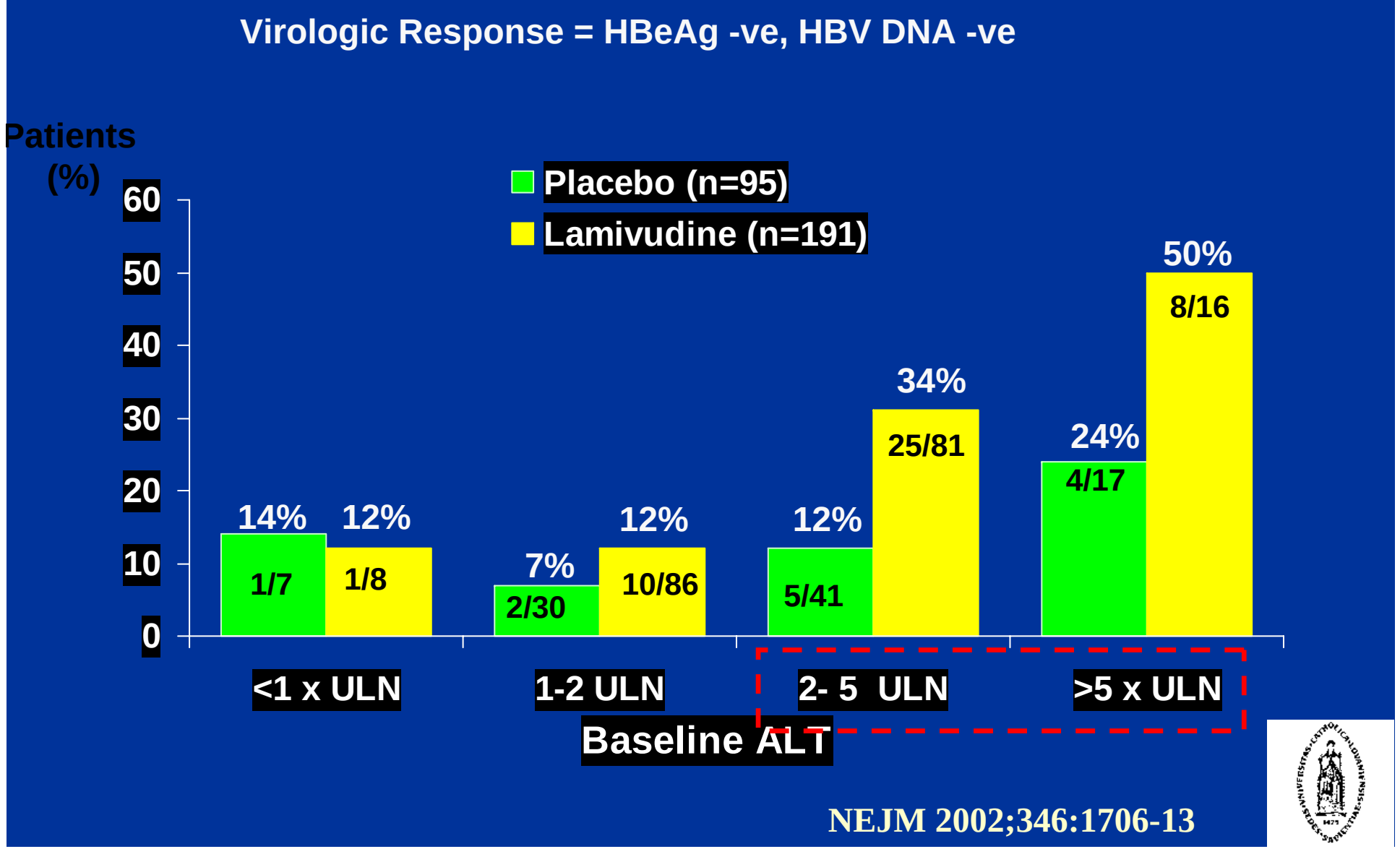
Kao Khao JH J Pediatr 2001; 139(3):349-352.

Virologic Response by Baseline ALT



NEJM 2002;346:1706-13

Cumulative Virologic Response
Pediatric Lamivudine Trial - 3 Y FU

	Lamivudine (24 mos.)[1]	Lamivudine (36 mos.)[2]
CVR	**30% (23/77)**	**21% (28/133)**
HBsAg loss	**1% (1/76)**	**2% (3/125)**
YMDD	**49%**	**64%**

CVR: HBeAg neg & HBV DNA neg

NEJM 2002;346:1706; Expert Opin Pharm 2002; 3:329
Hepatology 2006, in press

Non alphabetical: HSV1, Entero, Adeno

- Specific maternal disease, end of pregnancy
  - HSV1: stomatitis, …
  - Adenovirus: conjunctivitis, rhinitis,..
  - Enterovirus (cocksackie, Echo): diarrhea, rash,…
- Extensive liver cell necrosis, panlobular
- Variable severity up to fulminant hepatitis
- Transplacental (= severe) or horizontal (= mild to moderate) route of transmission

Non alphabetical: Adenovirus

- High fever
- Elevated AST>ALT, LDH+++,
- Neutropenia (prognostic ...)
- Rapid diagnosis direct fluorescent assay or blood PCR
- Viral cultures
- Histology: foci of confluent necrosis Immunostaining
- R/ cidofovir, broad spectrum anti-DNA viral agent, 1mg/kg three times per week. Recovery of fulminant hepatitis before transplantation in an immuno-competent child*

*Rocholl; Pediatrics 2004

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Non alphabetical: HSV1, Entero, Adeno ?

- Full term, uncomplicated pregnancy
- Neonatal period unremarkable
- D8: fever 37.8°, unwell, poor feeding
- D11: impaired general condition, fever 39°, stupor, encephalopathy.
  - AST 3000, ALT 2900, LDH 7500
  - INR 3 → 7
  - NH4: 125
- MOF, Generalized bleeding, death

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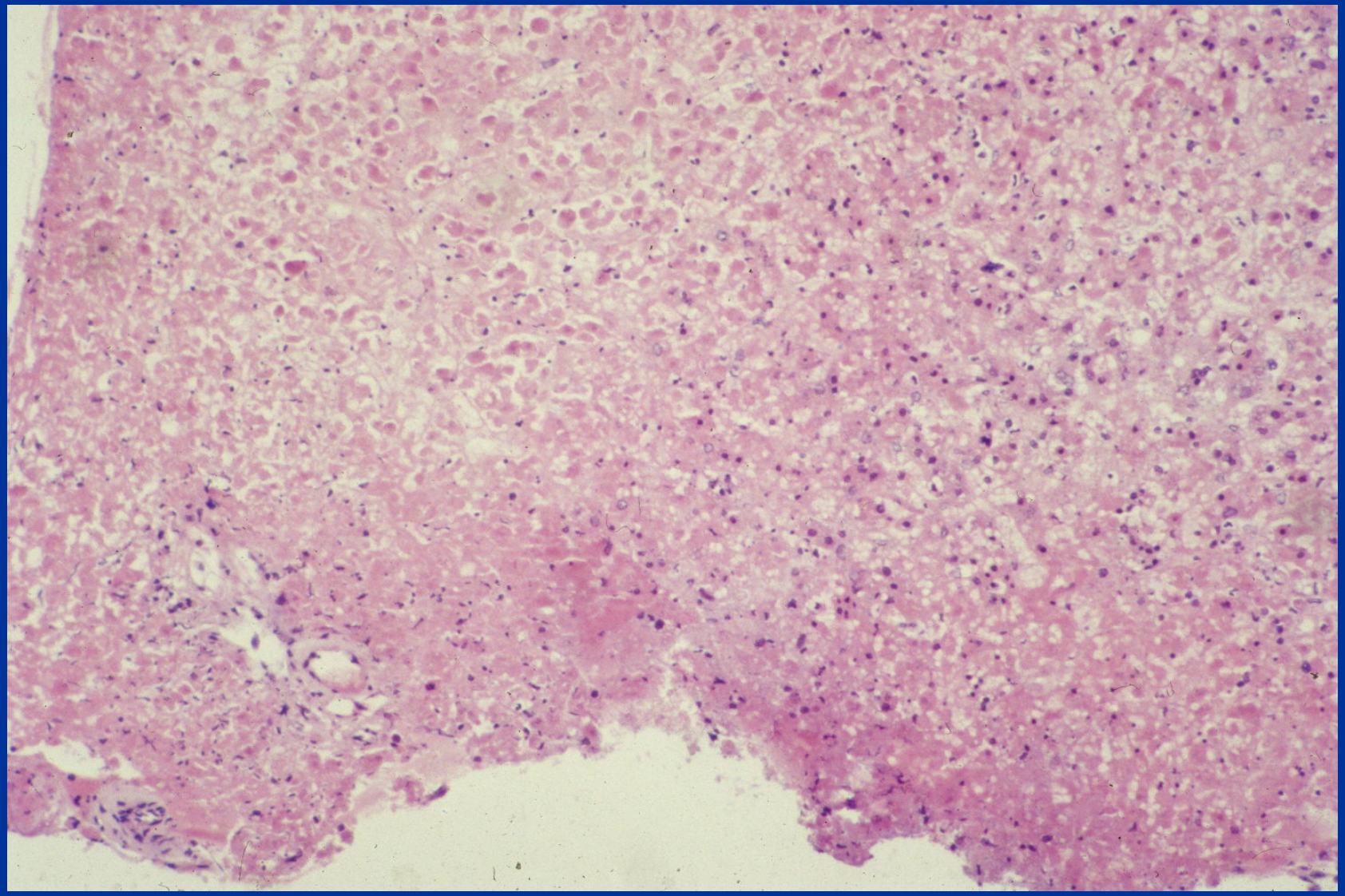
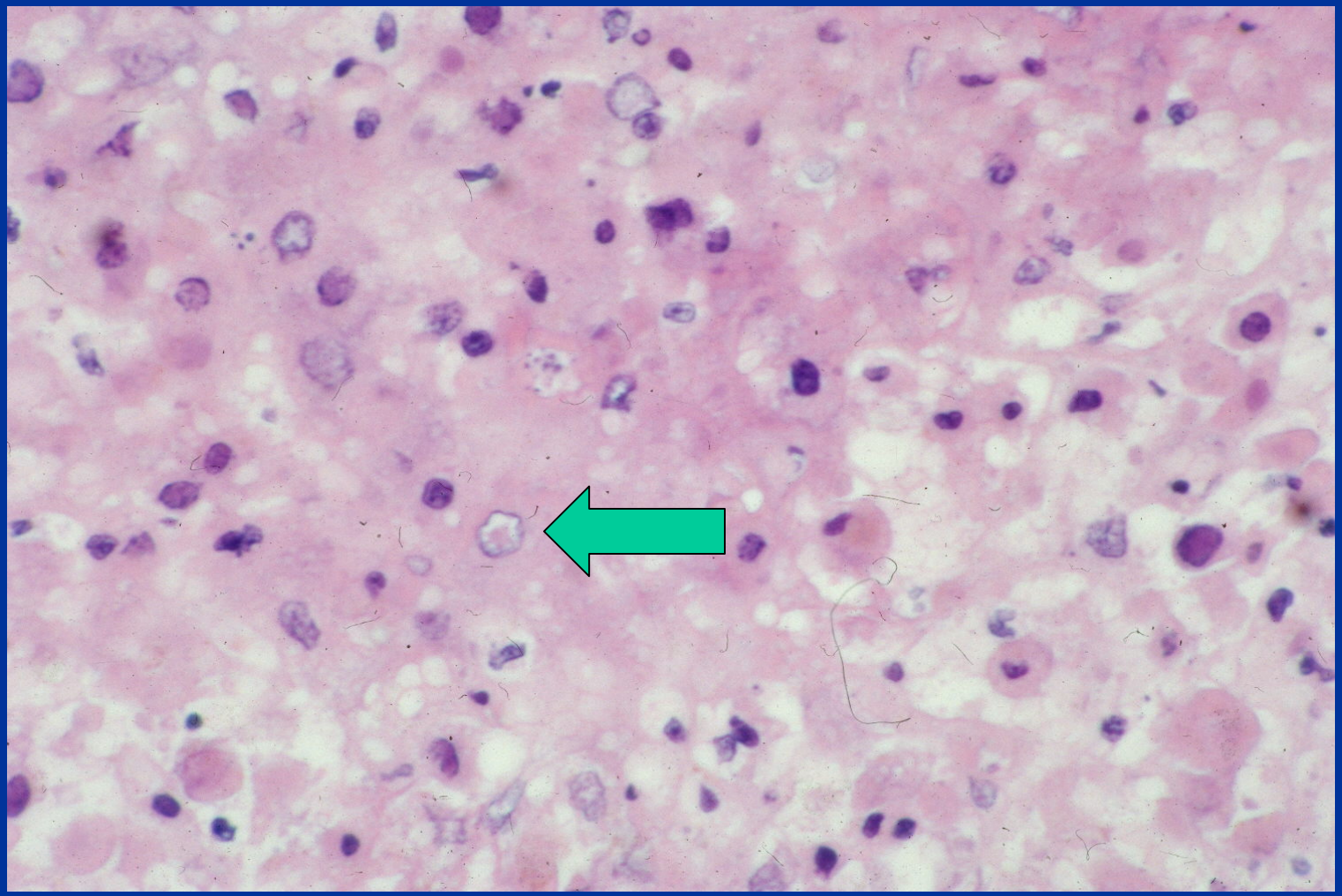
HSV I F H



Extensive panlobular necrosis

HSV I F H



Ground glass nuclear inclusions

HSVI HEPATITIS

D/
Direct immunofluorescent assay
Culture
Blood PCR
Immunostaining
R/ Acyclovir, valacyclovir

ENTEROVIRUS HEPATITIS

Meningoencephalitis, Thrombocytopenia, cardiomyopathy

Mimicking bacterial sepsis

Agent:

Cocsackie serotype B and echovirus 11

D/

Culture

PCR: stool, urine, CSF, throat swab…

R/anti-picornaviral drug pleconaril 5 mg/kg 3 times daily

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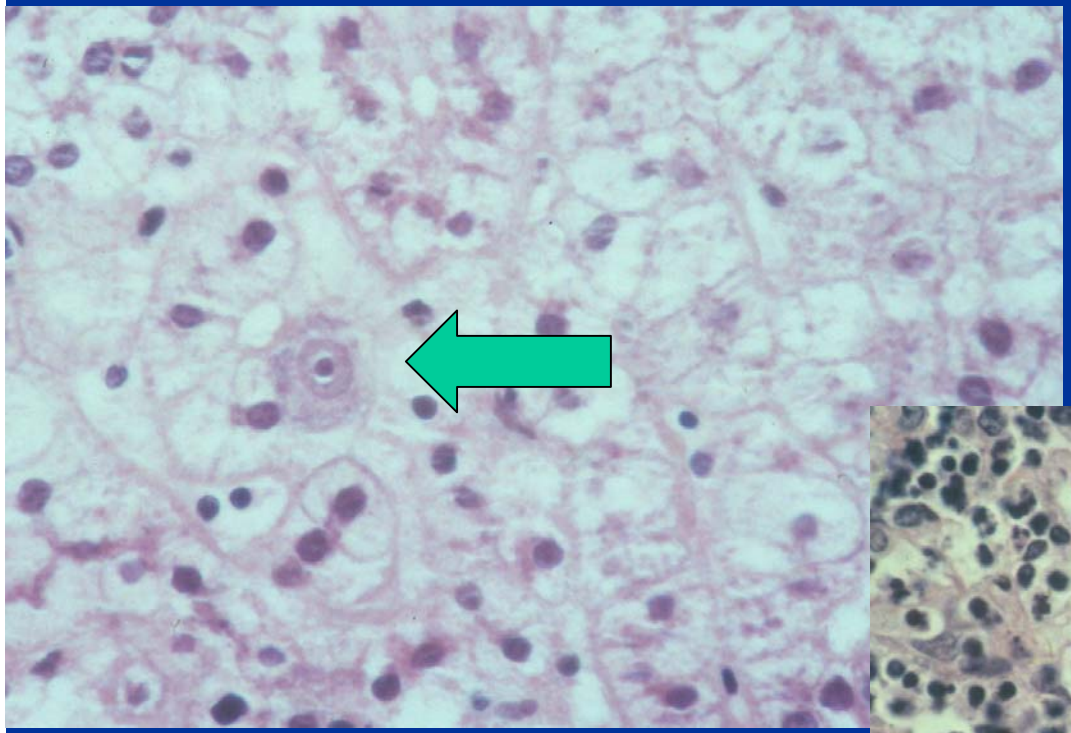
CMV HEPATITIS

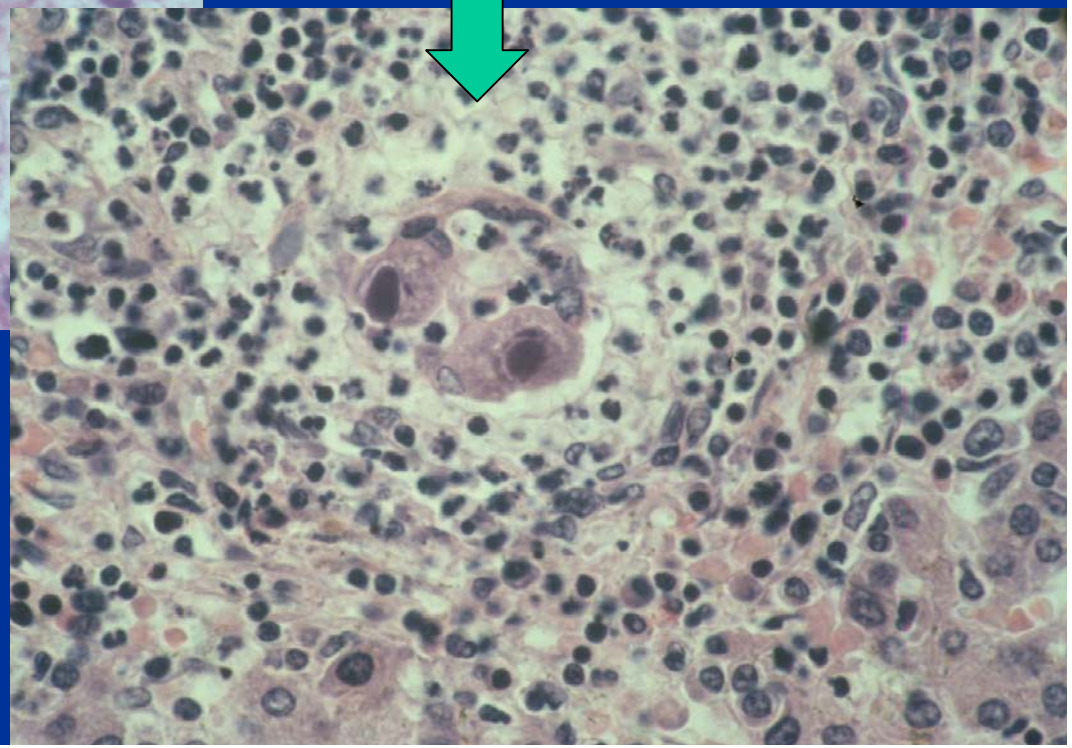
Neonate
Fever
Hepato splenomegaly
Pneumonitis, encephalitis, deafness
Thrombopenia
Deafness (neonatal) – progressive
AST 525, ALT 675, GGT 339
Hepatitis: microabcesses, target cells, inclusions
✍: CMV antigen, serology, cultures
Tt: Gancyclovir, valgancyclovir

CMV HEPATITIS

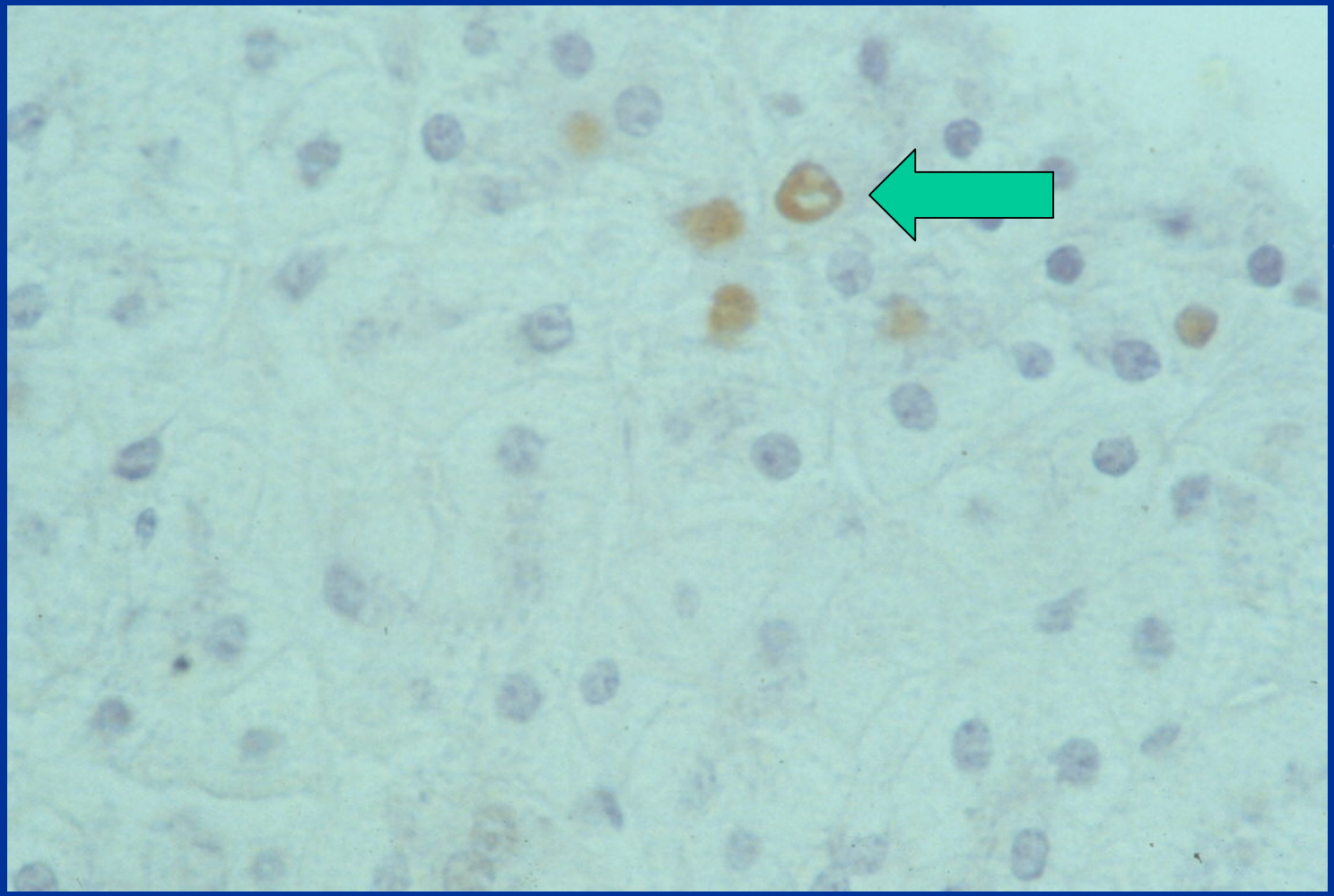


Target nuclei

µ abcess



CMV HEPATITIS
Immunostaining



CMV
antigen

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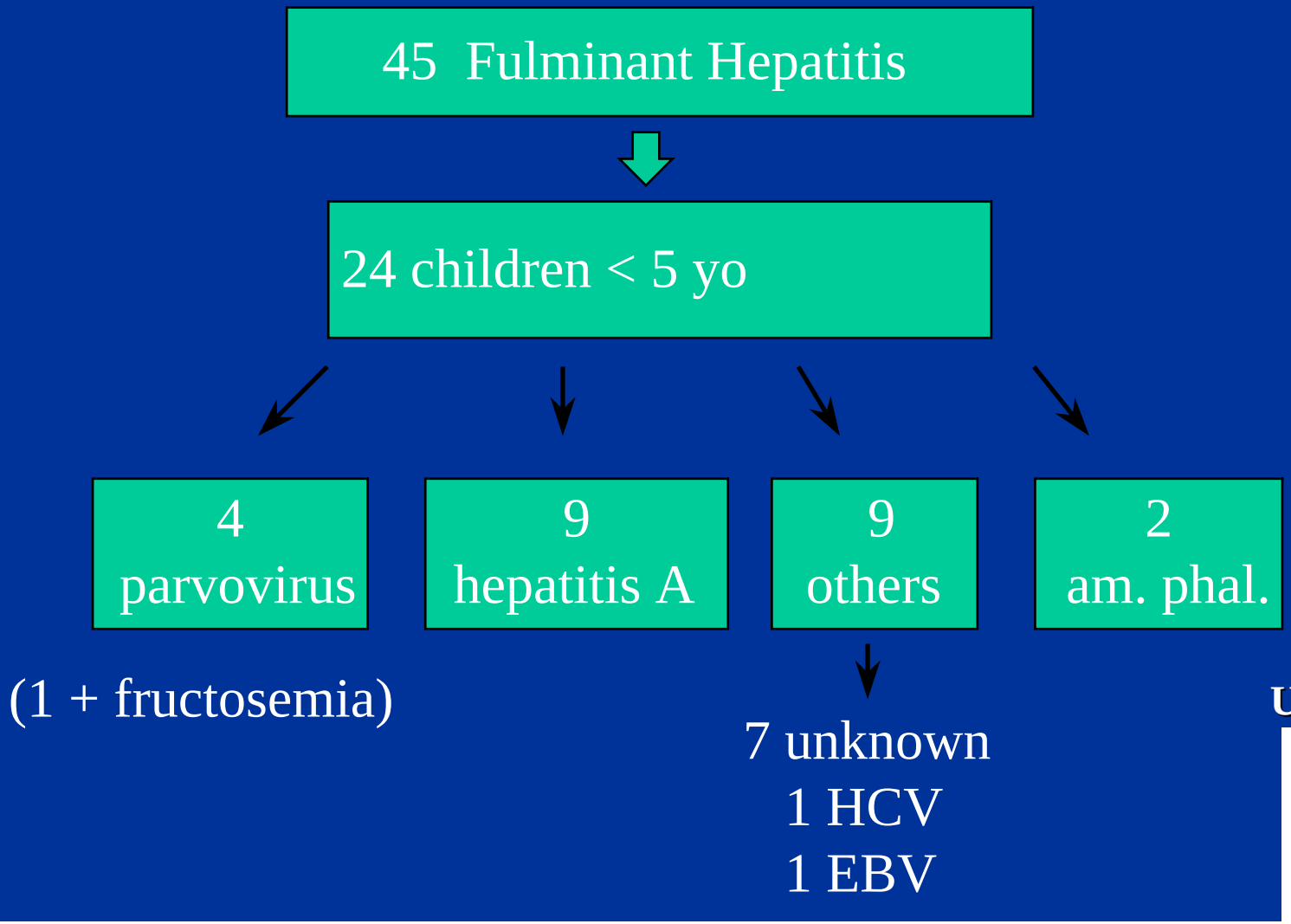
45 Fulminant Hepatitis
24 children < 5 yo
4
parvovirus
9
hepatitis A
9
others
2
am. phal.
(1 + fructosemia)
7 unknown
1 HCV
1 EBV

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PB 19 FULMINANT HEPATITIS

Clinical features

	Parvovirus n=4	HAV n=9	Others n=9
Age (months)	22 (4-52)	41 (30-48)	17 (3-29)
Clinique			
Fever	3 /4	2 /9	7 /9
Rash	0 /4	0 /9	2 /9
Jaundice	0 /4	7 /7	6 /9

Lancet 1998; 352(9142):1739-1741

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PB 19 FULMINANT HEPATITIS

Biochemistry

	Parvovirus n=4	Hepatitis A n=9	Others n=9
AST (IU/L)	13000 (3780-18200)	1320 (164-18200)	1002 (45-20280)
ALT (IU/L)	7170 (1828-10710)	1531 (123-9700)	1074 (57-9765)
Bili (μM/L)	54.7 (23.9-80.4)	461.7 (78.7-774.6)	372.8 (46.2-586.5)
NH_4 (μM/L)	57 (32-92)	130 (41-195)	91 (3.5-200)

Lancet 1998; 352(9142):1739-1741

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PB 19 FULMINANT HEPATITIS

Outcome

	Parvovirus n=4	Hépatites A n=9	Autres n=9
Evolution			
Alive	4	1	1
OLT	0	5	4
Dead	0	3	4

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Lancet 1998; 352(9142):1739-1741

TORCH INFECTIONS: RUBELLA

- **Prevented by universal vaccination**
- **Early cholestatic disease suggesting transplacental infection**
- **Hepatosplenomegaly**
- **Purpura, adenopathy**
- **meningoencephalitis**
- **Hepatitis, pneumonitis**
- **Cloudy cornea, retinopathy, cataract, deafness……**

♂ A.D., 2 months

- Full-term pregnancy
  - Young mother (18y. Old)
  - Father unknown
- No neonatal pathology
- Admitted to local hospital for :
  - Hyperthermia for 6 days (39.5°C)
  - Diarrhea

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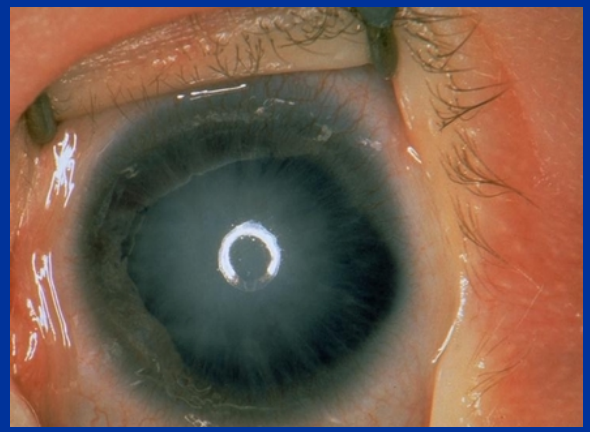
Physical examination

- Hepatosplenomegaly
  - Liver : 7 cm
  - Spleen : 6 cm
- Jaundice
- Maculopapular rash and petechia
- Hyperthermia = 39.5
- Bilateral corneal opacity



Congenital rubella ?

- **Transient**
  - Low birth-weight
  - Jaundice
  - Hepatosplenomegaly
  - Hepatitis
  - Thrombocytopenia
  - Pneumonia
  - Radiolucent bone lesions
- **Permanent**
  - Deafness
  - Cataracts
  - Corneal Opacity
  - Heart Defect
    PDA>PAS>AS>VSD
- **Developmental**
  - Psychomotor delay

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Biology

- **Hepatic**
  - ALT : 217 U/ml
  - AST : 138 U/ml
  - G-gt : 247 U/ml
  - Bilirubine tot/dir :11.6/7,1
  - Ferritine : 1360 U/ml
  - Cholesterol : 196 mg/dl
  - Triglycerides : 868 mg/dl
  - NSE : 16.9 U/ml
  - Alphafoetoprotein : 10.6 ng/ml
- **Hematology**
  - Hb : 6.7 g/dl
  - RBC : 2.470.000
  - WBC : 3490
    - (175 N, 1980 L)
  - Platelets : 20.000/mm
  - INR : 1.53
  - TCA : 60 sec

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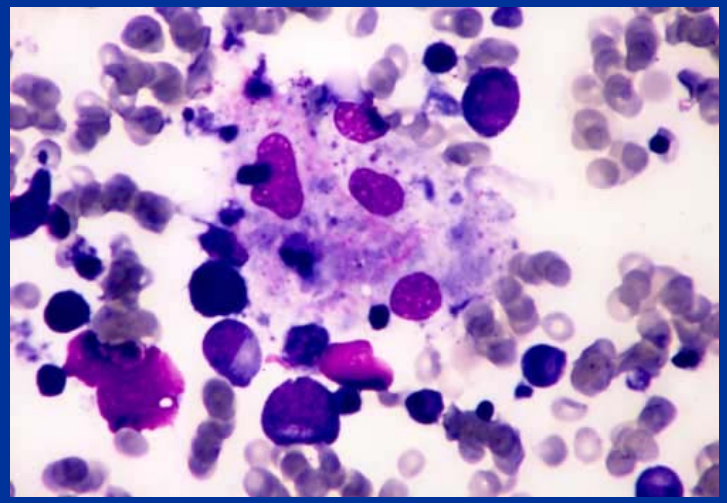
Bone marrow aspiration



- Histiocytes proliferation
- Erythrophagocytosis
- Leucophagocytosis
- ➔ Familial or secondary LH

Hemophagocytosis is not commonly found at initial bone marrow biopsy

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Liver Biopsy

- **Infiltration of Histiocytes**
  - **Portal area**
  - **Sinusoids**
  - **Bile duct**
- **Positive for non-specific esterase**
  - **Acid phosphatase**
  - **Alpha-1-antitrypsine**
  - **Lysosyme**
- **CD 11(+), CD 68(+) CD 1(-), S100(+)**

Electronic microscopy : Birbeck granules (-)

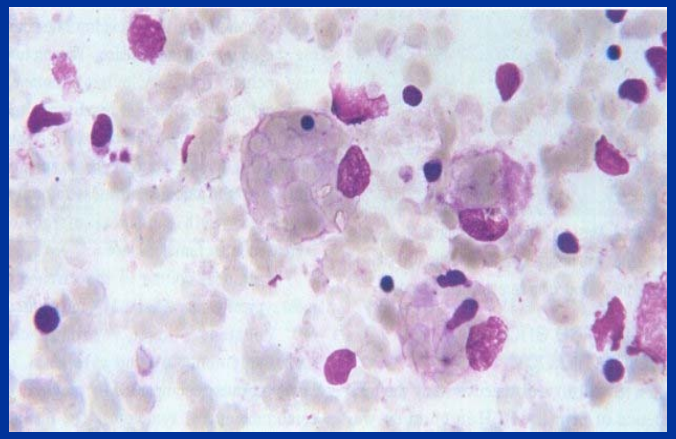
Langerhans cell Histiocytosis : positive

Lymphohistiocytosis

- **Familial Hemophagocytic Lymphohistiocytosis (FHL)**
  - **Infancy, early childhood**
  - **1 cas/50.000 live born**

    70 % within the first year

  - Perforin gene defect, deficiency of apoptosis
- **Secondary Lymphohistiocytosis (SHLH)**
  - **Viral induced: HSV, EBV,….**



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Conclusions

- Early recognition: specific antiviral treatments
- Urgent virological tests
- Urgent referal
- High degree of suspicion if maternal disease
- Jaundice more frequent in transplacental TORCH infections
- FHL often mistaken for viral disease, mainly Rubella

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