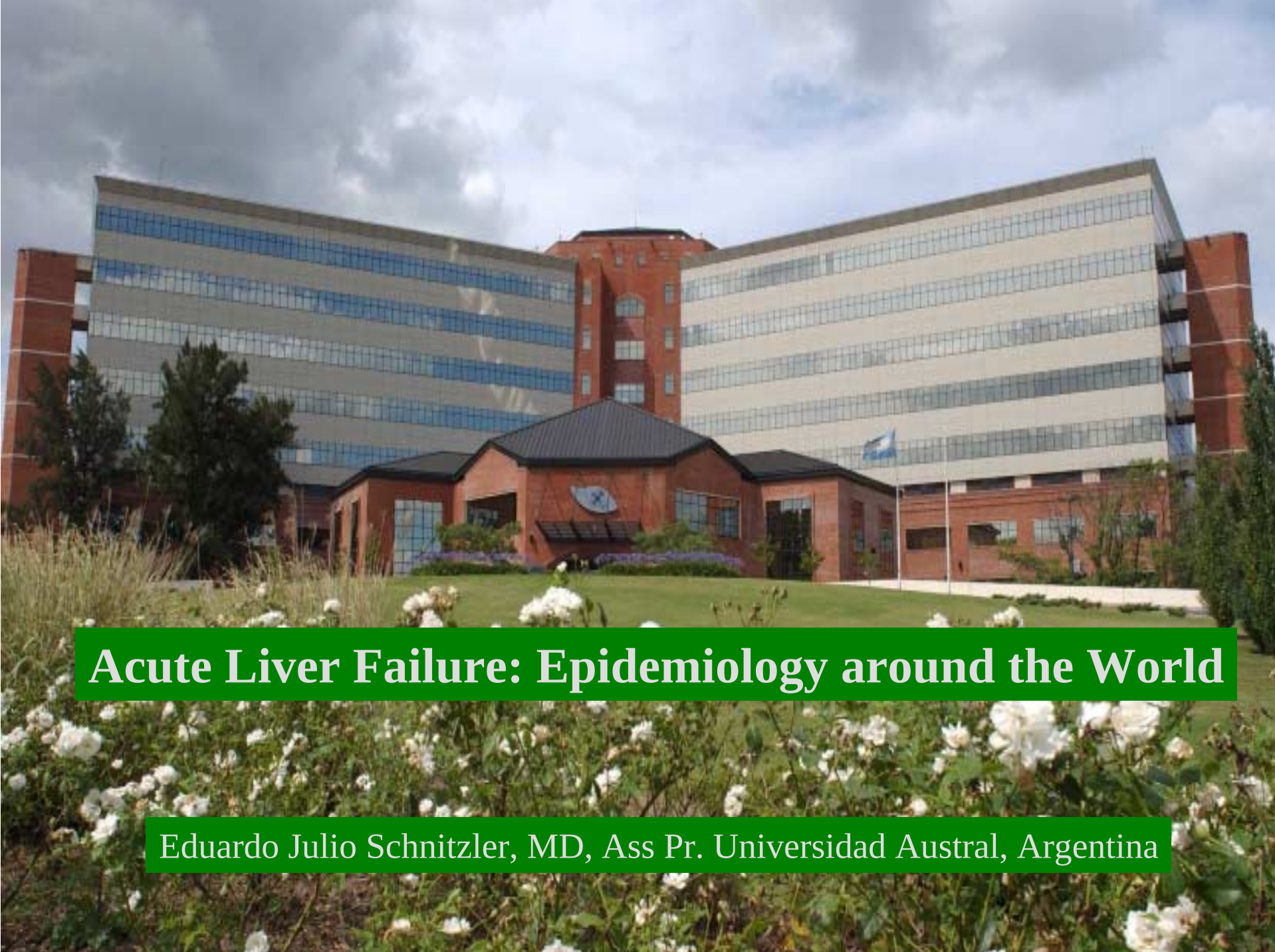


Acute Liver Failure: Epidemiology around the World

Eduardo Julio Schnitzler, MD, Ass Pr. Universidad Austral, Argentina

Acute Liver Failure

- Complex multisystemic illness
- Acute liver injury and hepatocellular dysfunction
- Coagulopathy + hepatic encephalopathy
- No previous history of liver disease
- SIRS & MODS (sepsis, immune deficiencies)
  - ARDS
  - ARF
  - DIC
- Cerebral edema, intracranial hypertension

Acute Liver Failure

Is a dramatic clinical syndrome in which previously healthy children rapidly lose hepatic function and become critically ill within days.

Squires R, Shneider B, Bucuvalas J. J Pediatr 2006, 148: 652-8

HE is difficult to assess in infants and children and may not be essencial to the diagnosis of ALF in children

Durand P, Debray D, Mandel R et al. J Pediatr 2001, 139: 871-6

Baker A, Alonso ME, Aw MM et al . J Pediatr Gastroenterol Nutr 2004, 39 (Suppl 2) S632-9

Acute Liver Failure
Classification of acute liver failure

International Association for the study of Acute Liver Failure

ALF: ocurrence of HE within 4 weeks after onset of symptoms.

Subclassification:

ALF hyperacute: within 10 days

ALF fulminant: 10 to 30 days

ALF: not otherwise specified

Subacute liver failure: (development of ascitis and/or HE from 5 to 24 weeks after onset of symptoms)

Tandon BN, Bernauau J, O'Grady J, et al: J Gastroenterol Hepatol 1999;14:403-404

PALF study group

NIH sponsored

24 active pediatric sites (21 USA, 1 Canada, 2 UK)

Patient enrollment since December 1999 (to December 2004, first report)

1-no known evidence of chronic liver disease,

2-biochemical evidence of acute liver injury,

3-PT > 15 s or INR> 1.5 not corrected by vitamin K (in the presence of HE) or PT > 20 sec or INR > 2 regardless of presence or absence of clinical HE.

Outcome determined at 3 wks after entry into the study

Death, death after transplantation, alive with native organ and alive with transplanted organ

www. palfstudy.org

Patient demographics

	Acetaminophen %	*Indeterminate %*	*All others*
Total (348)	**48 (14) vs 40%**	169 (49) **vs 17%**	131 (37) **vs 43%**
Female (181)	**38 (79)***	78 (46)	65 (50)
Age < 3 y (127)	**2 (4)**	68 (40)	57 (44)
Race black (54)	**5 (10)**	32 (19)	17 (13)
Race white (186)	**32 (67)***	79 (47)	75 (57)

Squires R et al. Acute Liver Failure in children: The first 348 Patients in the pediatric acute liver failure study group. J Pediatr 2006, 148:65
Ostapowicx G et al. Results of a prospective study of ALF at 17 tertiary care centers in the US. Ann Intern Med 2002, 137:947-954

Others: 37%

Squires R et al. Acute Liver Failure in children: The first 348 Patients in the pediatric acute liver failure study group. J Pediatr 2006, 148:65
Ostapowicx G et al. Results of a prospective study of ALF at 17 tertiary care centers in the US. Ann Intern Med 2002, 137:947-954

Diagnosis	< 3 y (%)	> 3 y (%)	**Total (%) 348**	**Adultos (%) 308**
Non-APAP drug induced liver disease Valproate, mushroom, INH	1 (1)	16 (7)	**17 (5)**	**40 (13)**
Metabolic Fatty acid oxidation defect, galactosemia, mitochondrial disorder, respiratory chain defect, tyrosinemia, Wilson disease (9)	23 (18)	13 (6)	**36 (10)**	**36 (3)**
Autoimmune	6 (5)	16 (7)	**20 (6)**	**13 (4)**
Infectious H-a, H-c, Herpes s, EBV	9 (7)	11 (5)	**20 (6)**	**36 (11)**
Shock	7 (6)	9 (4)	**16 (5)**	**17 (6)**
Other: Budd-Chiari; VOD HPS, Leukemia Neonatal iron storage disease	11 (9)	9 (4)	**20 (6)**	**5 (2)**

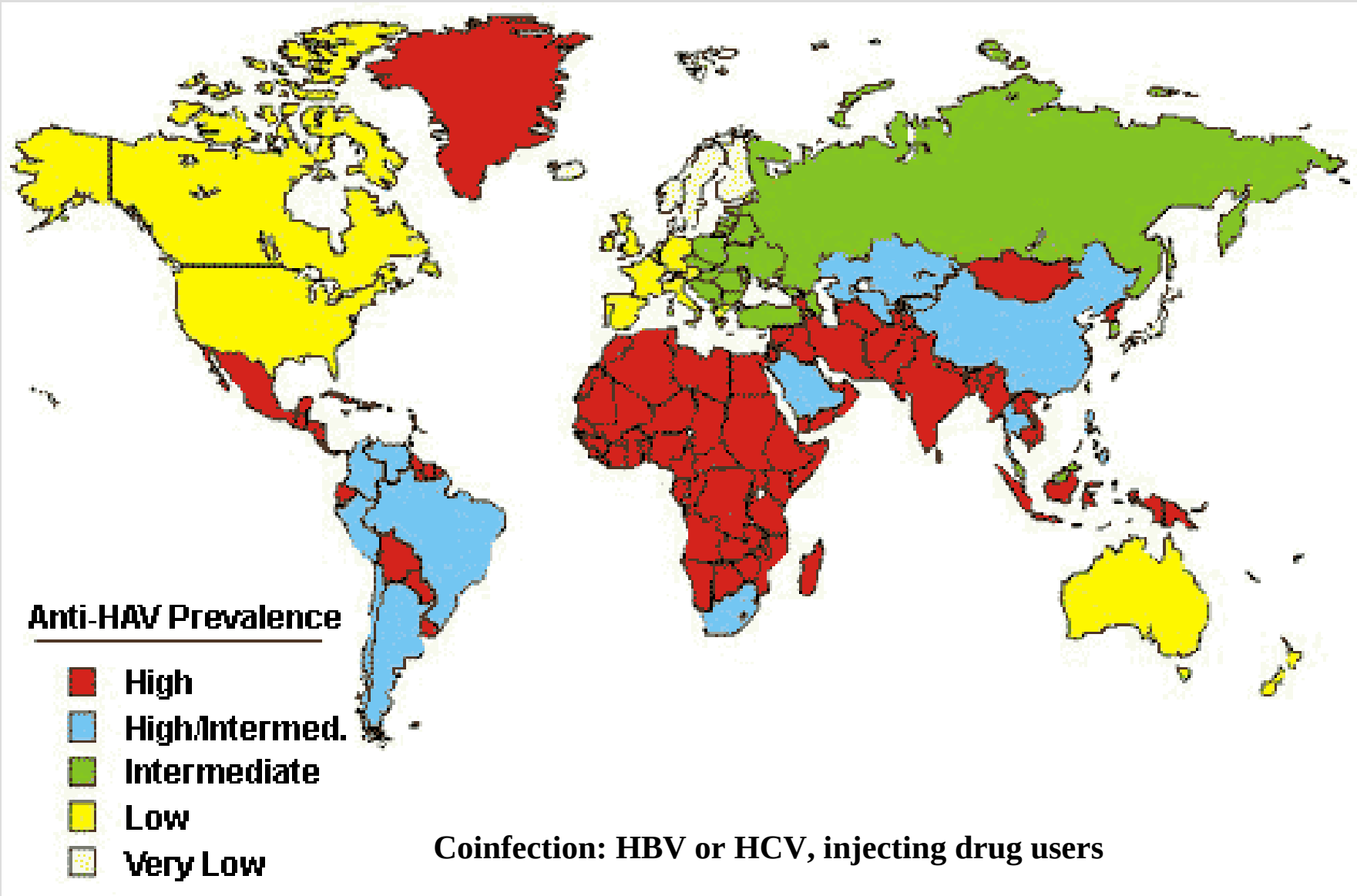
Etiology of ALF in infancy

N: 80	Total	Survived LT free: **19 (23.7%)**	OLT: **23 (28.7%) /50%**	Died **33 (47,5%)**
Metabolic disorders	**34 (42.5%)**	**10**	**10 (4)***	**14**
Tyrosinemia	12	5	5 (2)*	2
Mitochondrial cytophaties	17	1	5 (2)*	11
Neonatal Hemochromatosis	**13 (16,2%)**	**2**	**1 (0)***	**10**
Undetermined, Reye	**13 (16,2%)**	**4**	**3 (3)***	**6**
Acute Viral Hepatitis	**12 (15%)**	**1**	**6 (4)***	**5**
Hepatitis B	6	1	2 (2)*	3
Miscellaneous	**8 (10%)**	**2**	**3 (1)**	**3**
AIH	3	0	3 (1)*	0

Durand P et al.ALF in infancy: A 14 year experience of a pediatric liver transplantation. J Pediatr 2001, 139:871-6

* Number of survivors after LT

CDC

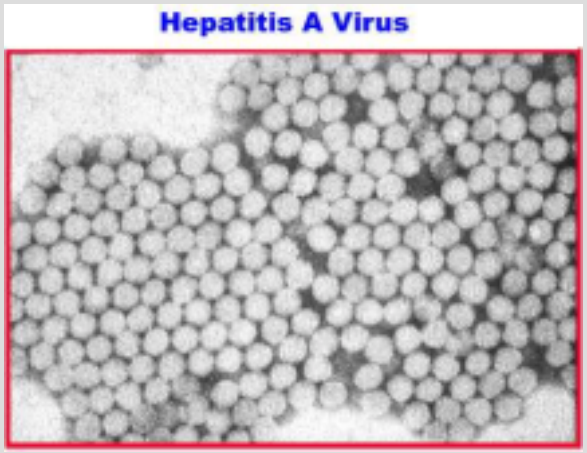


Coinfection: HBV or HCV, injecting drug users

Hepatitis A. World prevalence.

CDC HEPATITIS A

HAV is the most important etiological agent causing FHF in children It causes of 2/3 of AHF and it is the cause of 1/3 of LT in Argentina. 270000 cases/y was estimated in USA 29/925 ALFSG. UNOS 92/ 79250 LT (0.12%)



Endemicity	Disease rate	Peak age of infection	Transmission patterns
High Africa, South America ME and SE Asia	Low to high	Early childhood children <6 years of age most infections are asymptomatic	Person to person Outbreaks uncommon
Moderate China and Latin America	High	Late childhood, young adults fatality ratio increased from 0.2% among children 5–14	Person to person Food and waterborne outbreaks
Low Australia, USA, Western Europe	Low	Young adults	Person to person Food and waterborne outbreaks
Very low Northern Europe, Japan	Very low	Adults	Travelers, outbreaks uncommon

Low

Level of Economy development

High

2002-06

48 c AHF

Median: 60 m
(12- 192 m)

29 c HAV (60.5%)

14 c Indeterminate (29%)

5 c Others: 11,5%

22 c LT (46%)

26 c LT free (54%)

2 death (4%)

20(41%) survival

20 (41%) survival

6 death (12%)

83% survival

17% non-survival

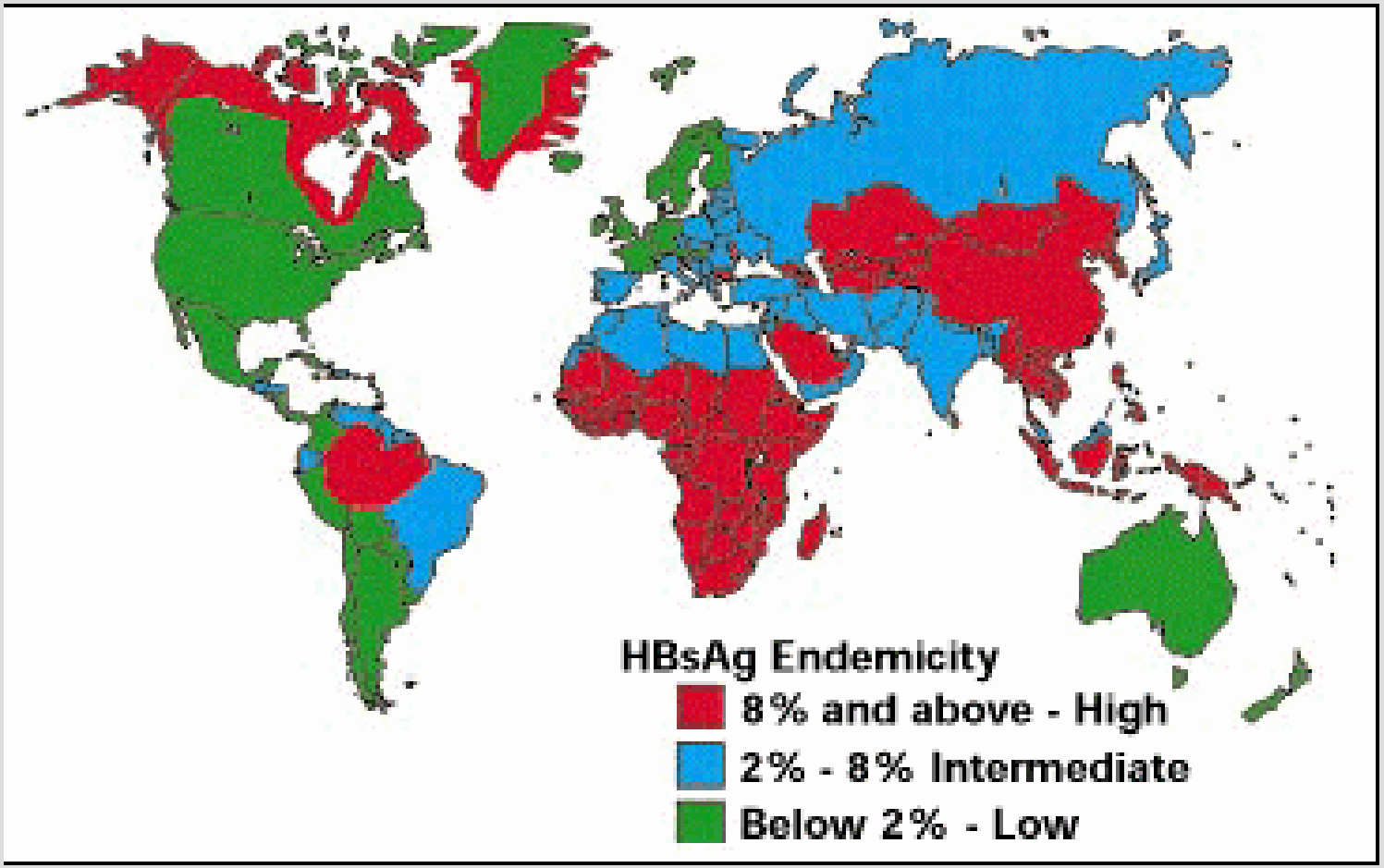
AHF: a perspective from the East

- Viral hepatitis causes 95- 100% of AHF in India
- HEV transmited by faecal-oral route, waterborne disease, outbreaks through contaminated water or food supplies. (low standards of sanitation) .Central and South East- Asia, North and West Africa and in Mexico. Mortality : 0.4- 4%. FHF in pregnant women.
- HAV infection alone or as co-infection caused 50-70% of AHF in children.*
- Co-infection with multiple hepatotropic viruses.

  24,6 % of patients with acute viral hepatitis and 26% of children with FHF.

Acharya S et al. Acute hepatic failure in India: A perspective from the East. J Gastroenterol Hepatol., 2000, 15: 473-9
Bendre S et al: Fulminant hepatic failure: etiology, viral markers and outcome. Indian pediatrics, 1999, 36:1107-1112
Kumar A et al. Does co-infection with multiple viruses adversely influence the course and outcome. J Gastroenterol Hepatol, 2006, 21: 1533-7

Acute disease: HBs Ag +, HBe Ag +
IgM anti HBc Ag +, Anti HBs Ag -



CDC- HEPATITIS B

Hepatitis B: hepadnaviridae (hepatotropic DNA virus) family.

Chronic hepatitis, Cirrhosis and Hepatocarcinoma.

Hyperimmune response and FHF.

HBV is the most important cause of FHF in endemic areas.

Co-infection or superinfection : HAV or HDV (ALF)

US : 2314 / 53312 LT (4,34 %) of LT were performed for diagnosis HBV.(1993-2004) UNOS database. 1816 chronic cases (78%) 498 acute liver failure (22%)

Camci C et al. Liver Transplantation for hepatitis B in the Unites States. Transplant Proc 2005, 37:4350-3

Korea: AHF (herbal medications and acute viral infection) 15.8 % HBV.

Hedo NY et al. Clinical features of FHF in a tertiary hospital with a LT center in Korea. Korean J Hepatol 2006, 12: 82-92

Others infectious cause of AHF

- Dengue: a major cause of AHF in Thai children

  40 subjects from 14 centres (2 years). Dengue: 12 cases (34.3%) 66%mortality

  Poovorawan Y et al. Dengue virus infection: a major cause of AHF in Thai children. Ann Trop Paediatr 2006, 26:17-23
- HSV, CMV, EBV
- Influenza A infection.
- Salmonella Thypi
- Malaria:

  37 patients from hospitals in Khartoum, Sudan . Malaria 3 cases (8%) .Mudawi et al

Drugs & Toxins

- Flurinated hydrocarbons trichloroethylene and tetrachloroethane (sniff glue or exposed industrial cleaning solvents)
- Amanita phalloides. Muscarinic effects (sweating, vomiting and diarrhea) *Penicillin G*, *Silymarin*
- Predictable liver injury (acetaminophen), dose-dependent *NAC*
- Idiosyncratic (INH, anticonvulsants)
- MDMA (ecstasy) is reported to be the 2nd cause of LI (Europe) in < 25 years old

HEPATOCELLULAR	MIXED	CHOLESTATIC
ACETAMINOPHEN	AZATHIOPRINE	AMOXICILLIN-CLAVULANIC
ALLOPURINOL	CAPTOPRIL	CHLORPROMAZINE
AMIODARONE	CARBAMAZEPINE	ORAL CONTRACEPTIVES
HAART DRUGS	CLYNDAMYCIN	ERYTHROMYCINS
HERBAL: KAVA KAVA	CYPROHEPTADINE	PHENOTHIAZINES
ISONIAZID (1,8 - 2,9%)	ENALAPRIL	
KETOCONAZOLE	HALOTHANE**	
METHOTREXATE	NITROFURANTOIN	
NSAIDS	PHENOBARBITAL	
OMEPRAZOLE	PHENYTOIN**	
RIFAMPIN	SULFONAMIDES	
RISPERIDONE	TMS	
FLUOXETINE	IRON	
VALPROIC ACID*	* Mitochondrial injury	** Hypersensitivity

DILI network report

Antibiotics (43%)
Anticonvulsants (10%)
Herbal therapies
Anesthetics
NSAIDs

Chalasani N et al
Am J Gastroenterol 2006,101(9)

modified from Navarro V and Senior J. NEnglJMed 2006, 354:731-9

Drug-induced liver disease

- Children may be more or less susceptible to hepatotoxity than adults. (halothane vs sodium valproate)
- Hy's Law : drug-induced hepatocelular jaundice is a serious lesion, mortality rate ranges from 10 to 40 % without LT. **(1) Mortality 11,7%. Anti-infective 32%, CNS 17%, NSAIS 17%**
  (2) Mortality HC 9,4%, C 7,8%, Mix 2,4%. Halothane 40%,
- Genetic variability: (low and fast acetylators & INH tox)
- Liver injury and adaptive tolerance (INH) vs serious hepatotoxicity (symptoms + biochemical evidence)

1- Andrade RJ et al Drug-induced injury: an analysis of 461 incidences submitted to the Spanich Registry over a 10-year period. Gastroenterology 2005, 129:512-21
2- Bjornsson E et al. Outcome and prognostic markers in severe drug induced liver disease, Hepatology 2005, 42: 481-9

ACETAMINOPHEN & AHF

- Acute coagulopathy and encephalopathy in a patient with aminotransferase levels > 1000 IU/l who had taken > 4 g/day of acetaminophen within the preceding 7 days with no other cause of AHF. (adults)
- Cofactor with viral hepatitis or other medications.
- Ethnic differences in acetaminophen metabolism.
- Attempted suicide (Blood levels confirmatory)
- Therapeutic misadventures, used for pain relief in excess of the dose over a period of several days. (Blood levels could be not elevated)
- Acetaminophen protein adducts in ALF of indeterminate cause is present in 12,5% of cases *(James L, Pediatrics 118,2006)*

*Watkins PB et al. ALT elevations in healthy adults receiving 4 grams of acetaminophen daily . JAMA 2006, 91:87-93

FHF & Autoimmune Liver disease

- May mimic an acute viral or toxic hepatitis.
- (< 10% of AIH have an acute presentation)
  Must be considered in all patients with a fulminant presentation.

- **Type 1** (**ANA > 1:80**, aAA, **SMA > 1:20**, aSLA/LP, ANCA)
  worldwide and any age, female 75%
  Type 2 (**a LKM > 1.20, aLC-1)**
  worldwide, rare in North America,
  childhood and young adulthood, female 95%
  Corticosteroid therapy may be lifesaving, but a rising serum Bi level heralds a poor prognosis and LT may be necessary.

Krawitt E. Autoimmune Hepatitis. N Eng J Med 2006, 354:54-66
Czaja A, Autoimmune liver disease. CurrOpin Gastroenterol 2007; 23:255-262

FHF & Metabolic diseases

Clues for diagnosis:

Family history of a similar illness, Consanguinity, failure to thrive, neurodevelopment delay and/or neuromuscular dysfunction.Onset of symptoms associated with a change in dietary habits

Ketotic hypoglycemia, organic acidemia, lactic acidemia (lactato/piruvate > 20 mol/mol), hyperammonemia.

Liver biopsy, Muscle biopsy, skin fibroblast.

- Disorders of CH metabolism: galactosemia, fructosemia, disorders of CH glycosylation.
- Disorders of Amino Acid and Protein metabolism: tyrosinemia (NTBC)
- Disorders of Metal Metabolism: Wilson disease, Neonatal Iron Storage Disease (NISD)
- Mitochondrial hepatopathies: disorders of FAO, oxidative phosphorylation and general mitochondrial dysfunction

Wilson Disease

Incidence: 1/ 100000 – 1/ 500000

Autosomal recessive disorder (chromosome 13, q14-q21) > 100 mutations

Accumulation of copper in the liver (mitochondria) and then in others organs

Clinically manifested after 5 y (liver disease) after 20 ys (brain disease)

- LD: Asymptomatic hepatomegaly, subacute or chronic hepatitis and FHF
- Neurologic and psychiatric disorders (Kayser Fleisher Ring)
- Hemolysis (may be initial manifestation) Coombs negative
- Fanconi Syndrome

Ceruloplasmin < 20 ug/dL. Serum copper level elevated and urinary copper excretion: > 40 ug/día. Liver biopsy : hepatic copper content > 250 ug/g dry weight. Bi values can exceed 30 mg/dL. AP level low . Bi/AP >

Genetic screening. ATP 7B gene

ALF: geographical variation in the etiology

	UK	US	France	India	Japan	Argentine
Paracetamol	**14** *54*	**14** *40*	*02*	-	-	-
Drug reactions	**16** *07*	**05** *12*	**15** *15*	*05*	-	-
Indeterminate	**37** *17*	**49** *17*	**54** *18*	**20** *24*	*45*	**30**
Hepatitis A or B	**10** *14*	**06** *12*	*49*	**50** *33*	*55*	**60** (HAV)
Hepatitis E	-	-	-	**30** *38*	-	-
Other causes	**23** *08*	**26** *19*	**11** *16*	-	-	**10**

Data shown as percentages / Black references is in children

Modified from O'Grady JG, Acute liver failure. Postgrad Med J 2005, 81:148-154


Thanks for your attention