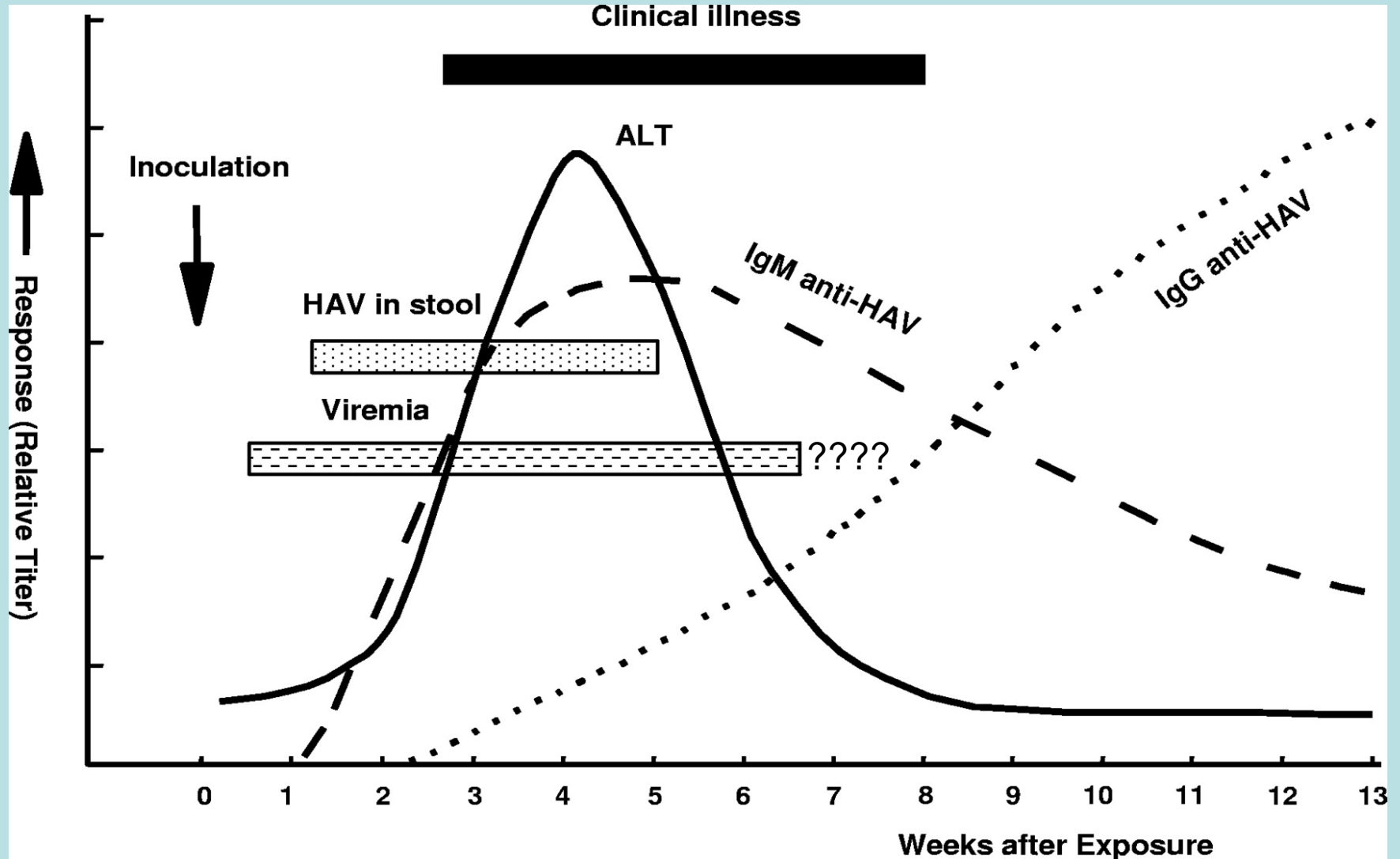


What are the risk-factors with an impact on fatality rate in fulminant hepatitis A?

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Hepatitis in Chimpanzees inoculated with HAV



*Adopted from Nainan et al. *Clinical Microbiology Reviews* 2006;19;:63

Cumulative Experience

- Acute HAV infection resolves spontaneously in > 99% of infected individuals
- Fulminant hepatitis is rare with a wide range of estimated rates, up to 1:10,000 or more in immuno-competent individuals
- Patients with chronic liver disease are at an increased risk for developing severe or fulminant hepatitis
- Mortality in fulminant hepatitis is rare and linked to hepatitis A in older age > 50 y

Patients Survival in Fulminant Viral Hepatitis Without OLT*

Etiology

Survival

Hepatitis A	66%
Paracetamol	50%
Hepatitis B	39%
Hepatitis C	20%
Halothane	13%

**O'Grady et al, Gastroenterology 1988; 94: 1186.*

Age-specific Mortality Due to Hepatitis A

<u>Age group (years)</u>	<u>Case-Fatality (per 1000)</u>
<5	3.0
5-14	1.6
15-29	1.6
30-49	3.8
>49	17.5
Total	4.1

Source: US Viral Hepatitis Surveillance Program, 1983-1989
Similar data CDC Hepatitis surveillance report No 58,2003 p 1

Fulminant Hepatitis A in children

Number of reports is rising?

- Turkey 4 cases (6/04-11/06)
- UK 9 cases (1991-2000)
- Argentina 128 cases (5/82-9/02)
- Argentina 41 cases (9/03-1/06)
- Brazil 13 cases (1998-2007)

Reports are retrospective and released by individual centers

J Viral Hepatitis 2008;15:S66; J Ped Gastroenterol & Nutr 2005;40:575; Pediat Crit Care Med 2002;3:227; Liver Int 2007; Arch Dis Child 2008;93:48

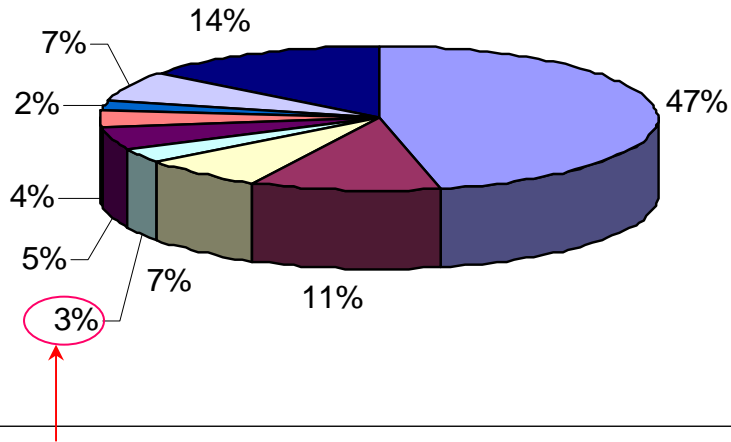
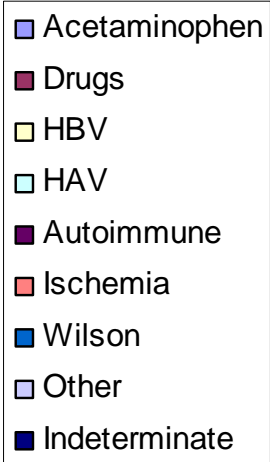
Rising Incidence of Fulminant Hepatitis A irrespective of age*

Year	%
2003	0
2004	3.4
2005	3.2
2006	6.0
2007	7.7
2008	13.0

- 35/568 HAV patients had fulminant hepatitis (KCH)
- Spontaneous survival 20/35 (57.1%)
- Transplanted 13/35 (37.1%)
- Died 5/35 (14.3%)

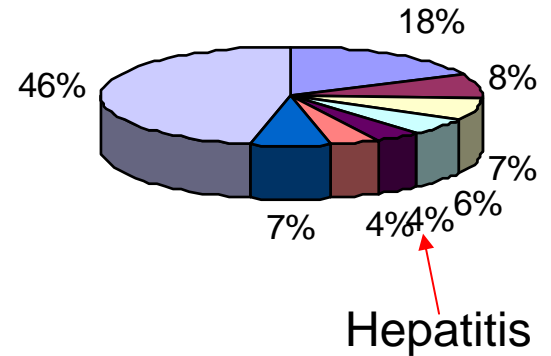
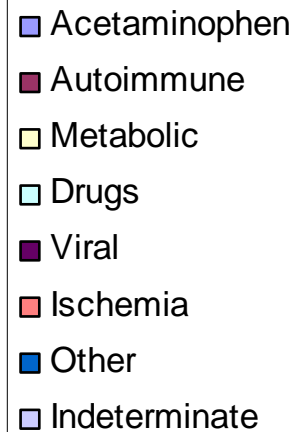
Total survival 85.7%

Etiology of Acute Liver Failure in Adults



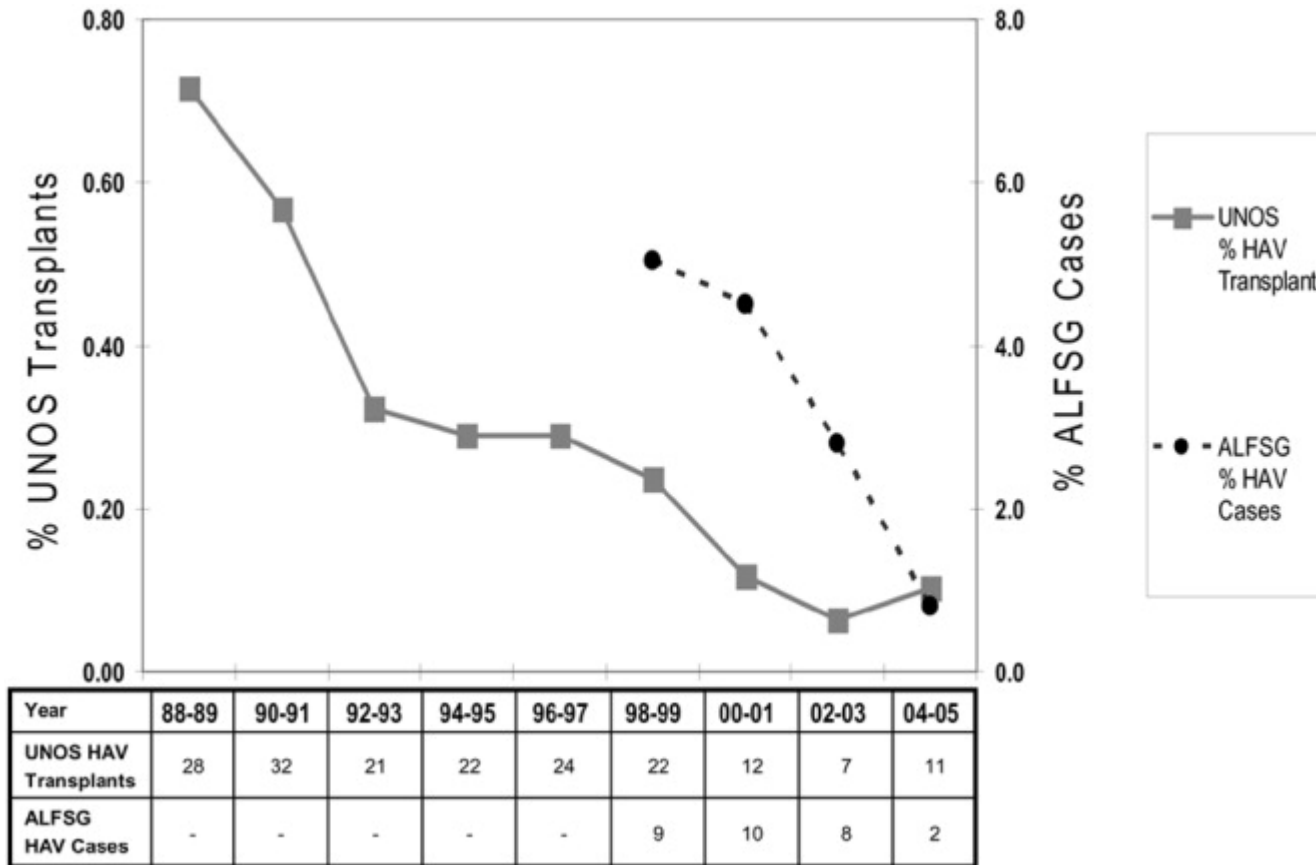
Hepatitis

Etiology of Acute Liver Failure in 3-18y olds



Hepatitis

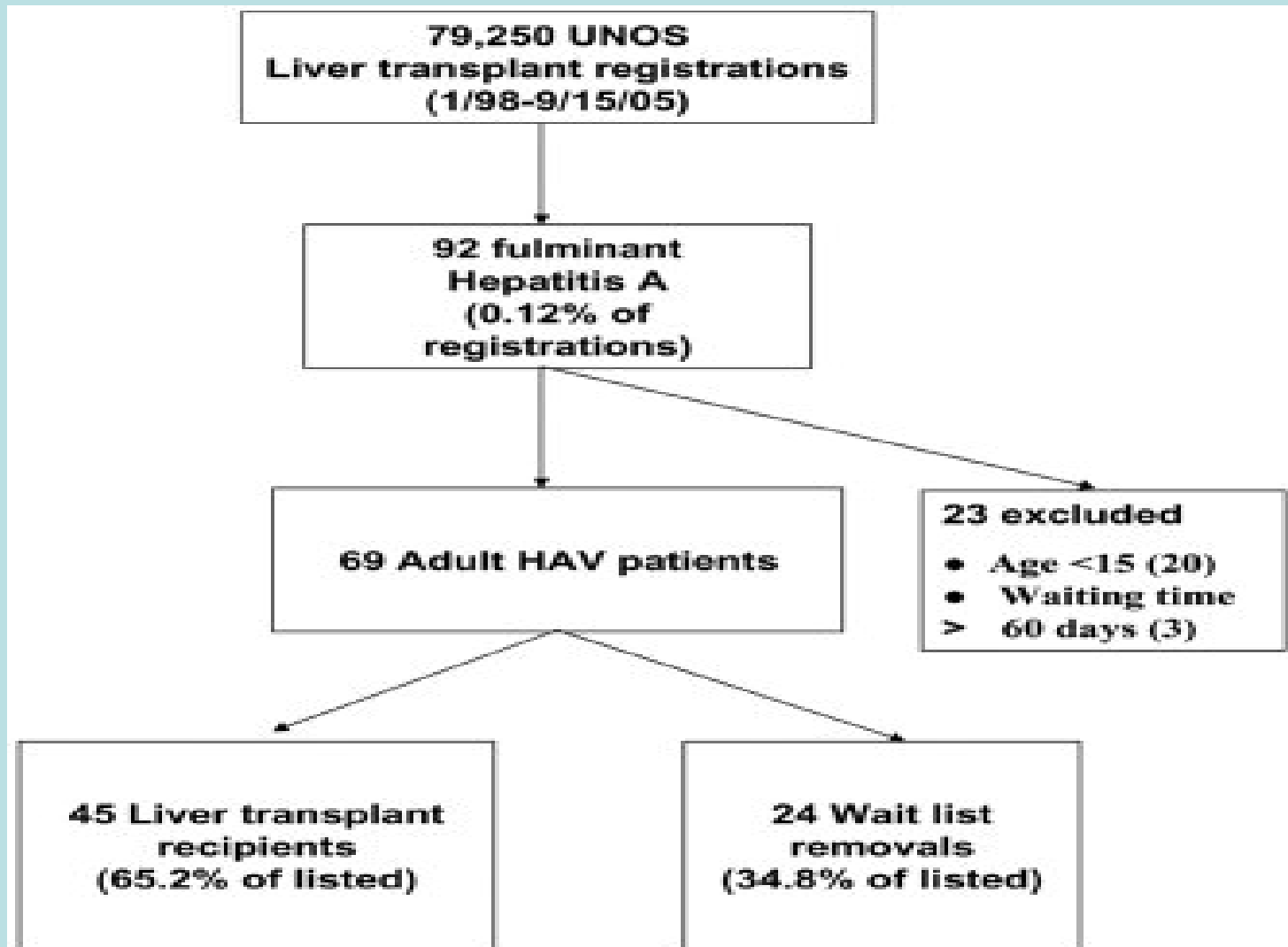
Trends in the incidence of hepatitis A virus related acute liver failure in the United States.



The incidence of patients undergoing liver transplantation for HAV related ALF in the UNOS database significantly declined between 1988 and 2005 ($P < .001$). Similarly, the frequency of HAV patients enrolled in the ALFSG significantly declined between 1998 and 2005 ($P = .007$).

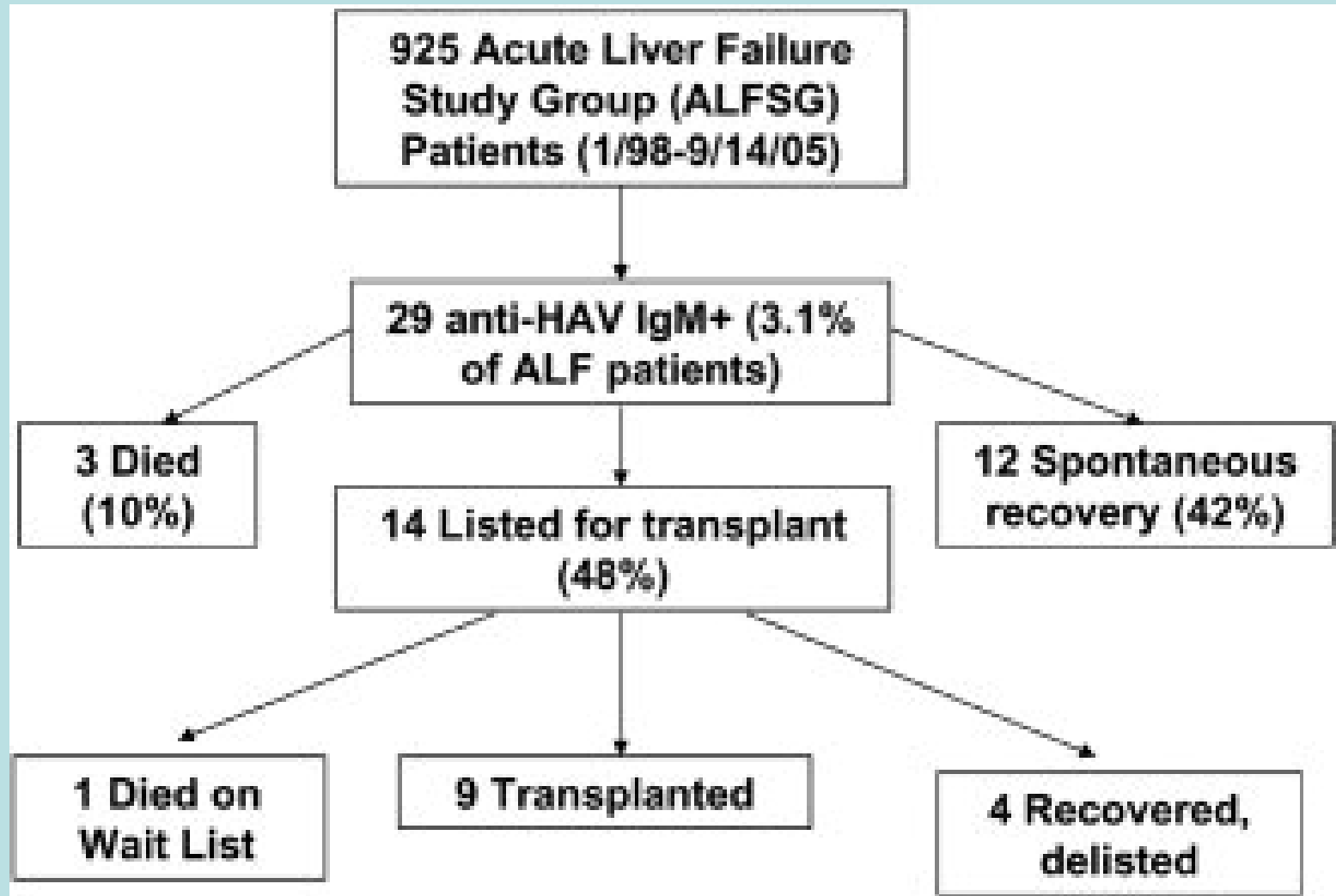
**Taylor RM et al. Hepatology 2006;44:1589*

Outcomes of patients with HAV listed for liver transplantation in the UNOS database. All patients were listed between 1/98 and 9/15/05



**Taylor RM et al. Hepatology 2006;44:1589*

Outcomes of patients with HAV enrolled in the Acute Liver Failure Study Group*
All patients were enrolled between 1/98 and 9/15/05
and followed for 3 weeks after enrollment



Outcomes of patients with HAV enrolled in the Acute Liver Failure Study Group*

**All patients were enrolled between 1/98 and 9/15/05
and followed for 3 weeks after enrollment**

Results

- 16 HAV patients recovered spontaneously (55%)**
- 13 HAV patients were transplanted or died (45%)**

Factors with an impact on fatality rate in fulminant hepatitis A

- **Host**

- **Age**

- **co-infection with hepatotropic viruses**

- **immune response?**

- **Virus**

- **genomic variations**

- **virulence**

- **Treatment for liver failure**

- **improved intensive care**

- **liver transplantation**

Risk factors associated with fulminant hepatitis A and liver failure

- Age of infection
 - Chronic liver disease and co-infection with other hepatotropic viruses (HBV, HCV)
 - Intake of paracetamol
 - Viral factors ?
-
- Pregnancy ???

Increased severity of HAV infection

- In the elderly: hospitalization rates rose from 3% in 40-49y olds to 42% <age of 70y (*Brown&Persley Southern Med J 2002;95:826*)
- In HCV, HBV and HIV co-infection (*Laurence JC Am J Med 2005;118:75*)
- In pregnancy (*Elinav E et al. * Gastroenterology 2006;130:1129, Gall A Am J Med 2005;118:96S*)

*34/79458 acute hepatitis

13/34 Acute HAV 'with premature contractions, placenta separation, membrane rupture

Fulminant hepatitis associated with hepatitis A virus super-infection in patients with chronic hepatitis C

- In a prospective study, 27/595 adults with chronic liver disease (HBV, n=163) and chronic HCV, n=432) developed acute hepatitis A
- **17/27** patients who developed acute HAV had chronic HCV infection
- **7/10** patients with chronic HCV developed fulminant hepatitis A Vs 0/10 HBV patients

Increased incidence of fulminant hepatitis A in previously unrecognized HBsAg carriers with acute hepatitis*

- Incidence of liver failure - 3.2% in patients hospitalized for acute hepatitis, irrespective of etiology (5/157)
- Incidence of liver failure in HBsAg+ subjects – 20.3% (36/177); $P < 0.001$

Conclusion: HBsAg carriers were at 9 Fold increased risk of fulminant hepatitis A than non-carriers

Search for host and viral factors associated with an increased risk for development of fulminant hepatitis A

- In spite of the unique single HAV serotype, some genetic diversity has been evident from the sequencing data obtained from a large number of HAV isolates
- Based on sequence variations at the VP1/2A junction, genotypes and subgenotypes have been defined
- So far - no confirmed correlation was found between defined HAV sequences and increased risk for developing fulminant hepatitis A. However the issue remains open.

Viral Risk factors associated with fulminant HAV*

- 19/76 subjects with acute ALF and encephalopathy were significantly older, had higher bilirubin levels, and were more likely to be females. (older age was not confirmed by multivariate analysis)
- 40/76 patients reported intake of medications of whom 19 took acetaminophen (<3.0gr/day) for less than 3 days
- 36/50 patients with available serum were HAV-RNA positive (>100 copies/ml)
- Phylogenetic analysis revealed 18 patients with genotype 1A, 12 patients 1B and 4 patients with genotype 3
- 9/19 patients with fulminant hepatitis A and encephalopathy had undetectable HAV-RNA (VP1/2A PCR), compared to 5/31 controls without ALF (P<.02)
- 8/19 patients recovered spontaneously and 10 were transplanted
- High bilirubin levels and low viremia were significantly related to risk of death or transplantation by multivariate analysis

Selected day 1 clinical features of patients with FH - ALFSG*

	Spontaneous survival	Transplanted /Died	P
Age	44	54	NS
Female (%)	69	23	.008
MELD score	29	34	NS
ALT (u) at admis..03	3362	1675	.03
Alk. Phosphat.	179	118	.02
Creatinine >2md/dl	13%	54%	NS
Grade 3- 4 encephalopathy	38%	69%	NS
Pressors	0%	46%	.0004
Intubation	25%	85%	.01

*Taylor RM et al. Hepatology 2006;44:1589

Models to Predict Transplant/Death in 29 Patients With Hepatitis A Enrolled in the Acute Liver Failure Study Group

<u>Model</u>	<u>n</u>	<u>Sensitivity</u>	<u>Specificity</u>	<u>PPV</u>	<u>NPV</u>	<u>AURO</u>
<u>ALFSG index*</u>						
≥1 Factor	20	100%	56%	65%	100%	.781
≥2 Factors	14	92%	88%	86%	93%	.899
≥3 Factors	9	62%	94%	89%	75%	.766
4 Factors	1	8%	100%	100%	57%	.538
<u>Other models</u>						
MELD ≥35	9	54%	88%	78%	70%	.707
King's College	5	31%	94%	80%	62%	.623

*Taylor RM et al. Hepatology 2006;44:1589

Phylogenetic analysis of HAV in sera of Japanese patients with fulminant hepatitis

- Association between severity of hepatitis and genomic variations
- Mutations at the 5' NCR corresponding to the internal ribosome entry site may increase severity of liver disease in HAV (N=27 patients)
- Full length genome study in 3 patients suggests that these changes are not related to genotype
- Similar changes were also found in HAV adopted for growth in tissue culture

Investigators conclusion: Genetic organization of HAV may influence replication and virulence

Fujiwara K. et al. Dig Dis Sci 2000;45:2422

Fujiwara K et al. J Hepatol 2001;35:112

Fujiwara K et al. Liver Int 2005;25:194

Fujiwara K et al. Liver Int 2008, Epub

Molecular characterization of HAV in children with fulminant hepatic failure in Argentina: 9/2003-1/2006*

- N=41 children, age M 6.8y (1-15y), 22F/19M
- HAV-RNA analyzed through probes of the 5' non-coding and VP1/2A regions
- 18/41 HAV cases positive for the 5' NCR (39%) and 18/41 HAV cases for the VP1/2A region (39%)
- FHF variants had some minor differences in nucleotide or amino acid sequences as compared to self limited acute HAV cases with no common pattern of substitution, temporal and geographic parameters

Putative Host Factors (Familial Clustering)*

- 3 siblings developed fulminant hepatitis A in a family in Israel
- Cloning and sequencing of HAV in progress

Conclusions

- The incidence of fulminant hepatitis A is low but there seems to be an increase in reports in children
- Improved intensive care and liver transplantation have markedly changed the fatality rates from fulminant hepatitis A
- Major risk factors include age, underlying liver disease and intake of paracetamol
- Conflicting and yet unconfirmed data have been reported on minor genetic substitutions of viral sequences with a putative impact on viral replication and cytopathic effect

Thank You



The Hadassah-Hebrew University Campus – Jerusalem, Israel