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

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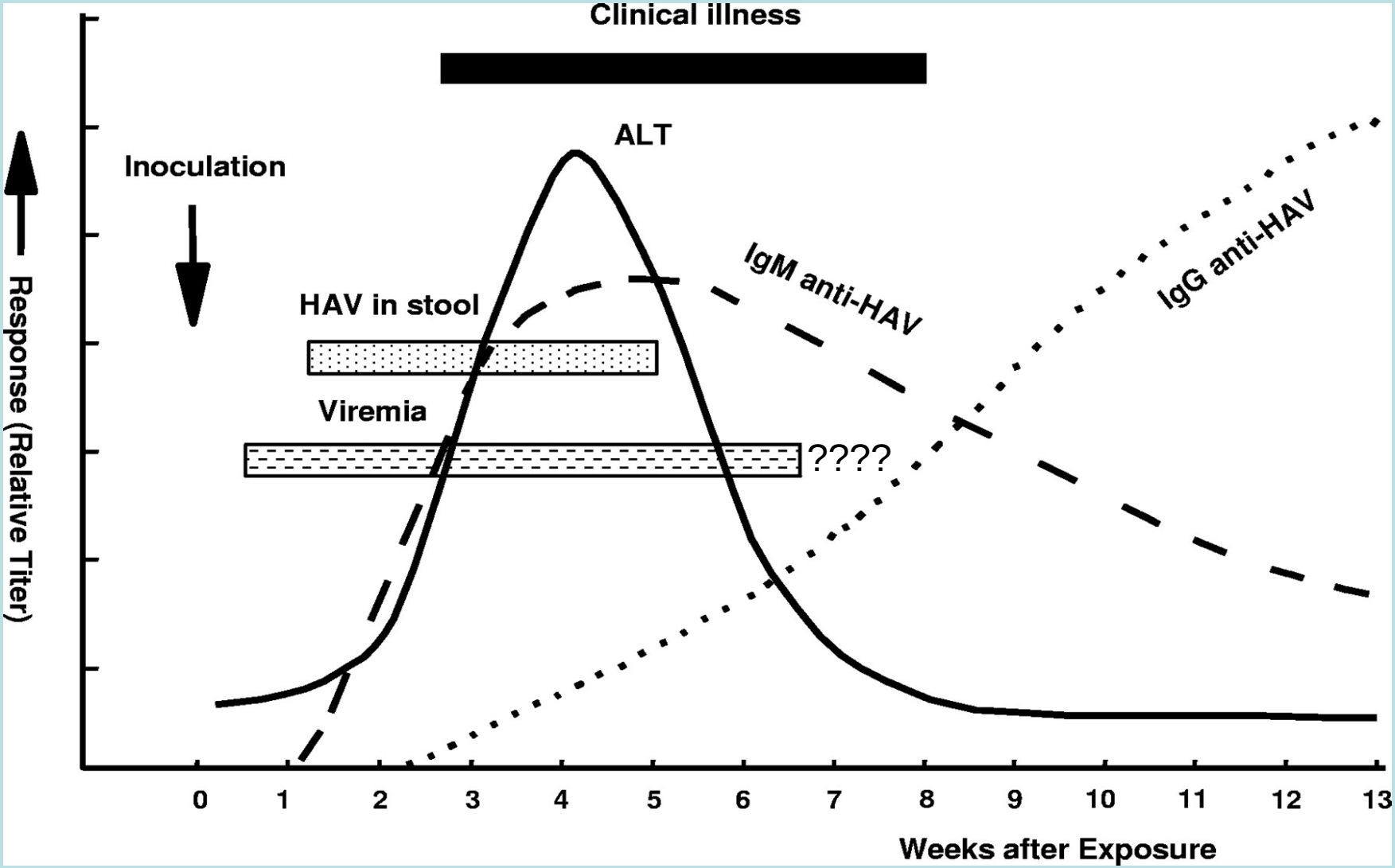
Hepatitis in Chimpanzees inoculated with HAV



*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

Age group (years)	Case-Fatality (per 1000)
<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

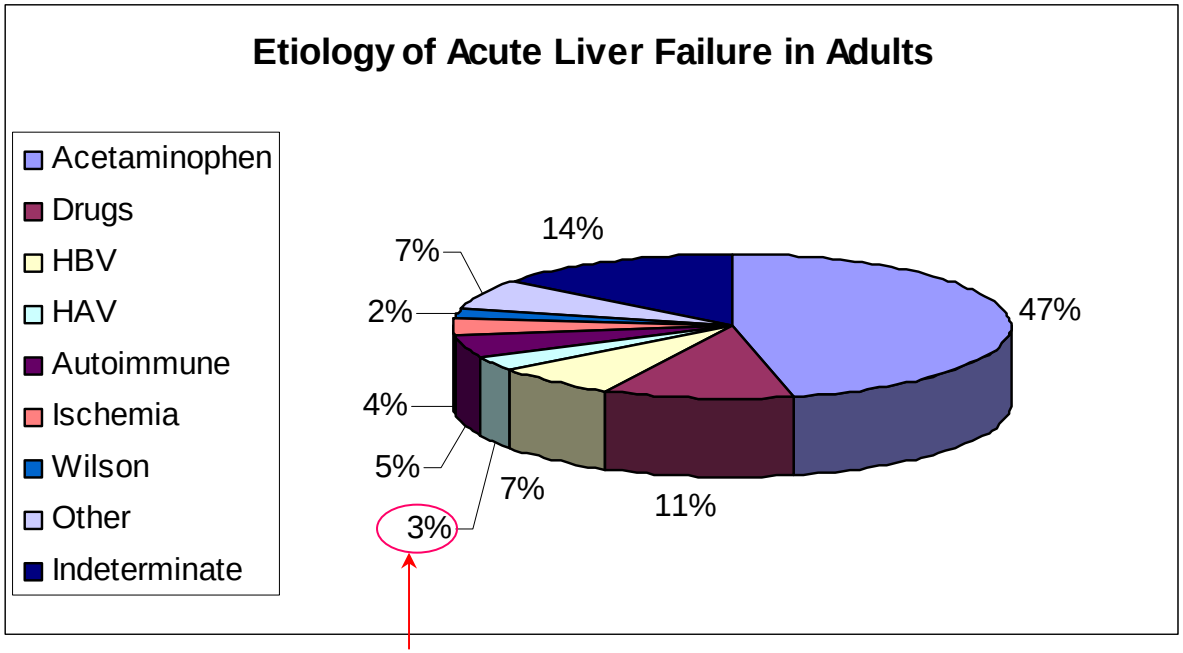
Rising Incidence of Fulminant Hepatitis A irrespective of age*

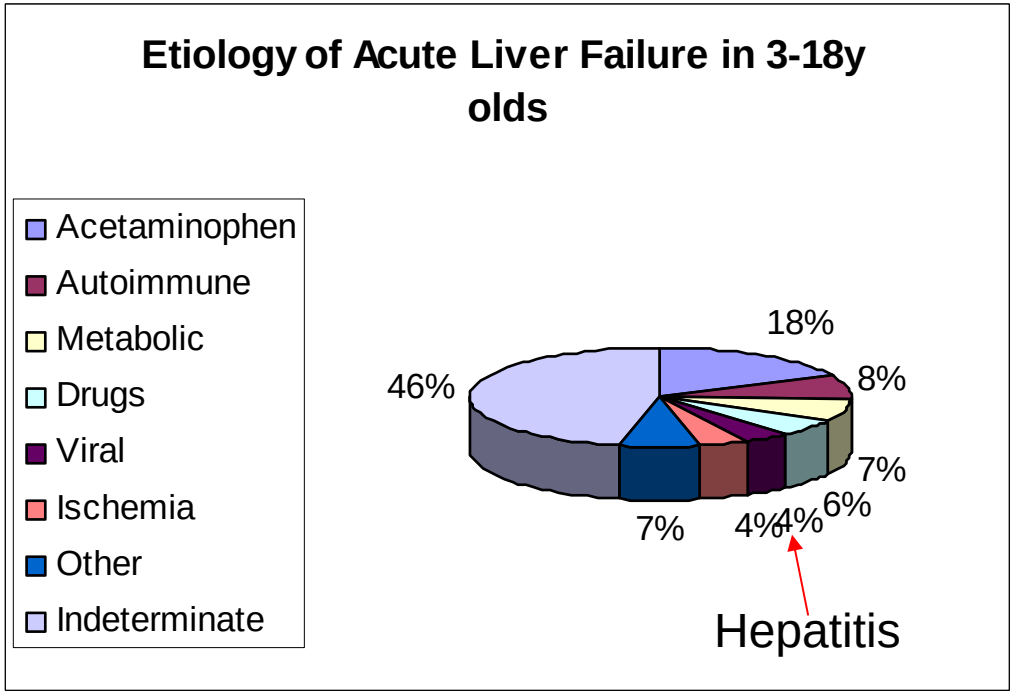
Year	%
2003	0
2004	3.4
2005	3.2
2006	6.0
2007	7.7
2008	13.0

- **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%

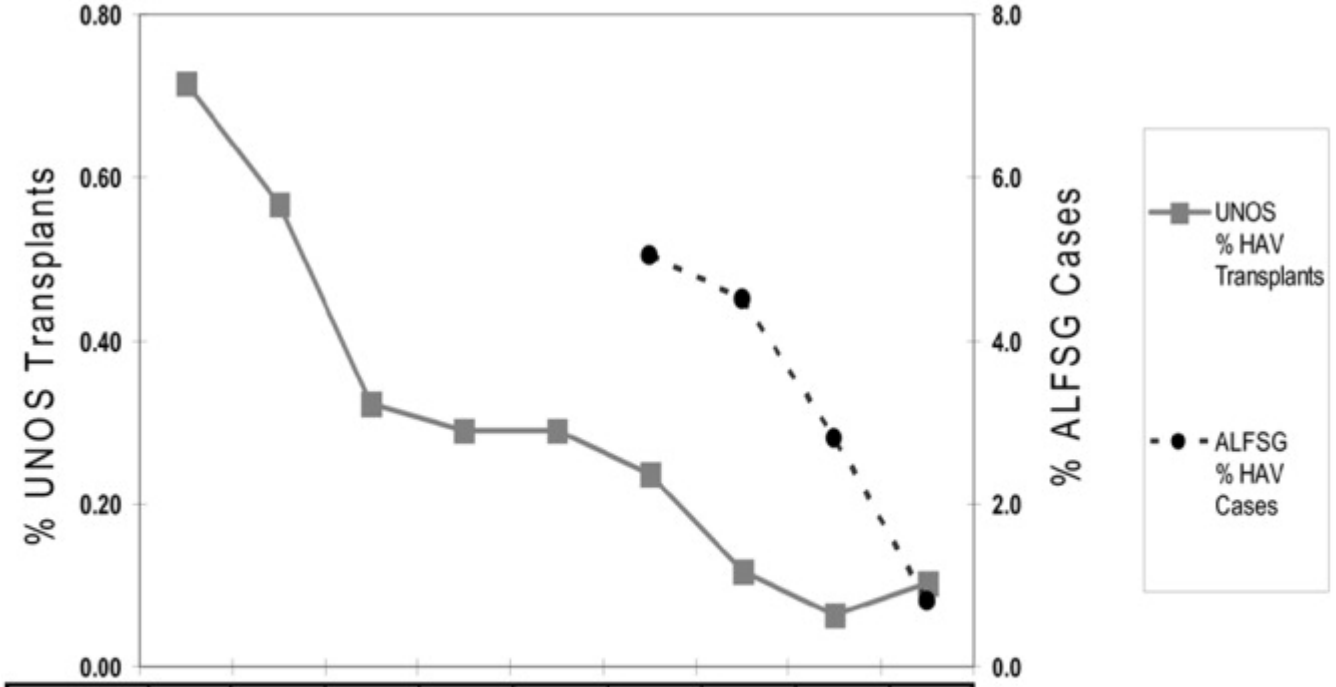
**Kim JM et al. Korean J Hepatol 2008;14:474*





*Acute Liver Failure (US)/ Hepatology 2008;47:1401

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

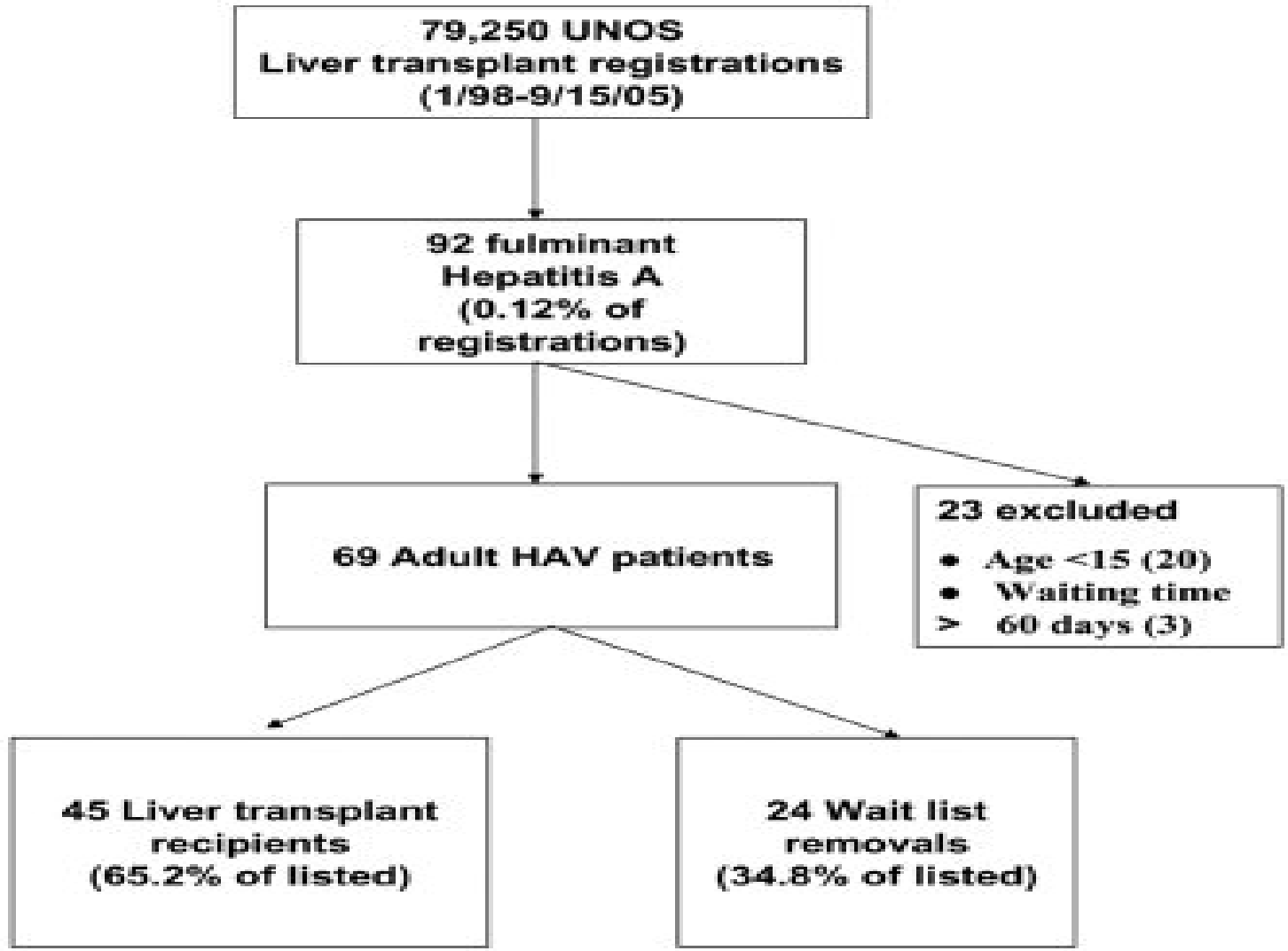


Year	88-89	90-91	92-93	94-95	96-97	98-99	00-01	02-03	04-05
UNOS HAV Transplants	28	32	21	22	24	22	12	7	11
ALFSG HAV Cases	-	-	-	-	-	9	10	8	2

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) .

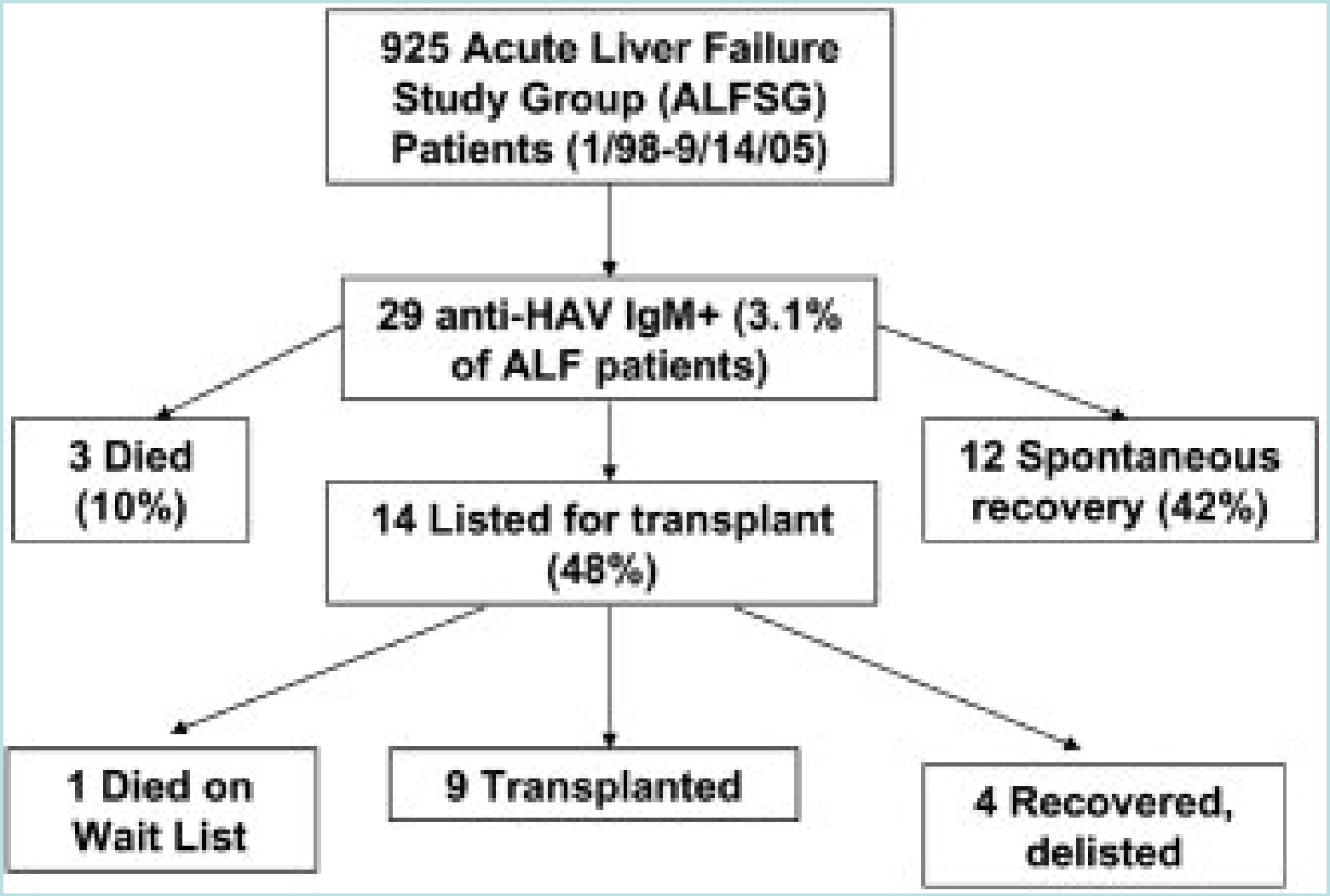
**Taylor RM et al. Hepatology 2006;44:1589*

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



*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

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 hepatotrophic 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 hepatotrophic 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

Vento S et al. NEJM 1998;338:286

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

- Incidene 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-cariers

*Chu CM, Liaw YF. Infection 2005;33:136

Search for host and viral factors associated with an increased risk for developement 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 mutivariate analysis

**Rezende G et al. Hepatology 2003;38:613*

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

Model	n	Sensitivity	Specificity	PPV	NPV	AURO
ALFSG index*						
≥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
Other models						
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

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Fujiwara K. et al. Dig Dis Sci 2000;45:2422
Fujiwara K et al. J Hepatol 200135:112
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

**Munne MS et al.Liver Int 2008*

Putative Host Factors (Familial Clustering)*

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

**Durst RY et al. J Clin Gastroenterol. 2001;32:453*

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