Hepatitis C and renal disease: An overview

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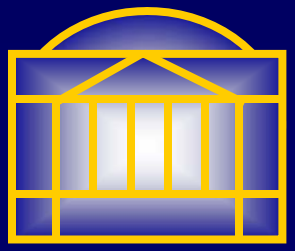
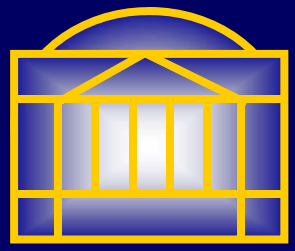




Disclosure of Financial Relationships

No Disclosures

Hepatitis C and renal disease

- Basic HCV virology and epidemiology
- Impact of HCV on patients with ESRD
- Role of hepatoma screening
- HCV associated renal disease

HCV: A primer

Characteristics of Hepatitis A, B and C

	Hepatitis A	Hepatitis B	Hepatitis C
No of acute inf. in the US/yr	• 179,000	• 185,000	• 38,000
No of chronic infected persons	• - - - - -	• 1,250,000	• 2,700,000
No of chronic infected persons in the world	• - - - - -	• 350 Million	• 170 Million
Treatment	• None	• IFN alpha, lamivudine, adefovir	• IFN alpha+RBV
Prophylaxis	• Vaccine, immune globulin post exposure	• Vaccine, Hep B immune globulin post exposure	• None

Lauer GM, Walker BD, NEJM 2001

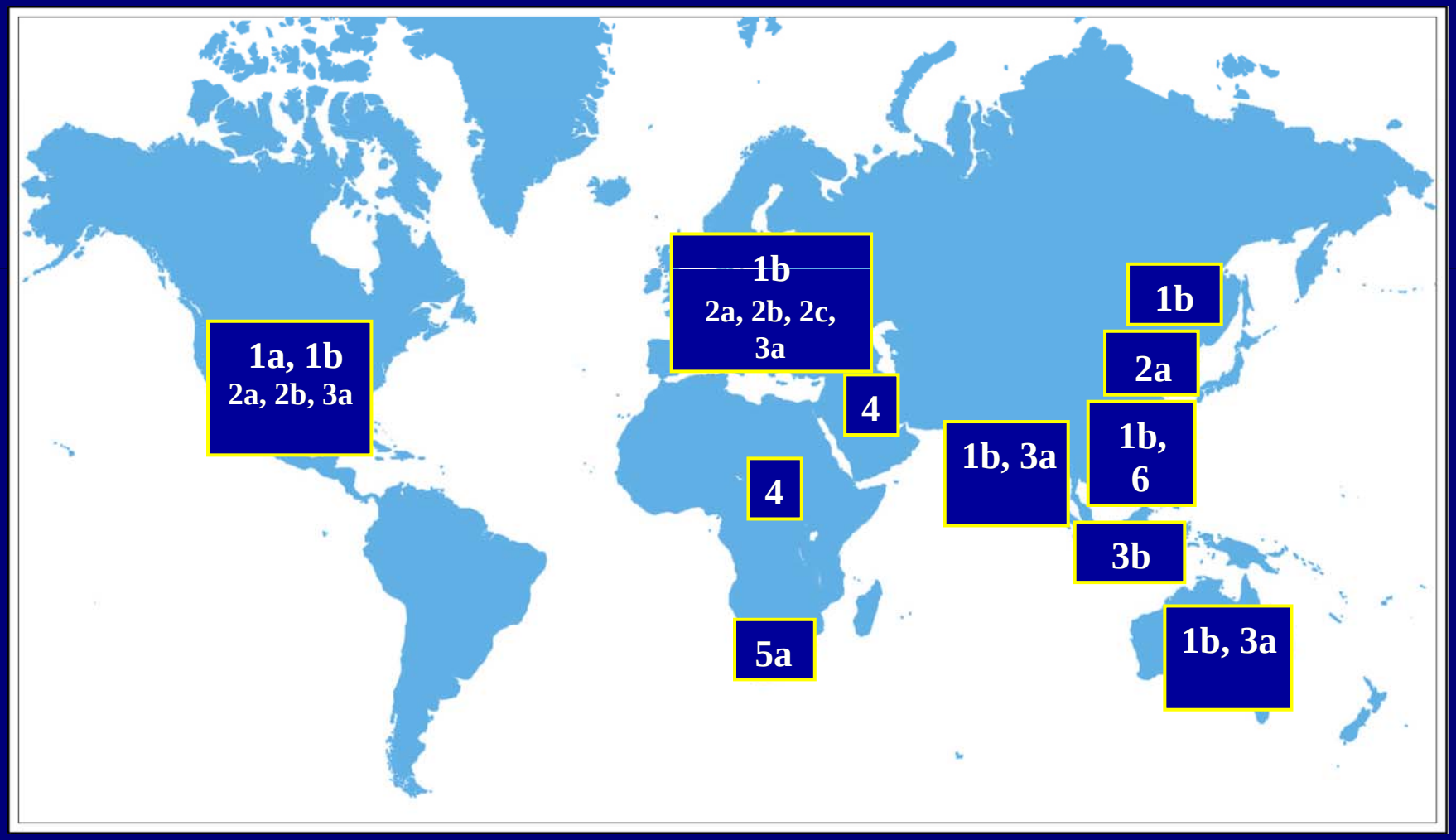
Hepatitis C Virus Infection:
United States

• New infections (cases)/year 1985-89	242,000
1997	38,000
• Deaths from acute liver failure	Rare
• Persons ever infected (1.8%)	3.9 million (3.1- 4.8)*
• Persons with chronic infection	2.7 million (2.4 - 3.0)*
• HCV-related chronic liver disease	40% - 60%
• Deaths from chronic disease/year	8,000 - 10,000
• Liver Transplants**	
– Number	~2,000/year

*95% Confidence Interval
**UNOS, 1999l
Source: CDC/Hepatitis Branch

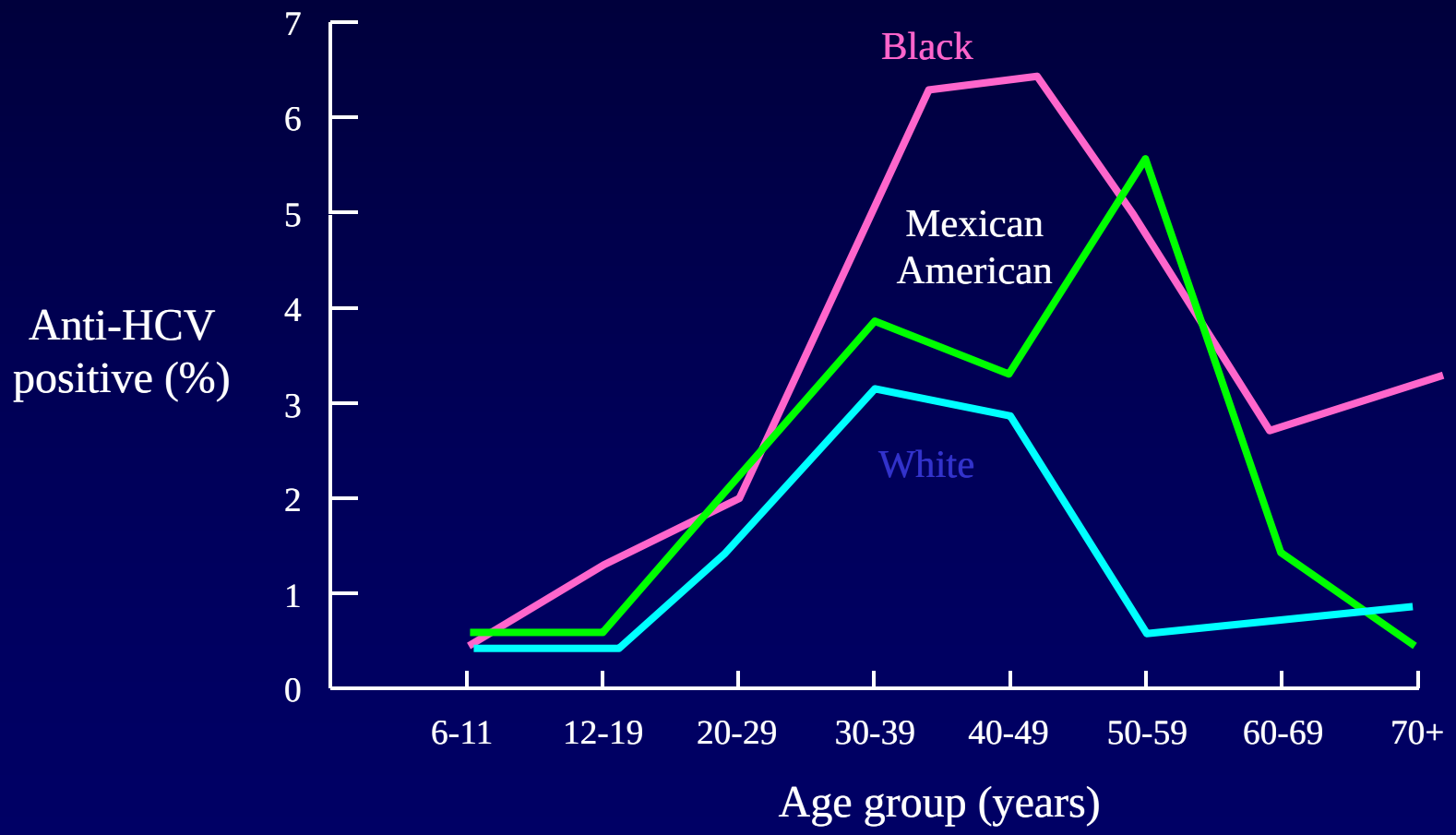
HCV Infection

Genotype Distribution



Adapted from Fang J. *Clin Liver Dis*. 1997;1:503.

Prevalence of HCV Infection, United States, 1990



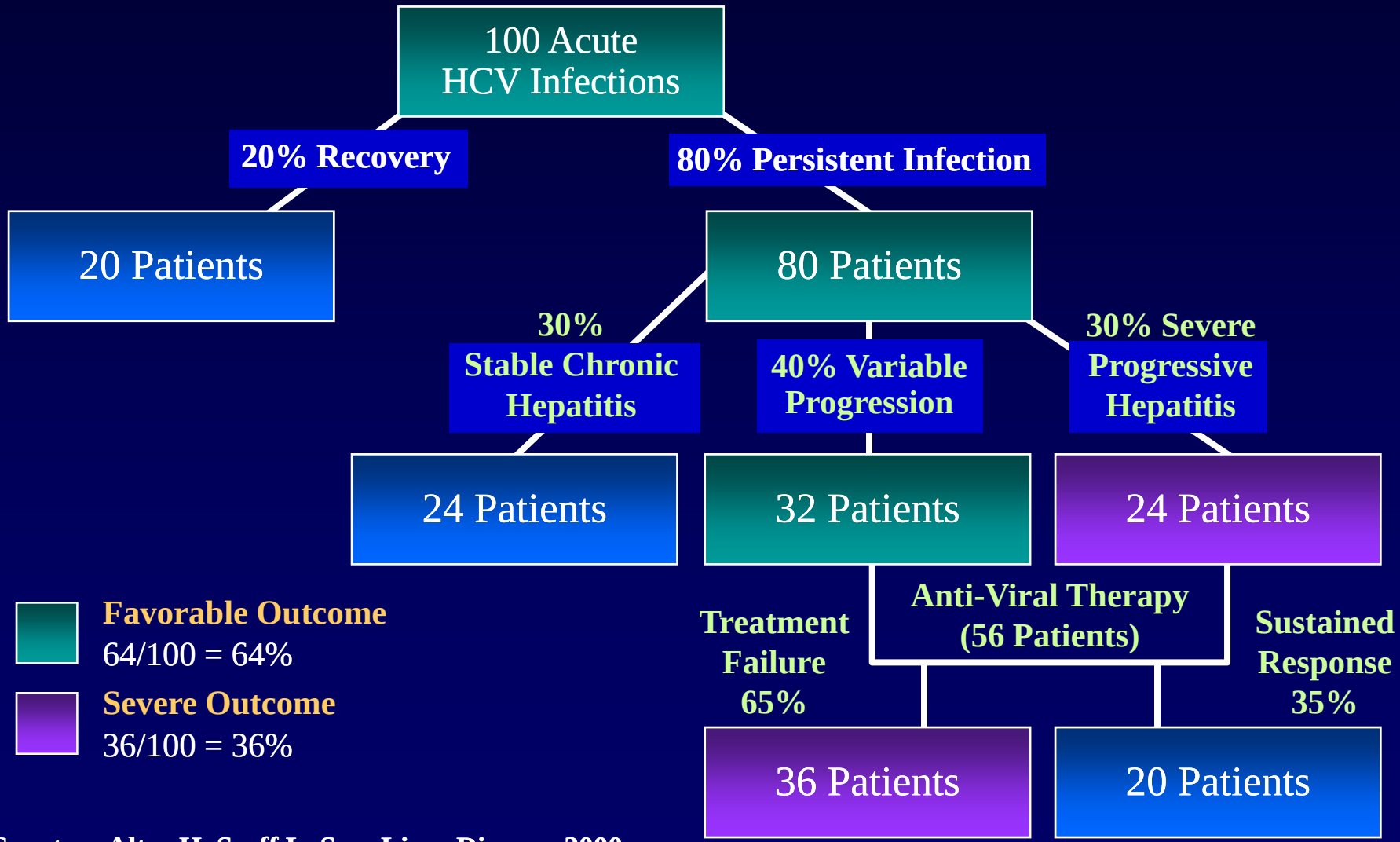
Adapted from Centers for Disease Control and Prevention. *MMWR*. 1998;47(RR-19):4.

Groups at Increased Risk

Group	Average Prevalence
• Persons who have ever injected illegal drugs	~80%
• Clotting factor recipients (before 1987)	~85%
• Transfusion or solid-organ recipients (<July 1992)	~5%
• Long-term hemodialysis patients	~10%
• Persons with high-risk sexual behavior	~5%
• Incarcerated	~30%

Centers for Disease Control and Prevention. *MMWR*. 1998;47(RR-19):5,8.

Natural History of Hepatitis C Virus Infection in General Population



Courtesy Alter H, Seeff L. Sem Liver Disease, 2000

Risk Factors for Accelerated Progression to Fibrosis/Cirrhosis

- Modifiable
  - Alcohol consumption
  - ?Hepatic steatosis, insulin resistance
- Non-modifiable
  - Increased age at infection
  - Longer duration of infection
    - Mean time to cirrhosis is ~20-25 years
  - Male gender
- Co-infection with HIV (25% vs. 6.5% HCV alone) or HBV
- Viral load, HCV Genotype ***not*** associated with progression

Poynard T et al. *Lancet*. 1997;349:829.

HCV in patients with ESRD: Diagnostic testing

Diagnostic testing in HCV

- 3rd generation EIA
  - 95+ % sensitivity and specificity
- Transcription mediated assays
  - Able to detect HCV RNA down to <10 IU/mL
  - Typical viral load in ESRD patients in the 100,000 IU/mL range
- Genotyping typically successful when viral load > 1000 IU/mL

Diagnostic testing for HCV in MHD

TMA-Transcription Mediated Amplification

EIA-Enzyme Immunoassay

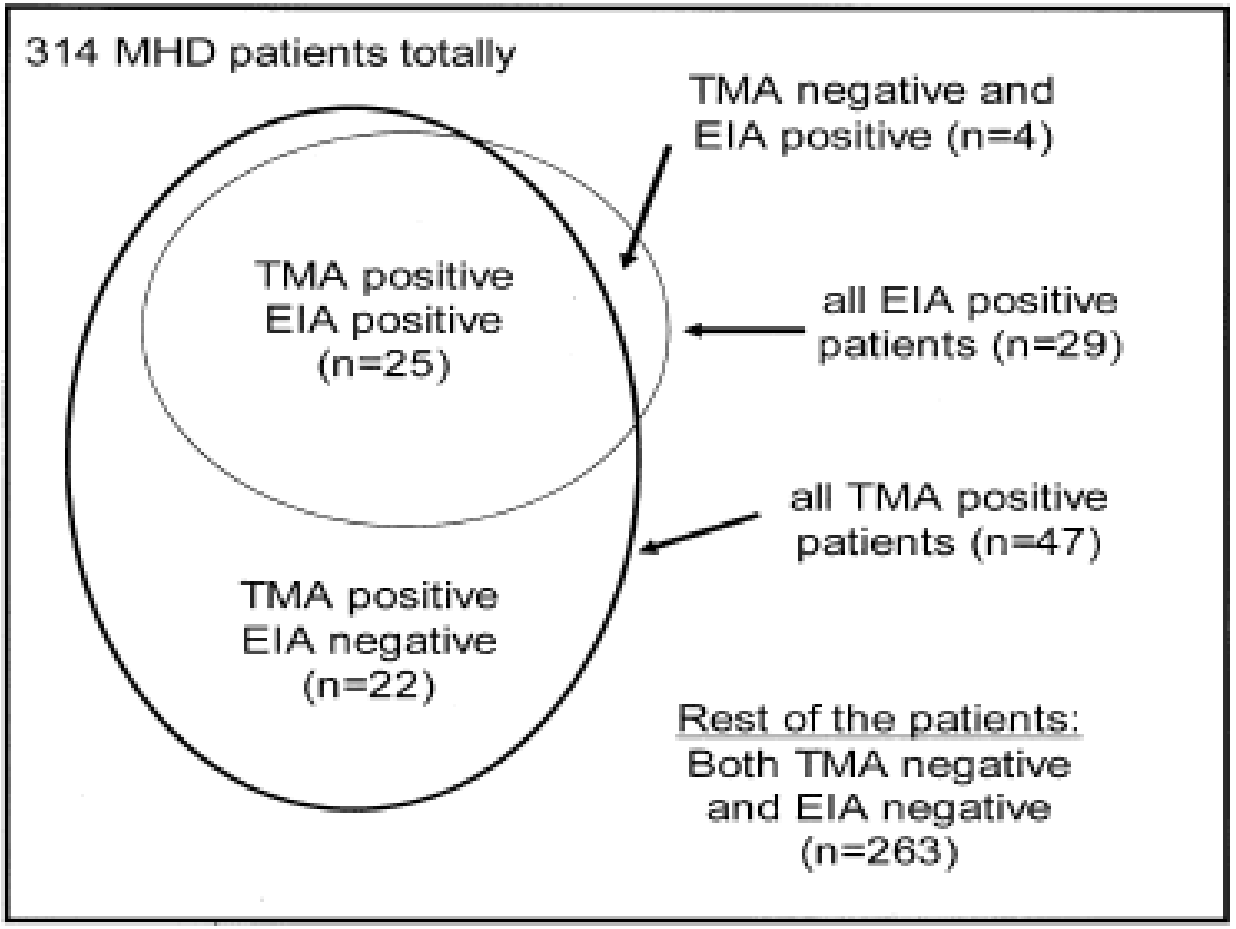


Fig 1. Diagnostic tests for HCV infection in 314 MHD patients.

Kalantar-Zadeh et al., Am J Kidney Dis 2005;46:290-300-UCLA

Diagnostic testing for HCV in ESRD

Table 1. Comparison of the TMA and EIA Diagnostic Tests for HCV Infection

	TMA^+	TMA^-	
EIA^+	25 (8)	4 (1)	29 (9)
EIA^-	22 (7)	263 (84)	285 (91)
	47 (15)	267 (85)	314 (100)
		Sensitivity (%)	Specificity (%)
EIA^+ (TMA as reference)		53	99

Kalantar-Zadeh K et al., Am J Kidney Dis 2005;46:290-300-UCLA

Prevalence of HCV in RRT

	HBV	HCV
Netherlands		2.9-3.4%
Switzerland	1.5%	5%
Germany	4.6%	7%
Spain	2.8%	19-30%
Italy	4.3%	47-60%
USA	2.4%	8.4%
Brazil	12-45%	11-26%
Saudi Arabia		68%
Japan	2.1%	27%

Fehr T, Ambuhl PM. Nephrol Dial Transplant 2004;19:1049-1053

Testing for HCV in ESRD: KDIGO Recommendations

- 1.1.2 Testing for HCV should be performed in patients on MHD and kidney transplant candidates (Strong)
  - CDC recommends EIA testing
  - NKF-KDOQI recommends EIA in low prevalence centers/populations, NAT testing in high prevalence centers/populations
  - Must take into account individual patient risk factors as well-?EIA for low risk patients, NAT for high risk patients

Gordon CE, et al., Am J Kidney Dis 2008;52:811-825

Testing for HCV in ESRD: KDIGO Recommendations

- 1.2.2 For patients on hemodialysis who test negative for HCV, retesting every 6-12 months with EIA should be considered (Moderate)
  - NKF-KDOQI concurs with role of EIA rather than more expensive NAT testing in conjunction with monthly LFTs
  - NKF-KDOQI: Optimal frequency of follow-up testing in US HD units requires further study
  - Consistent with CDC recommendations

Gordon CE, et al., Am J Kidney Dis 2008;52:811-825

Testing for HCV in ESRD: KDIGO Recommendations

- **1.2.3 Testing for HCV with NAT should be performed for hemodialysis patients with unexplained abnormal transaminase levels (Strong)**

Testing for HCV in ESRD: KDIGO Recommendations

- 1.2.4 If a new HCV infection in a hemodialysis unit is suspected to be nosocomial, testing with NAT should be performed in all patients who may have been exposed (Strong)

- Repeat testing with NAT is suggested within 2-12 weeks in initially NAT-negative patients (Weak)

Gordon CE, et al., Am J Kidney Dis 2008;52:811-825

Clinical outcomes of HCV infection in ESRD

Histologic findings in HCV and ESRD

Table 2. Histopathologic changes among hemodialysis and normal renal function patients

Variable	Group with ESRD (n = 36) [mean ± SD (range) or n (%)]	Group with NRF (n = 37) [mean ± SD (range) or n (%)]	p
Fibrosis staging			
0	19 (52.8)	10 (27)	0.025[a]
1	11 (30.6)	15 (40.5)	
2	4 (11.1)	7 (19.5)	
3	2 (5.5)	5 (13)	
4	0 (0)	0 (0)	
Inflammatory activity			
0	14 (39)	6 (16.2)	0.003[a]
1	12 (33.3)	9 (24.3)	
2	10 (27.7)	15 (40.5)	
3	0 (0)	7 (19)	
Steatosis			
yes	6 (16.3)	21 (56.8)	<0.001[a]
no	30 (83.3)	16 (43.2)	

Trevizoli JE et al., Clin J Am Soc Nephrol 2008;3:1385-1390

Spectrum of liver disease in HCV positive dialysis patients

Reference	No. of pts	Normal ALT	Bridging fibrosis	Cirrhosis
Caramelo	33	21%	3%	9%
Pol	17	69%	NR	12%
Sterling	50	96%	11%	11%
Glicklich	22	59%	5%	0%
Martin	37		8%	24%
Cotler	46	74%	5%	9%
Roth	152		5%	5%

Adapted from Meyers CM, Seeff LB et al. Am J Kid Dis 2003:42:632-657

Liver biopsy in ESRD

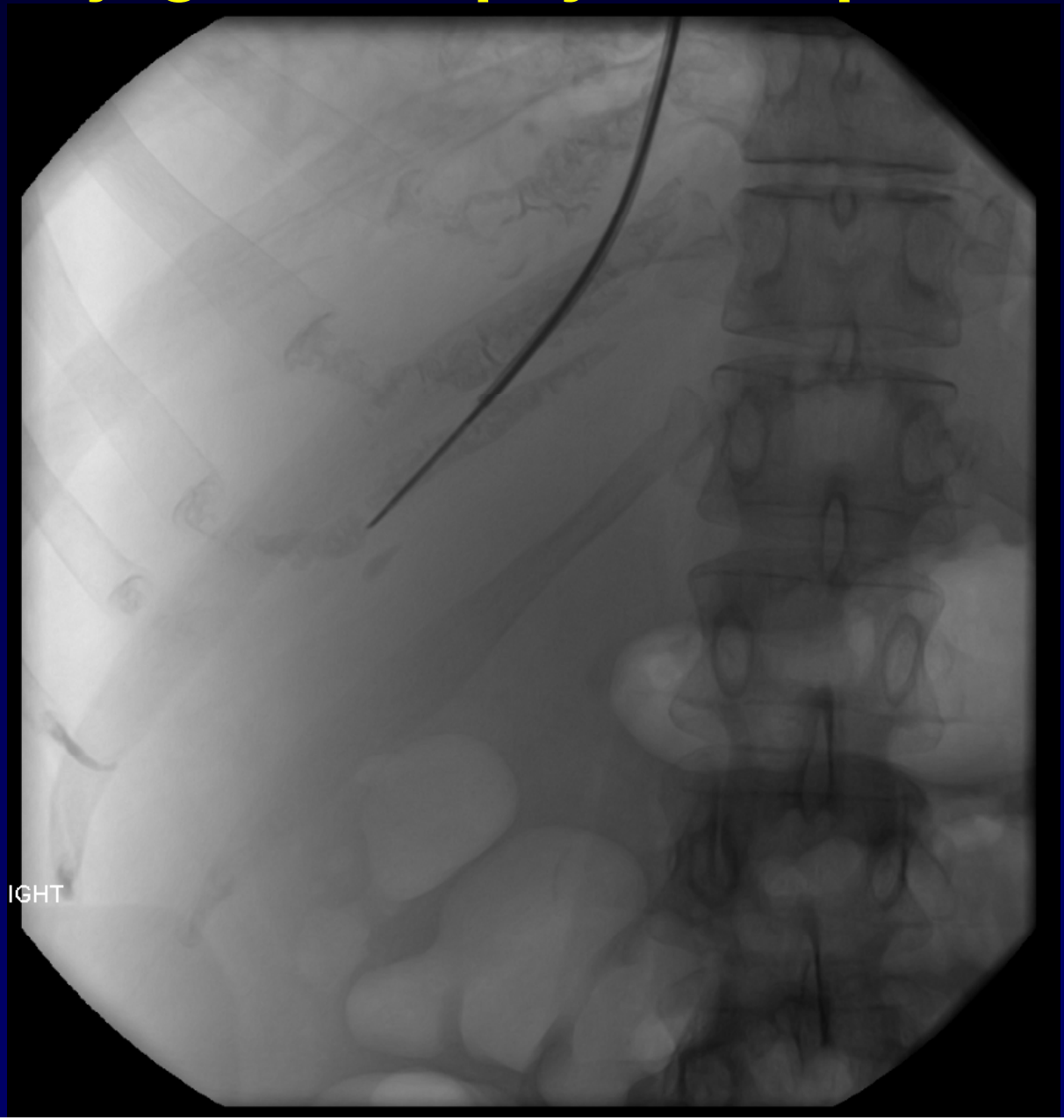
- Only reliable method to determine histology
- Risks appear comparable to non-ESRD patients (~1% complication rate)
- Use of DDAVP controversial, and without significant data to support
  - We do not use it any longer
- We recommend non-heparin dialysis day after procedure
  - Others recommend no heparin day before and day after procedure (i.e. Penn)
  - Data to support either approach limited to anecdotes

Pawa S et al., Clin Gastro and Hepatol 2007;6:1316-1320

"Patients on chronic hemodialysis should be well dialyzed prior to liver biopsy and heparin should be avoided if at all possible" (Class I, Level C)

Rockey et al., Hepatology 2009;3:1017-1044.

Transjugular biopsy in PD patients?



General care of the HCV infected renal patient

- Alcohol avoidance
- Vaccination for HAV and HBV when appropriate
- Avoidance of chronic marijuana usage
- Control of obesity/insulin resistance
  - ? If applicable in ESRD
- Consideration of hepatoma screening in patients with bridging fibrosis or cirrhosis
  - No data in ESRD
  - Practice guidelines recommend AFP and imaging q 6-12 months in patients with stage 3 or 4 fibrosis

Bruix J and Sherman M, Hepatology 2005;42:1208-1236.

HCV and renal disease

HCV associated rheumatologic diseases

- Cryoglobulinemia
- Sjogren's syndrome
- Fibromyalgia
- Membranoproliferative GN
- Membranous GN
- Antiphospholipid antibody syndrome
- ?SLE

Autoantibodies in HCV

- ANA 10-30%
- ASMA 60-70%
- RF 60-80%
- Anticardiolipin Abs 22%
- Antithyroid Ab 42%

McMurray et al, Rheum Clin N Am 1998

HCV and cryoglobulinemia

- Essential mixed cryoglobulinemia (type II)
  - Not essential anymore
  - >90% related to chronic HCV infection
- Cryoglobulins consist of:
  - Rheumatoid factor
  - IgG
  - HCV specific antibodies
  - HCV protein

Agnello V, Chung RT, Kaplan LM NEJM 1995;327:1490-1495

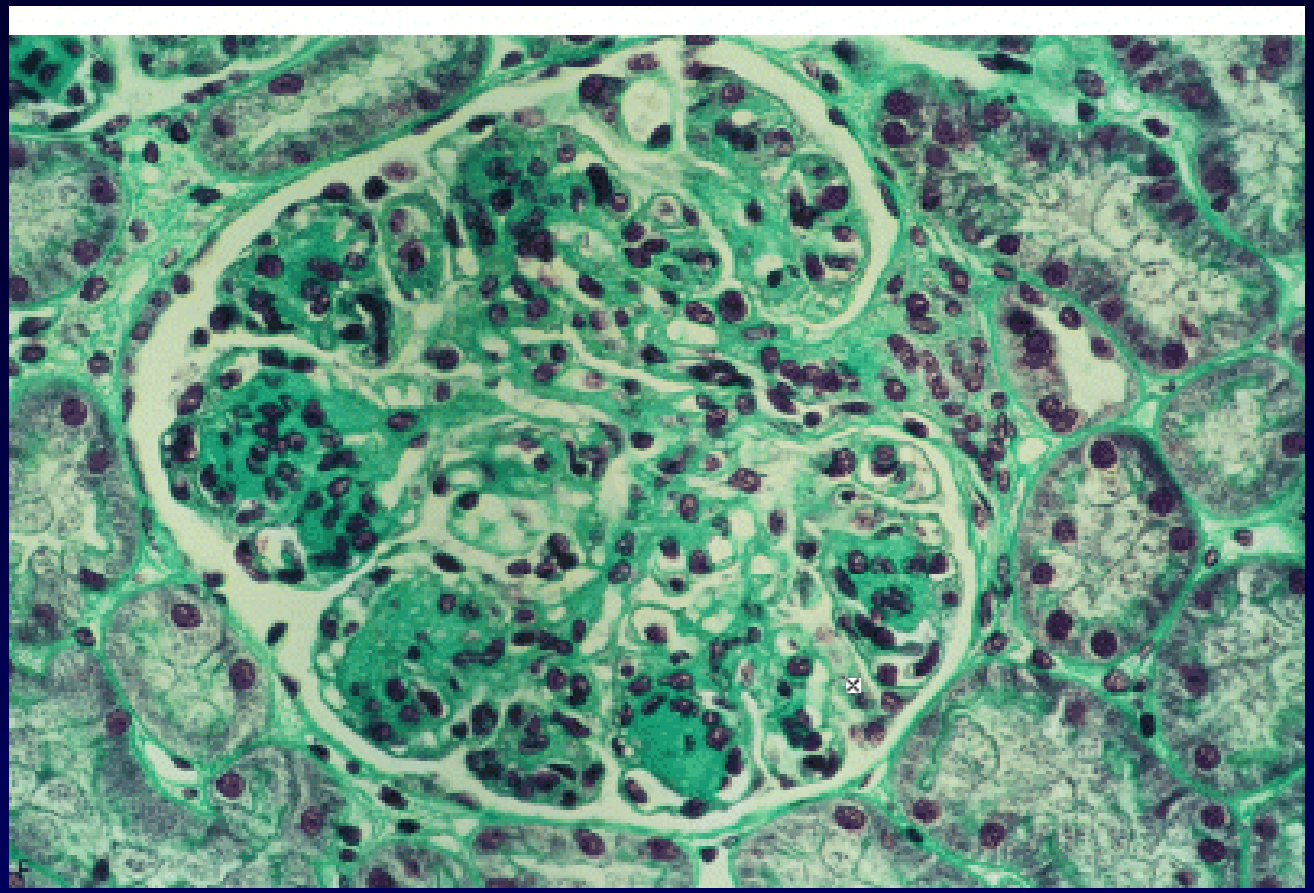
HCV and cryoglobulinemia

- B cell mediated
  - thus may respond to rituximab
- Cryoglobulins present in up to 50% of unselected HCV patients
  - Typical cryocrit < 3%
- Symptomatic cryoglobulinemia occurs in ~1% of chronic HCV patients
  - Cryocrit tends to be higher
- Leukocytoclastic vasculitis, purpura, neuropathy, renal disease

HCV and MPGN

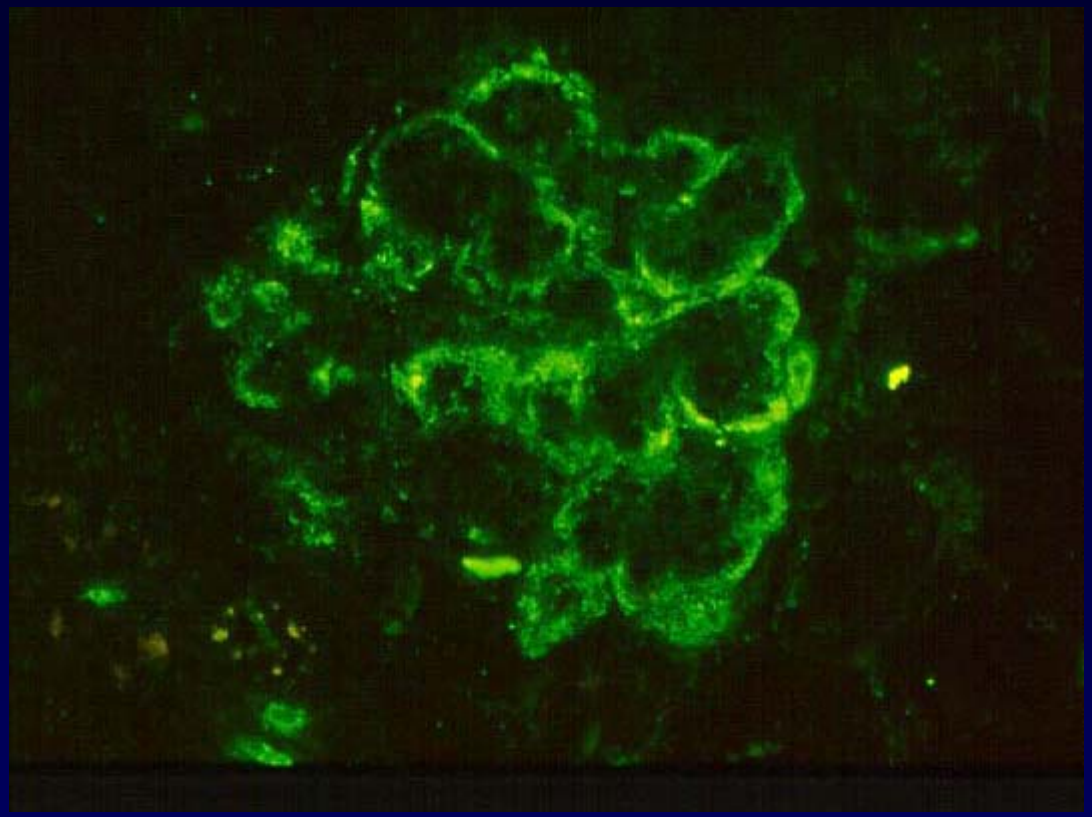
- HCV major cause of MPGN
- Associated with longstanding HCV
- Liver disease often mild or clinically not apparent
- Cryoglobulins present 50-70% of cases, but other systemic manifestations may be absent
- HCV Ab (ELISA) positive
- HCV RNA measurable
- Complement low
- RF positive

Meyers CM, Seeff LB et al. Am J Kid Dis 2003:42:632-657



A membrano-proliferative pattern, with intense mesangial proliferation and peripheral expansion associated with centrolobular sclerosis (lobular MPGN) is evident. Moderate endocapillary infiltration of mononuclear leukocytes also is present (Masson trichrome x 250).

Kidney International 1998;54:650-671



Immunofluorescence staining for C3 in MPGN

Therapy of HCV MPGN

- Treat the HCV!
- Published results poor
  - Bulk of published data used suboptimal pharmacologic therapy
  - Virtually no data on PEG-IFN/ribavirin
  - Results should parallel HCV outcomes and should be much better than older reports (more from Bob Brown in a few minutes)
- Need to be careful with ribavirin dosing in renal insufficiency

Summary

- HCV common in patients with ESRD and transplant recipients
- Diagnostic testing in MHD patients challenging and not optimally worked out
- Advanced HCV relatively uncommon in ESRD
- HCV an infrequent but recognized cause of renal disease
- Excess deaths in HCV renal transplants due to liver disease - **DON'T IGNORE IT!**
- Therapy of HCV in ESRD and post-transplant challenging but improving

Questions?