Liver and the Kidneys

APSN/HKSN CME Course
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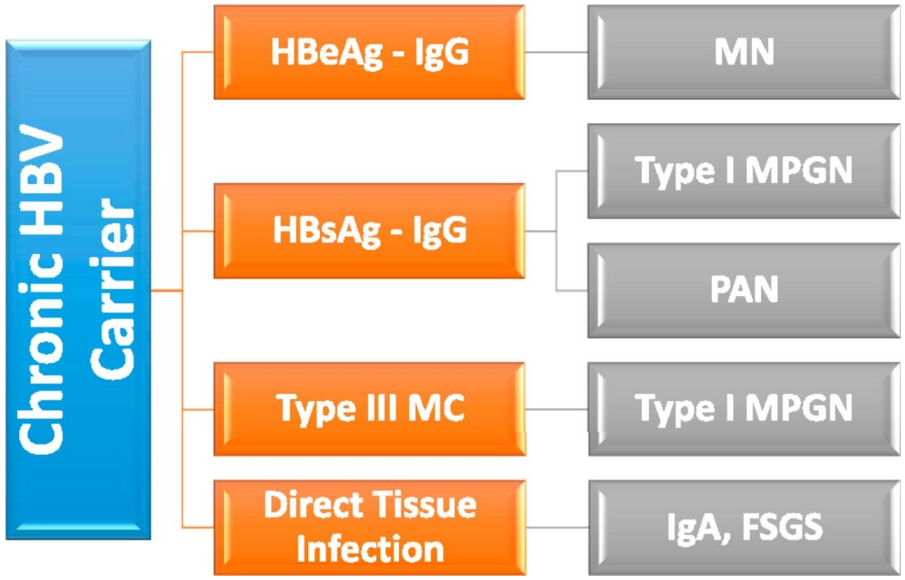
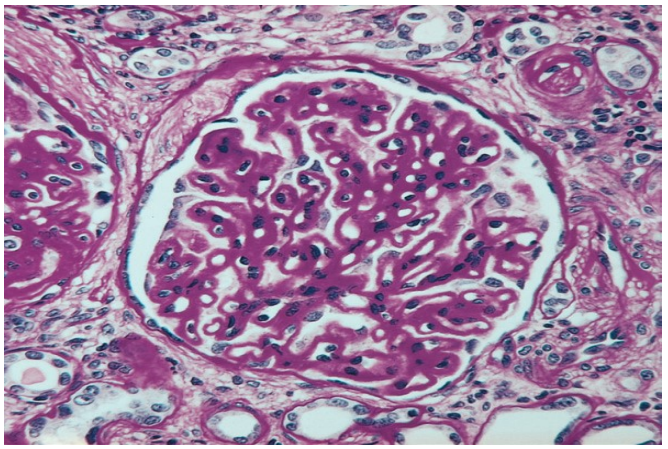
Liver & the Kidneys

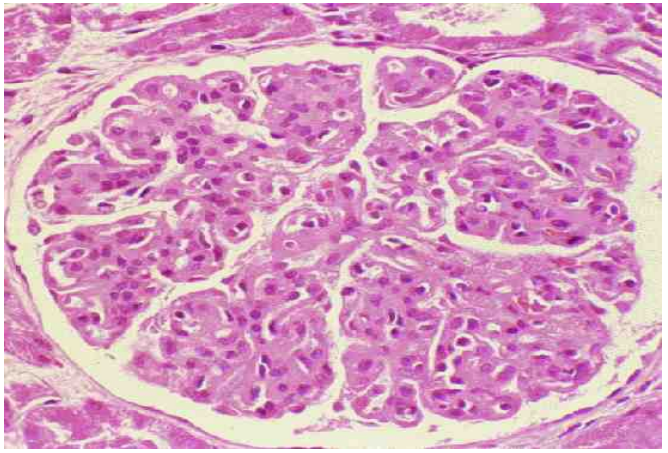
- **Liver & Kidneys** are two **vital** organs in the body
- **Disease in the liver** can have significant impact on the kidneys
- **Management of liver diseases** can be challenging in the face of renal failure
- **Viral hepatitis & kidneys**
  - Effect of viral hepatitis infection on kidneys
  - Management of chronic viral hepatitis infection (HBV, HCV & HEV) in renal failure patients
- **Hepatorenal syndrome (HRS)**
  - New insights on pathogenesis & management
  - Diagnosis & prediction

HBV & the Kidneys

HBV associated GN







HBV-associated membranous GN

- Spontaneous remission common in children but uncommon in adults

- Prognosis: 30% CKD; 10% ESRD after 5 yr FU

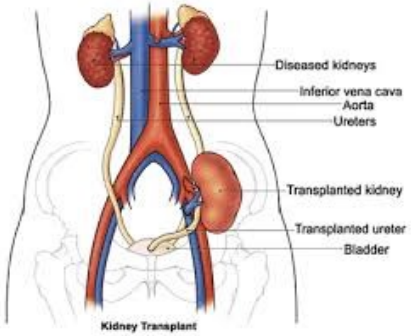
- Management
  - Poor response to IFN Rx;
  - Oral NA appeared to be effective (CR 40% & 60% at 6 & 12 months); 3-yr renal survival 100% vs. 58% (no Rx)
  - role of adding immunosuppressive Rx uncertain

Lai KN, et al. N Engl J Med 1991
Yi Z, et al. Ann Hepatol 2011
Zhang XY, et al. World J Gastroenterol 2012
Tang S, et al. Kidney Int 2005
Sin SK, et al. Kor J Nephrol 1999

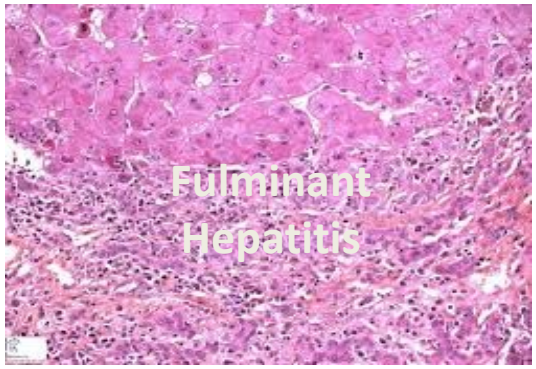
Management of Chronic HBV infection in kidney transplant recipients

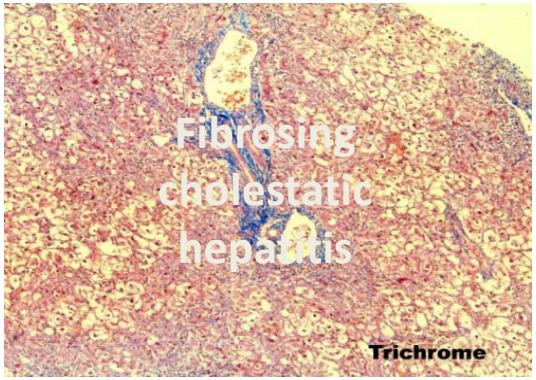
Chronic HBV infection in renal transplant recipients

- Chronic HBV infection associated with adverse outcomes in kidney transplant recipients (KTRs)

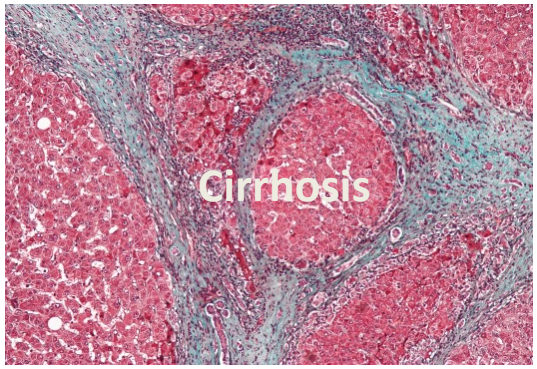


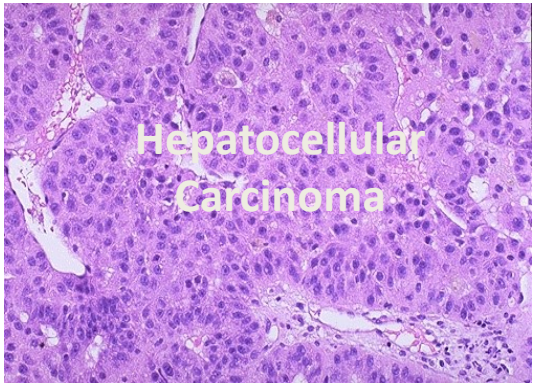
Early Complications





Late Complications





Chan TM et al. Gastroenterology 1998
Fornairon S et al. Transplantation 1996
Mathurin P et al. Hepatology 1999
Cheung CY et al. Renal Failure 2014

Available options for HBV infection

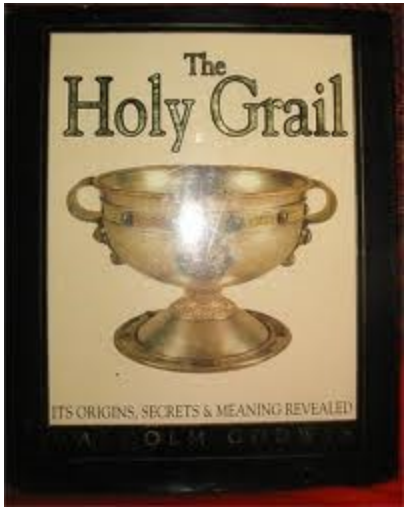
- Interferon (IFN)
  - Low efficacy
  - Precipitate graft dysfunction

- Oral nucleoside/tide analogues (NA)
  - Lamivudine (LAM)
  - Adefovir (ADV)
  - Entecavir (ETV)
  - Tenofovir (TDF)
  - Telbivudine (TBV)

Rostaing L et al. Nephron 1996
Durlik M et al. Transplant Int 1998

Anti-viral Rx in KTR

- Ideal antiviral Rx in KTR
  - High efficacy
  - Low resistance rates
  - Prevent short- and long-term hepatic complications !
  - Lack of nephrotoxicity (?Reno-protective effects)



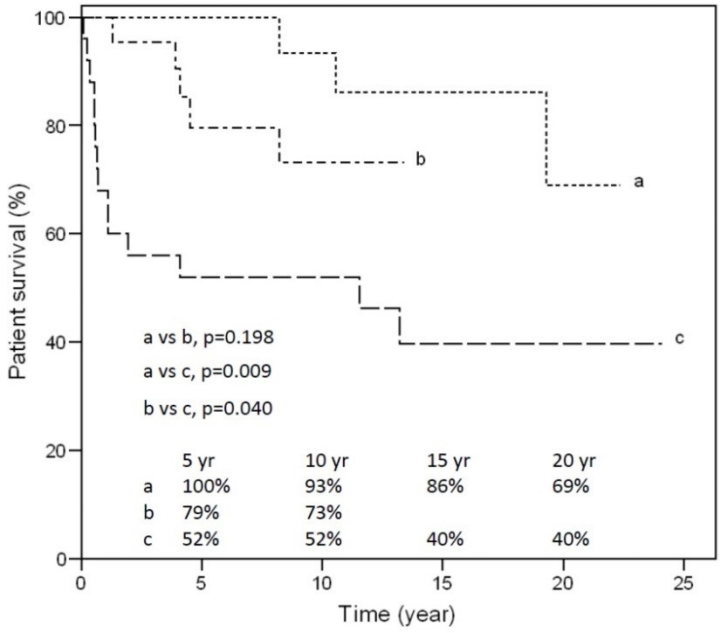
Lamivudine (LAM) in KTR

- First oral NA available
- Most extensive efficacy and safety data in KTR
- Effectively suppress HBV DNA and improve LFT
- Meta-analysis (at 14 months):
  - HBV undetectability: 91%
  - HBeAg clearance (27%)
  - ALT normalization (81%)
  - LAM-resistance (18%)
- Long-term outcome data also available
- Relatively lower costs

Chan TM et al. Hepatology 2002
Chan TM et al. Am J Transplant 2004
Fabrizi F et al. Transplantation 2004
Fabrizi F et al. Am J Transplant 2005
Yap DY et al. Transplantation 2010

Long-term data of LAM in KTRs

Figure 5. Survival of HBsAg+ve kidney transplant recipients stratified according to lamivudine treatment. Patient survival was worst in those who underwent kidney transplantation prior to the availability of anti-viral therapy.

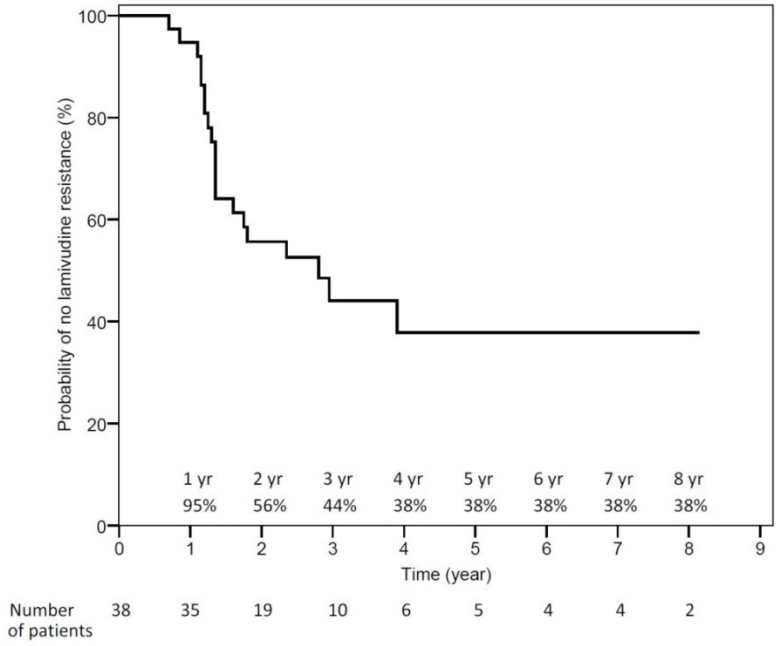


a = kidney transplantation before 1996 and treated with lamivudine, n=17

b = kidney transplantation after 1996 and treated with lamivudine, n=21

c = kidney transplantation before 1996 and not treated with lamivudine, n=25

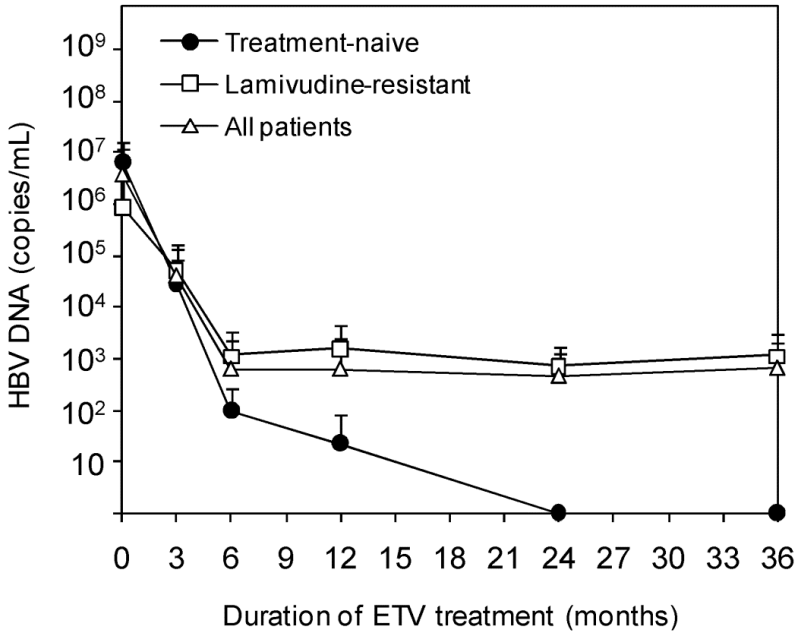
Figure 1. Relationship between the incidence of drug resistance and treatment duration in HBsAg+ve kidney transplant recipients treated with lamivudine.

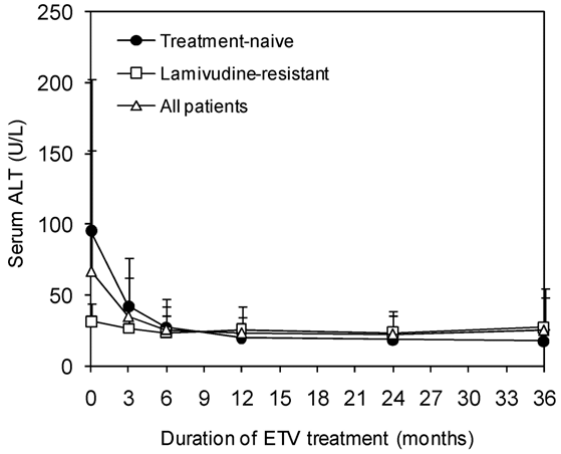


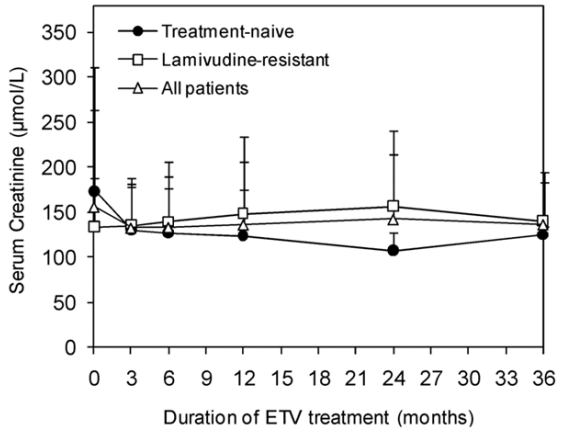
High risk of LAM-resistance
>60% after 5 years of Rx

Yap DY et al. Transplantation 2010

Entecavir (ETV) in HBsAg+ KTR





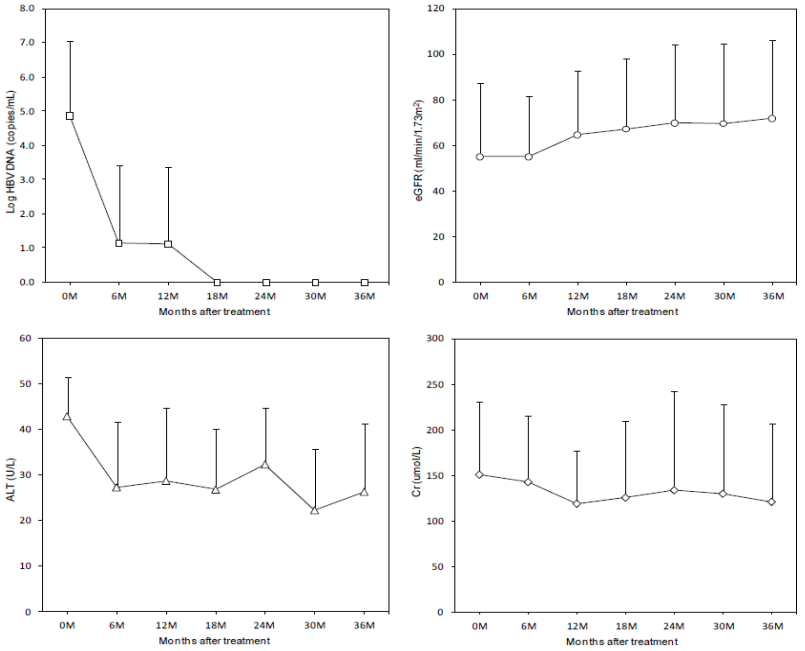


Genotypic resistance ~20% with ↑HBV DNA and ALT after 20±3.5 months in LAM-resistant cases

Yap DY et al. Clin Transplant 2014

Other NAs in HBsAg+ KTR

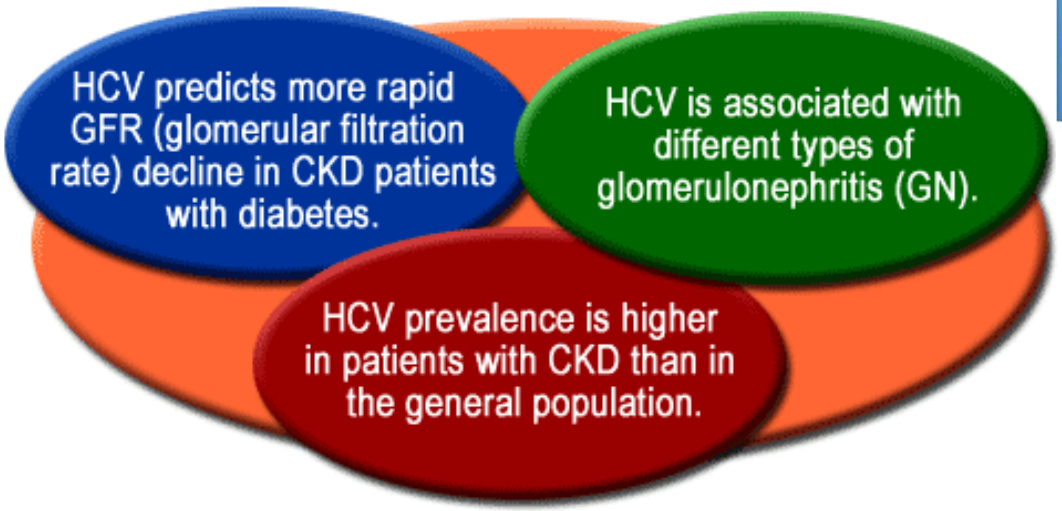
- Adefovir and Tenofovir:
  - nephrotoxic potential (e.g. 30-50% ADV-treated KTRs; some required discontinuation)
- Telbivudine
  - Promising anti-viral and renal profile



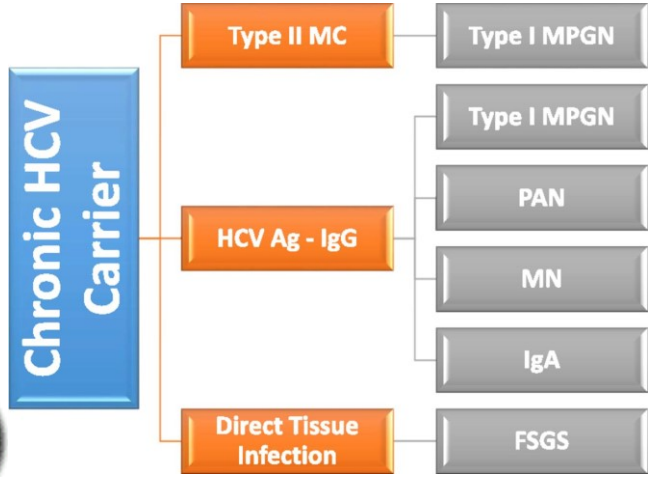
Fontaine H et al. Transplantation 2005
Lampertico P et al. Nephrol Dial Transplant 2011
Tse KC et al. Clin Transplant 2010
Daude M et al. Transplantation 2011
Yap DY et al. Nephrology (Carlton) 2014

HCV & the Kidneys

HCV and the Kidneys



High HCV RNA
Genotype 2



Tsai TL, et al. Kidney Int 2017
Kupin W, et al. C J Am Soc Nephrol 2016

Management of HCV-associated GN

- Depends on renal parameters & severe extra-renal complications

- Mild to mod UP, stable RFT
  - Anti-viral therapy (IFN/ribavirin/DAA)

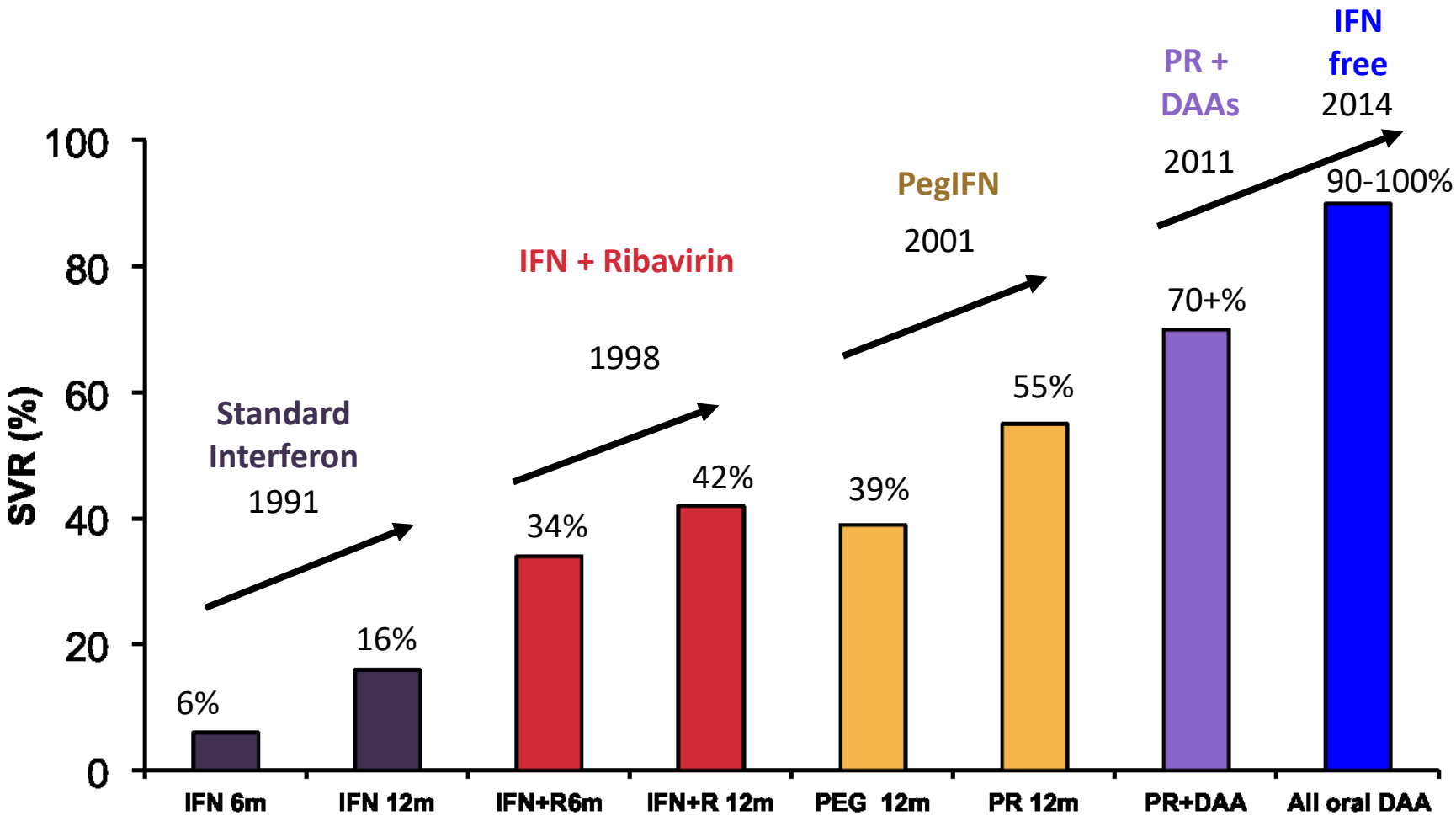
- Nephrotic-range UP, progressive renal deterioration, presence of severe extra-renal manifestations (e.g. pulmonary hemorrhage)
  ➔Immunosuppressive Rx
  - CYC
  - Steroids
  - Anti-CD20
  - Plasmapheresis
  - Anti-viral therapy

Ozkok A, et al. World J Gastroenterol 2014

Management of chronic HCV infection in renal failure patients

Milestones in Therapy of CHC: Average SVR Rates from Clinical Trials

SVR12 (HCV RNA neg 12wks after end of therapy)=cure

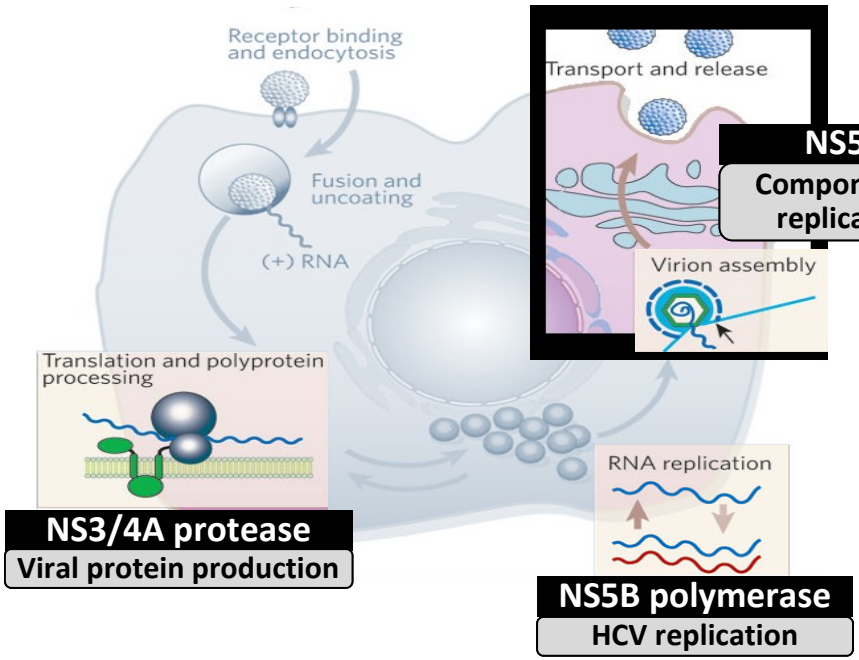


Adapted from US Food and Drug Administration,
Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring MD.

Most DAAs Currently in Development Target One of Three Viral Proteins: NS3/4A, NS5A and NS5B

NS3/4A protease inhibitors

- Glecaprevir (GLE)
- Asunaprevir (ASV)
- Boceprevir (BOC)
- Grazoprevir (GZV)
- GS-9857
- Paritaprevir (PTV)
- Simeprevir
- Sovaprevir
- Telaprevir
- Vedroprevir



NS3/4A protease
Viral protein production

NS5A protein
Component of the HCV replication complex

NS5B polymerase
HCV replication

NS5A inhibitors

- ACH-3102
- BMS-824393
- Daclatasvir (DCV)
- Elbasvir
- Velpatasvir (VEL)
- GSK2336805
- Ledipasvir (LDV)
- Ombitasvir (OBV)
- Samatasvir
- MK-8408
- Ravidasvir

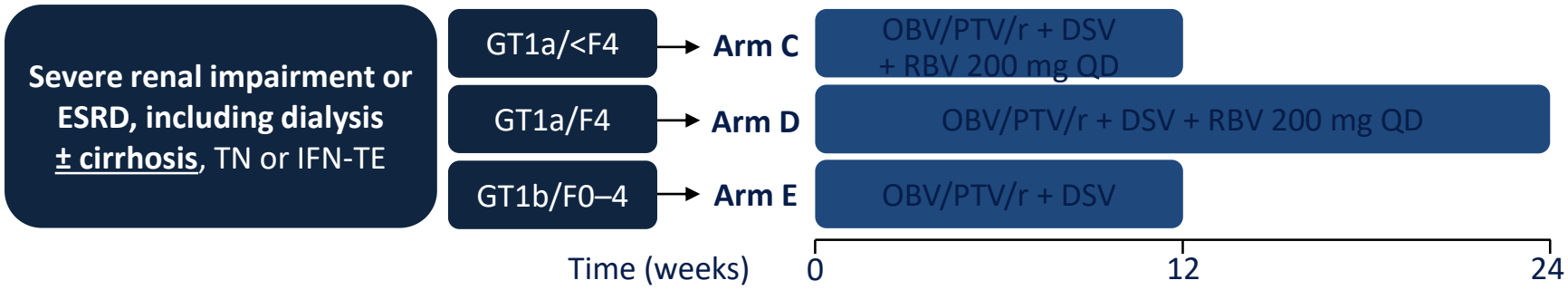
NS5B polymerase inhibitors

Nucleoside	Non-nucleoside	
MK-3682	Beclabuvir	PPI-383
Sofosbuvir (SOF)	Dasabuvir (DSV)	TMC647055

Abbvie
BMS
Gilead
Merck

Need at least ≥2 drugs of different classes for effective HCV regimen

#886, Vierling: RUBY-I: Safety and Efficacy of OBV/PTV/r + DSV ± RBV in GT1 Patients With Severe Renal Impairment or End-stage Renal Disease

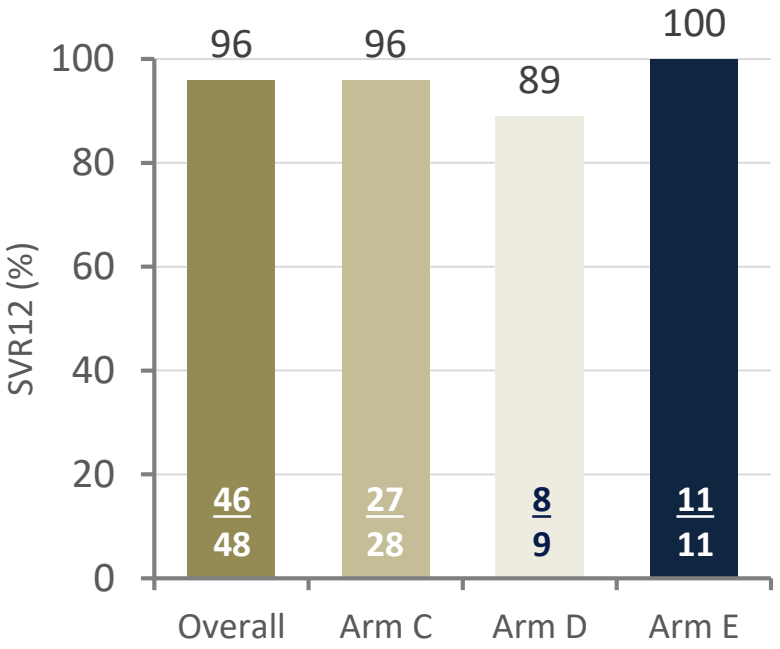


Demographics, n (%)	Patients (N=48)
Black	26 (54)
Cirrhosis F4	**15 (31)**
Stage 4/5 CKD	8 (17)/40 (83)
Hemodialysis	33 (69)

Safety, n (%)	Patients (N=48)
Any AE	41 (85)
Anemia	19 (40)
SAEs	13 (27)
Discontinuation	2 (4)

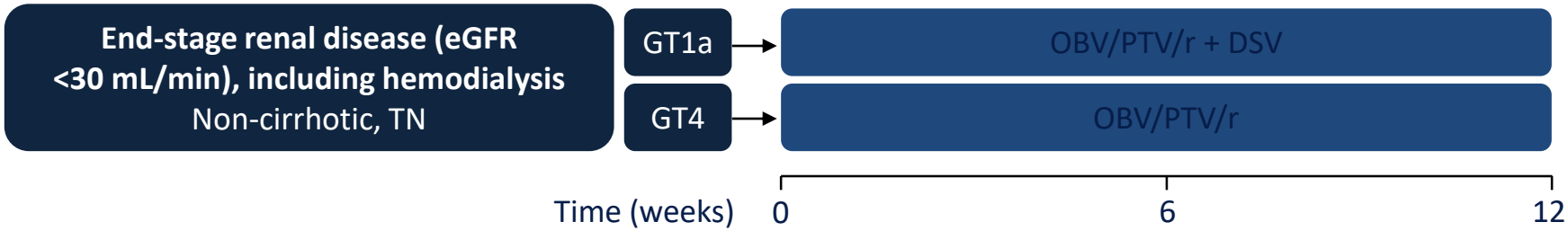
Anemia

- Occurred only in patients receiving RBV
- Mild: n=11; moderate: n=6; severe: n=2
- 2 patients required interruption of study drugs
- Erythropoietin: n=7; transfusion: n=2

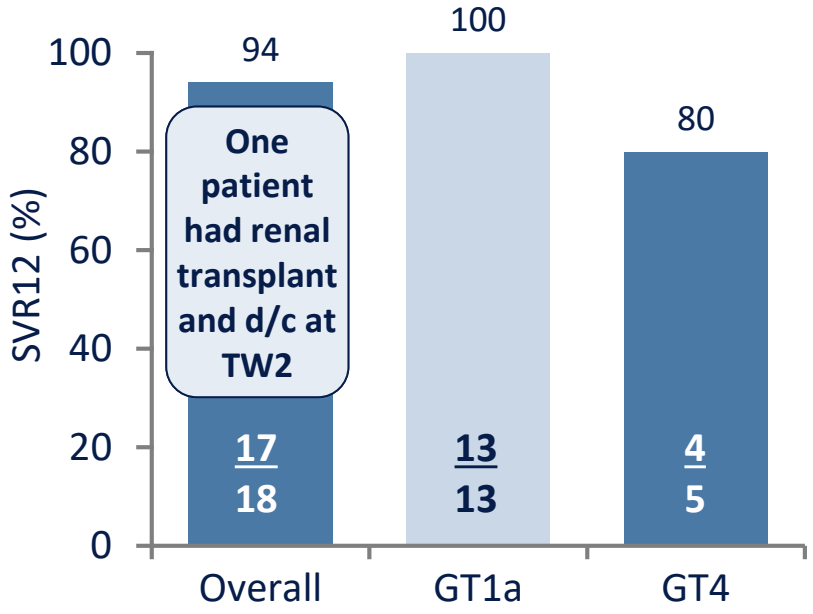


The data being presented may represent off-label data; please refer to your local country's approved label for specific prescribing information for OBV/PTV/r + DSV ± RBV

#935, Gane: RUBY-II: Efficacy and Safety of a RBV-free OBV/ PTV/r ± DSV Regimen in GT1a and GT4 Patients With Severe Renal Impairment or End-stage Renal Disease



Demographics	Patients (N=18)
GT1a/GT4	13 (72)/5 (28)
Dialysis	17 (94)



Safety, n (%)	GT1a (n=13)	GT4 (n=5)
Any AE	13 (100)	5 (100)
SAEs	3 (23)	1 (20)
AE leading to d/c	1 (8)*	1 (20)†
Hemoglobin, Grade ≥2 (<10 g/dL)	4 (31)	2 (40)
ALT, Grade 3 (>5–20 x ULN)	1 (8)	1 (20)
Total bilirubin, Grade ≥2 (>1.5 x ULN)	0	0

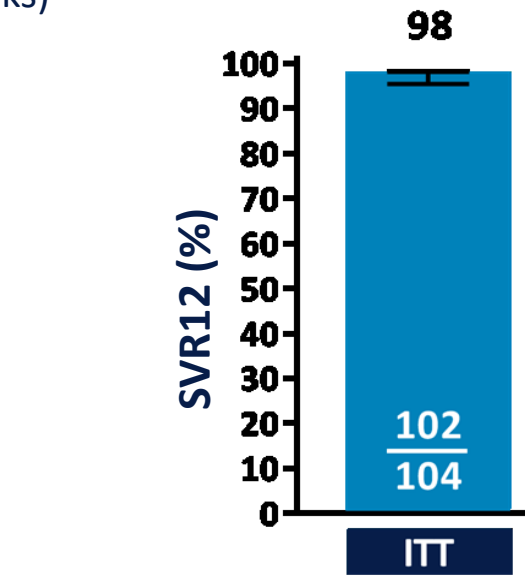
*Discontinued study drug but achieved SVR12

†Discontinued because of renal failure and transplant

The data being presented may represent off-label data; please refer to your local country's approved label for specific prescribing information for OBV/PTV/r + DSV ± RBV

#LB-11, Gane: EXPEDITION-IV: Safety and Efficacy of Glecaprevir/ Pibrentasvir in Adults with Renal Impairment and Chronic HCV GT1–6 Infection

Demographics	N=104
Treatment-experienced, IFN / SOF, n (%)	42 (40) / 2 (2)
Compensated cirrhosis, n (%)	20 (19)
HCV genotype, n (%) GT1a / GT1b / GT1 other GT2 GT3 GT4 / GT5 / GT6	 23 (22) / 29 (28) / 2 (2) 17 (16) 11 (11) 20 (19) / 1 (1) / 1 (1)
CKD stage 4 / 5, n (%) eGFR <15 mL/min/1.73 m², n (%) Dialysis, n (%)	13 (12) / 91 (88) 86 (83) 85 (82)



Breakthrough	0
Relapse	0
Discontinuation	1
LTFU	1

mITT - 100% SVR $_{12}$; No virologic failures

HEV & the Kidneys

Chronic HEV infection in kidney transplantation recipients

- HEV infection usually acute & self-limiting

- HEV infection in solid organ transplant recipients

  ➔ chronic hepatitis (66%); cirrhosis (~10%)

  Most data reported: genotype 3

Management:

Ribavirin monotherapy (genotype 3)

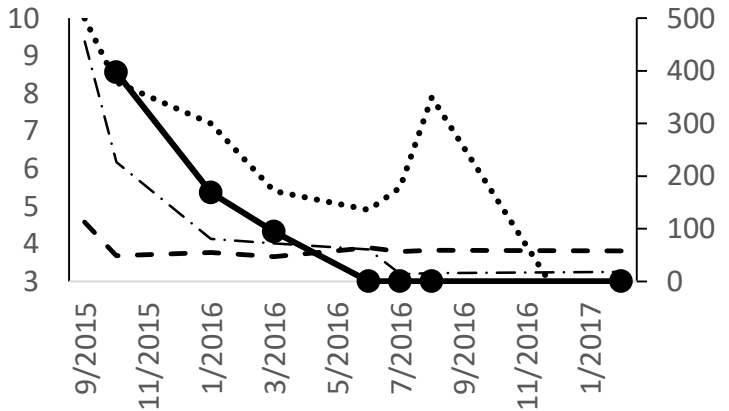
HEV clearance (95%); recurrence (18.9%); SVR (75%)

Main S/E: anemia

Kamar N et al. N Engl J Med 2008
Kamar N et al. Gastroenterology 2011
Kamar N et al. N Engl J Med 2014

Chronic HEV infection in kidney transplantation recipients – Local Situation

- 4 patients HEV IgM + out of 446 kidney transplant recipients (prevalence ~ 0.9%)
- Three progressed to chronic HEV infection (all genotype 4)
- Two showed good response to ribavirin
- One with poor response (K1383N mutation identified in the RdRp gene



Sidd S, Yap DY, Tang S, et al. J Vir Hepatitis 2017

Hepatorenal Syndrome (HRS)

Hepatorenal syndrome (HRS)

- Occurs in 10-20% patients with advanced cirrhosis

- High mortality without liver transplantation

Type 1 HRS:

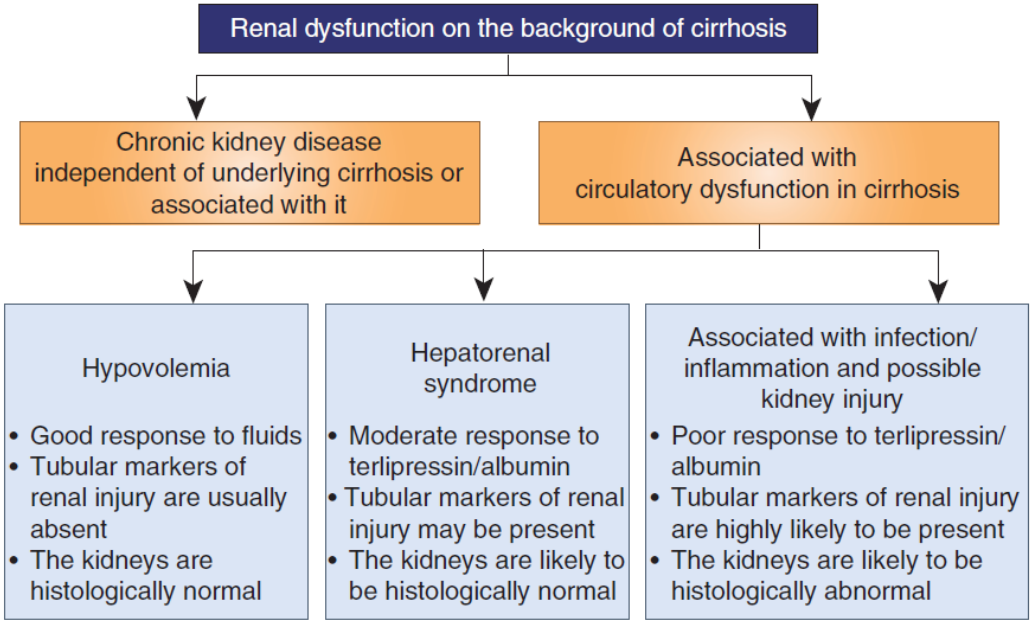
  - Rapid deterioration in renal function (doubling within 2 wks)
  - Mortality 80% in 2 weeks

Type 2 HRS:

  - Progressive course with moderate SCr to (133 mol/L)
  - Associated with ascites & refractory to diuretics
  - Median survival 4-6 months

Planas R, et al. Clin Gastroenterol Hepatol 2006
Salerno F et al. Gut 2007
Gines P, et al. Lancent 2003
Adebayo D, et al. Kidney Int 2014

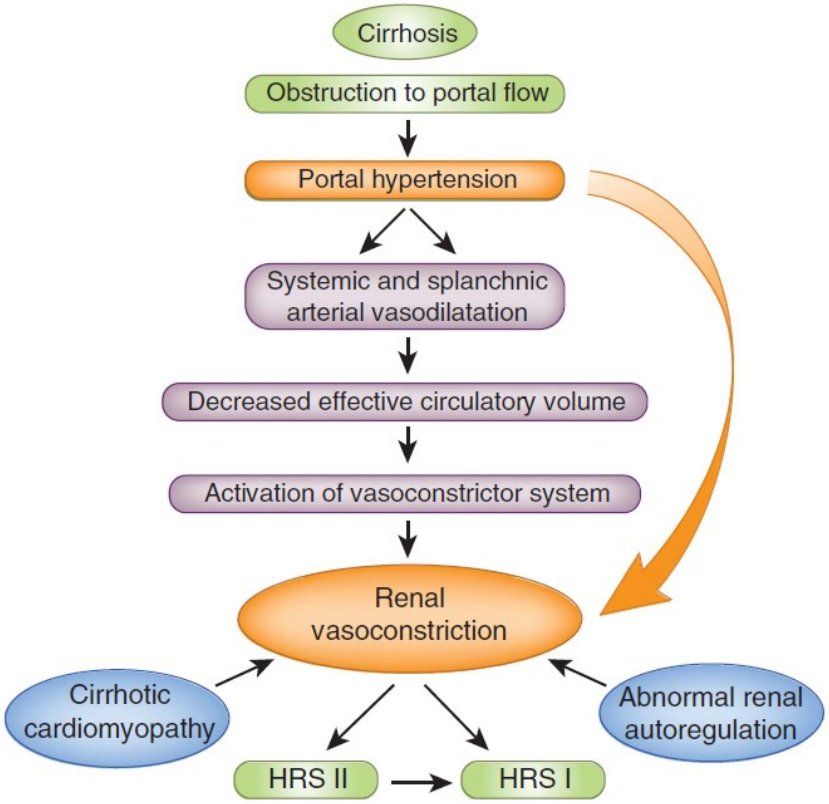
Renal impairment in advanced cirrhotic patients



	Hypovolemia	HRS	ATN
Urinary Na	<20 mmol/L	<10 mmol/L	>40 mmol/L
Urine/plasma Cr	>40:1	>40:1	<20:1
Urine/plasma osmolarity	>1.2	>1.2	1.0±0.1
Urinary sediment	normal	Normal	Granular casts

Adebayo D, et al. Kidney Int 2014

Pathophysiology of HRS



Conventional Belief:

- Vasomotor dysfunction

Novel Insights (Non-vasomotor mechanisms):

- Upregulation of inflammatory mediators
- TLR4
- IL-17A
- Biliary Cast nephropathy
- ↑Intra-abdominal pressure

Adebayo D, et al. Kidney Int 2014

Management of HRS

- **Prevention of HRS is very important**
  - Prevent precipitating factors (e.g. over-diuresis/paracentesis; infection; GIB)
  - Avoid nephrotoxic agents (e.g. contrast, NSAIDs)

- **Definitive treatment**: Liver transplantation

- **Bridging therapy**
  - Cautious volume expansion
  - Terlipressin + albumin
  - Other vasoactive drugs: midodrine, octreotide, pentoxyfylline
  - Dialysis (CVVH)
  - TIPS in exceptional cases

Diagnosis & Prediction of HRS

- Development of HRS:
  - often unpredictable & patients commonly deteriorate rapidly once HRS sets in
  - Serum creatinine (Cr) remains the conventional indicator of renal function.

- Interpretation of SCr in advanced cirrhotic patients confounded by:
  - Malnutrition and reduced muscle mass
  - Abnormal fluid distribution
  - Hyperbilirubinemia

- Serum Cr abnormality occurs late & relying on serum Cr alone or Cr-based equations results in delayed diagnosis and management of HRS.

Novel biomarkers in HRS diagnosis

	PRA N=55	HRS N=16	ATN N=39	p
Tubular injury markers				
NGAL (ng/ml)	54 (17–180)	115 (51–373)	565 (76–1000)***, ##	<0.001
IL-18 (pg/ml)	15 (15–49)	37 (15–90)	124 (15–325)***, #	<0.001
KIM-1 (ng/ml)	4.4 (1.8–11.7)	7.6 (4.5–10.1)	8.4 (4.1–18.3)**	0.03
L-FABP (ng/ml)	9 (4–18)	14 (6–20)	27 (8–103)***	0.002
Tubular function marker				
FENa (%)	0.27 (0.13–0.58)	0.10 (0.02–0.23)**	0.31 (0.12–0.65)##	0.01
Glomerular injury marker				
Albumin (mg/dL)	21 (4–70)	24 (13–129)	92 (44–253)***, #	<0.001

	Optimal Cut Point	Proportion Over Cut Point with ATN	AUC (95% CI)	Validation AUC*
Tubular injury markers				
NGAL (ng/ml)	365	25/35 (71%)	0.78 (0.69–0.88)	0.787
IL-18 (pg/ml)	85	21/33 (64%)	0.71 (0.61–0.81)	0.711
KIM-1 (ng/ml)	15.4	15/24 (63%)	0.64 (0.53–0.75)	0.639
L-FABP (ng/ml)	25	21/30 (70%)	0.69 (0.57–0.80)	0.688
Tubular function marker				
FENa (%)	0.1	22/62 (35%)	0.56 (0.45–0.68)	0.563
Glomerular injury marker				
Albumin (mg/dL)	44	29/52 (56%)	0.73 (0.64–0.83)	0.734

Belcher JM, et al. Hepatology 2014

Biomarkers which predict HRS in cirrhotic patients with normal SCr

	Cut-off value	AUC	95% CI		PPV	NPV	P value
Baseline urine NGAL	18.72 ng/mL	0.84	0.672	1.000	66.7%	91.3%	0.005
Baseline urine KIM-1	1.499 ng/mL	0.78	0.607	0.963	75.0%	84.2%	0.008

	RR	95% CI	P value
Either urinary NGAL or urinary KIM-1 above cut-off	5.600	1.780-17.621	0.001
Both urinary NGAL and urinary KIM-1 above cut-off	6.125	2.611-14.369	<0.001

Incorporating these biomarkers into MELD score might better prioritize liver allograft?

Yap DY et al. Dig Liver Dis 2017

Questions

THANK YOU