Hepatorenal Syndrome and AKI in Cirrhosis

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HRS

Hepatorenal Syndrome

2007 Criteria

GUT 2007;56:1310-1318

- Cirrhosis with ascites
- Cr > 1.5 mg/dL (Classic but suboptimal criteria?)*
- Absence of shock.
- No decrease of creatinine to < 1.5 mg/dL after 2 days of :
  - Diuretic withdrawal +
  - Volume expansion with albumin 1 g/kg per day (up to 100 g/day).
- No current or recent treatment with nephrotoxic drugs.
- Absence of parenchymal kidney disease:
  - Proteinuria < 500 mg/dL,
  - Urine sediment with < 50 RBC/hpf &
  - U/S without obstruction or parenchymal renal disease.

***Best Criteria:** an increase, in < 48 hours, of serum creatinine >/= 0.3 mg/dL, or 1.5 times from baseline if CrCl was < 60 mL/min by MDRD-6 (Stage 1 AKI)

Granular and epithelial casts may be due to high bili; FENa may be < 1% in ATN + Cirrhosis

Proposed Diagnostic Criteria of Kidney Dysfunction in Cirrhosis

Wong F. GUT 2011, 60:702-9

Diagnosis	Definition
Acute Kidney Injury (AKI)	• A rise in Scr ≥ 50% from baseline, or a rise Scr > 0.3 mg/dL • Type-1 HRS is a specific form of acute kidney injury
Chronic Kidney Disease (CKD)	• GFR < 60 ml/min for > 3 month calculated using MDRD-6 formula
Acute on Chronic Kidney Disease (ACKD)	• Rise in Scr ≥ 50% from baseline, or a rise of Scr > 0.3 mg/dL in a patient with cirrhosis whose GFR is < 60 ml/min for > 3 month calculated using MDRD-6 formula

Hepatorenal Syndrome Subtypes

- ***TYPE I***

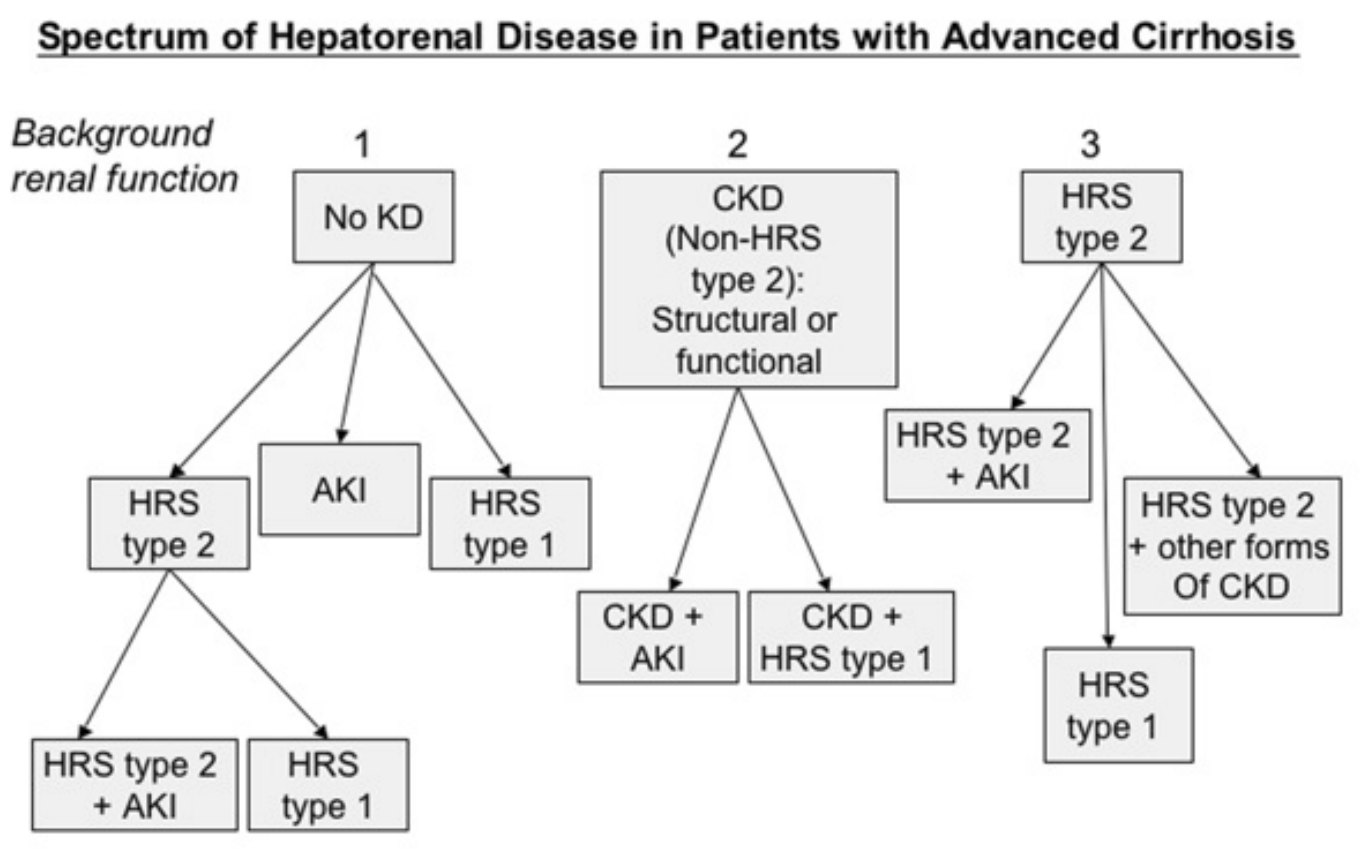
- Rapidly progressive decrease in GFR
- Doubling Cr to >2.5 *(or 50% drop of Cr Cl to < 20 ml/min)* in < 2 weeks
- Pattern: AKI

- ***TYPE II***

- Slowly progressive renal failure
- Cr = 1.25-2.5 mg/dL or *(Cr Cl < 40 mL/min).*
- Pattern: refractory ascites

Spectrum of Hepatorenal Disorder

Critical Care 2012, 16:R23

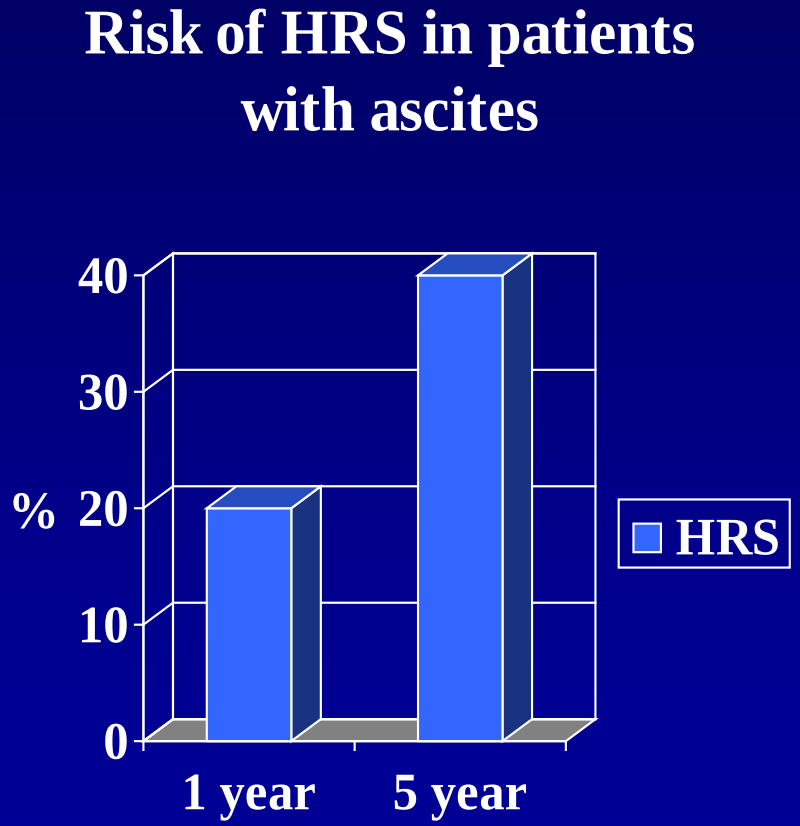


Precipitating Factors

- Ascites
- Cirrhosis with:
  - Infection (SBP and others)
  - GI Bleed
  - Refractory ascites (NSAIDs may trigger refractory ascites)
- Alcoholic hepatitis
- Worsening chronic liver failure
- Fulminant liver failure (including massive metastasis)

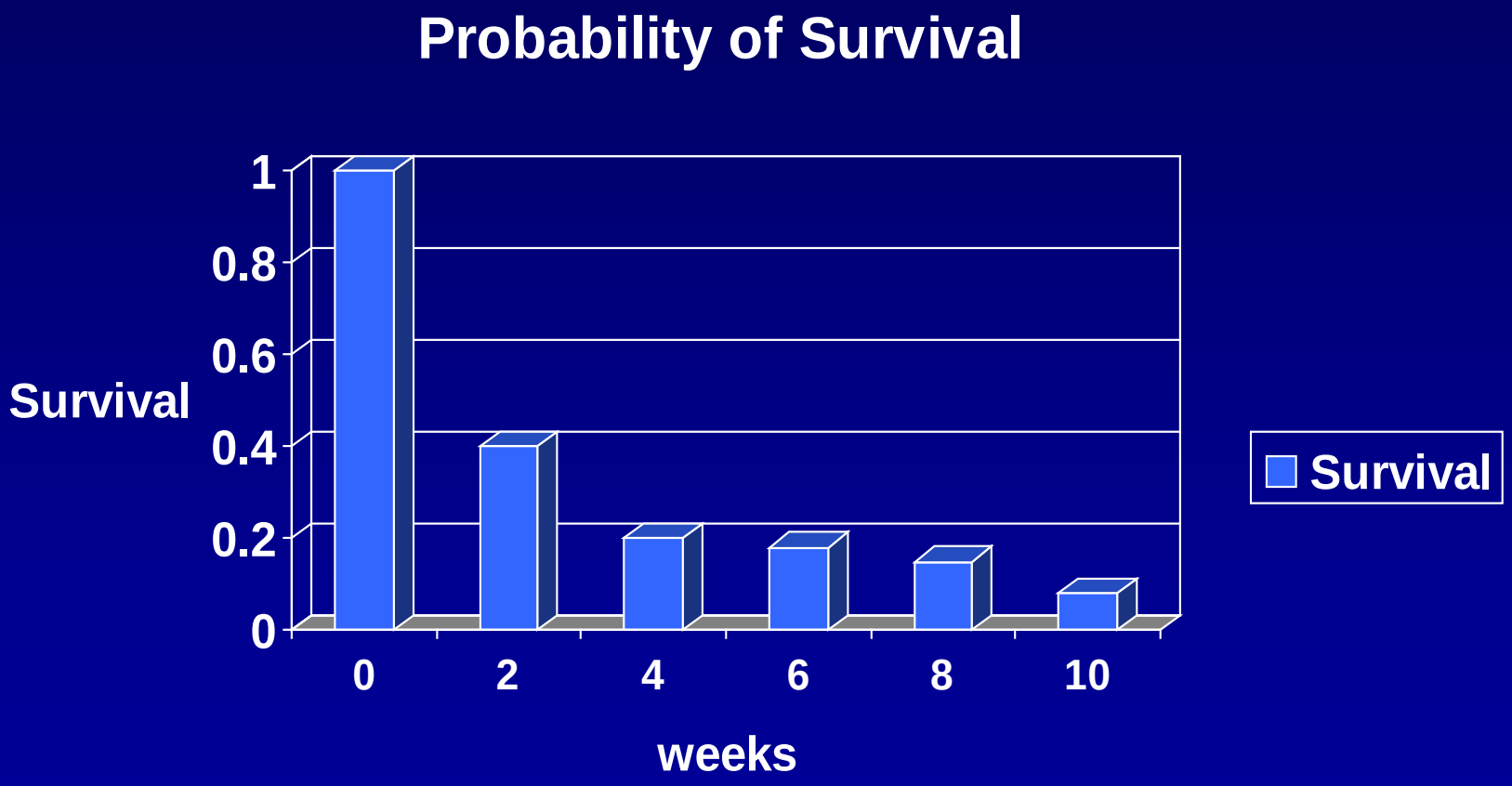
Hepatorenal Syndrome
Predisposing Factors

- Ascites
  - Diuretic resistance or intolerance.
  - Extreme activity of renin-angiotensin & sympathetic system
  - Infection



Mortality of HRS-1

Gastroenterol 1993;105:229

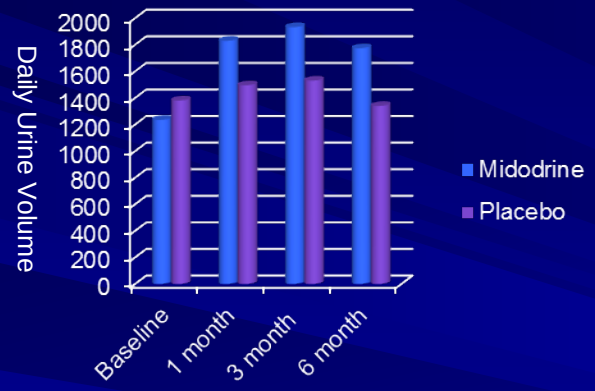


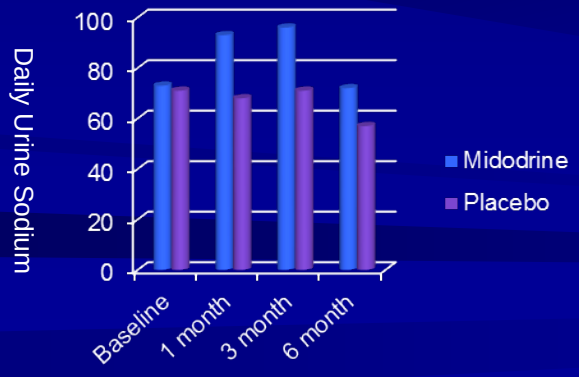
Refractory Ascites
(Impending HRS)

- **Definition:** in a patient with ascites while in a 2 g (88 mEq) Na diet a day, the presence of:
  - ascites that does not respond with a weight loss of > 0.8 kg over 4 days (or with spot urine Na/K < 1), after at least 7 d of maximal diuretics (Spironolactone 400 mg/d + Furosemide 160 mg/d), or
  - diuretic therapy that causes:
    - azotemia (doubling of creatinine to >/= 2 mg/dL),
    - overt HE in the absence of other cause,
    - drop of serum Na > 10 mEq/L to serum Na < 125 mEq/L, or
    - hyper-kalemia (> 6 mEq/L) or hypo- kalemia (< 3 mEq/L) despite proper measures.
- **Significance:** Median survival of 6 months.
  - Management with Midodrine or as HRS should be considered.

Ascites & Refractory Ascites

Midodrine in Refractory/Recurrent Ascites
Singh V; Journal of Hepatology 2012; 56:348–354





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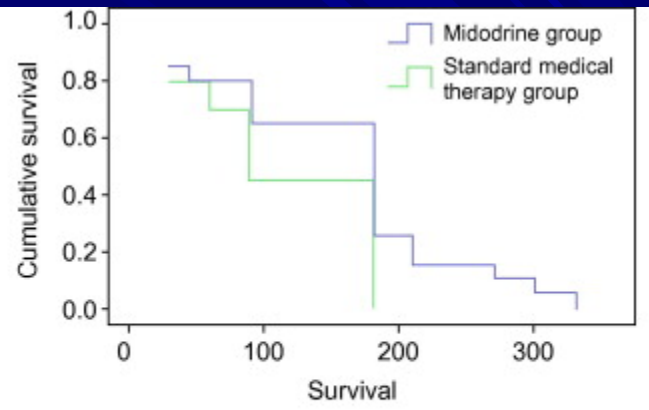


Group	Days from randomization								
	0	30	45	60	90	180	210	300	330
Standard medical therapy	20	16	16	14	9	5	5	5	5
Midodrine	20	17	16	16	13	12	12	12	12

In Refractory ascites, Midodrine 7.5 mg TID increases Natriuresis and improves Survival

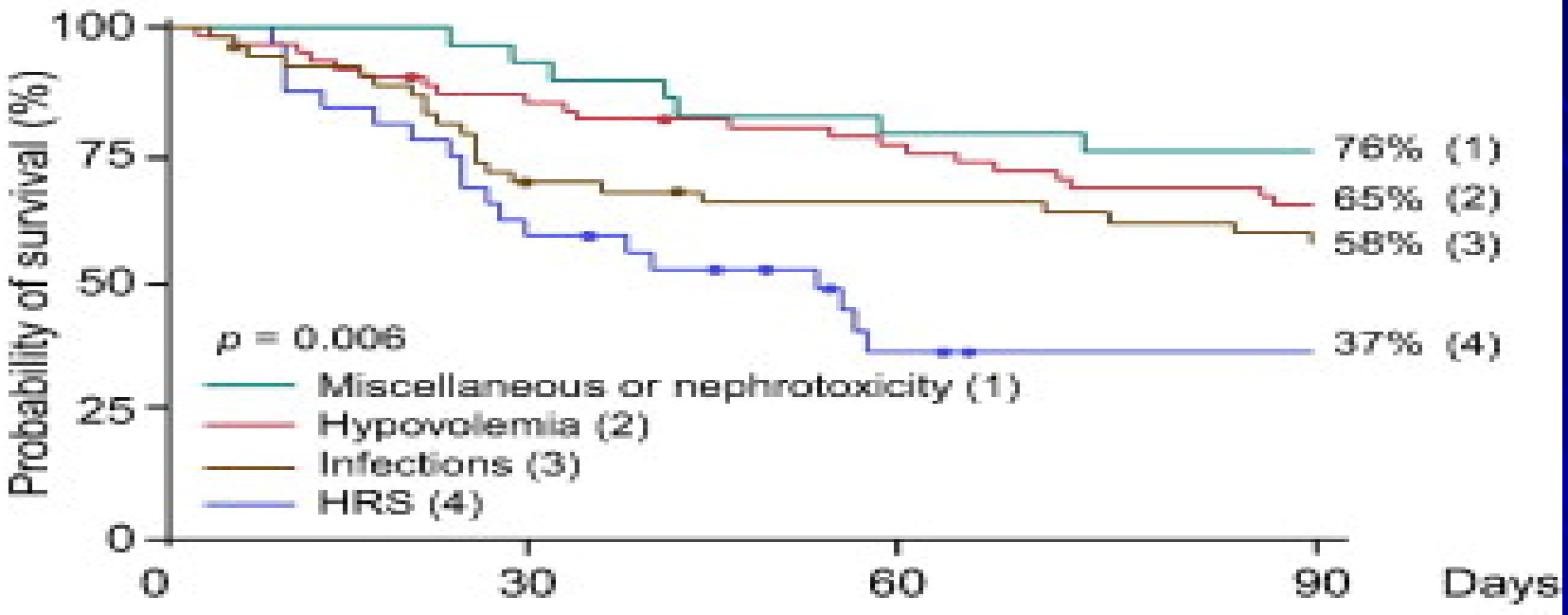
AKI in Cirrhosis

Classification/Staging System for AKI According to AKIN

AKI Stage	Serum Creatinine criteria	Urine output criteria
1	-Increase in serum creatinine >/= 0.3 mg/dL, or -Increase to >/= 150% to 200% from baseline	-Urine output 0.5 mL/kg/h for > 6 h (-No HRS)
2	-Increase of serum creatinine to more than 200% to 300% from baseline	-Urine output < 0.5 mL/kg/h for > 12 h (-Many have HRS-2)
3	-Increase of serum creatinine to > 300% from baseline, or -Serum creatinine >/= 4.0 mg/dL ***After:*** -An increase of at least 0.5 mg/dL, or -Treatment with renal replacement therapy	-Urine output < 0.3 mL/kg/h for 24 h, or -Anuria for 12 h (-Many have HRS -1)

Survival in AKI in Cirrhosis, by Type

Fagundes C et al. J Hepatol. 2013 May 10

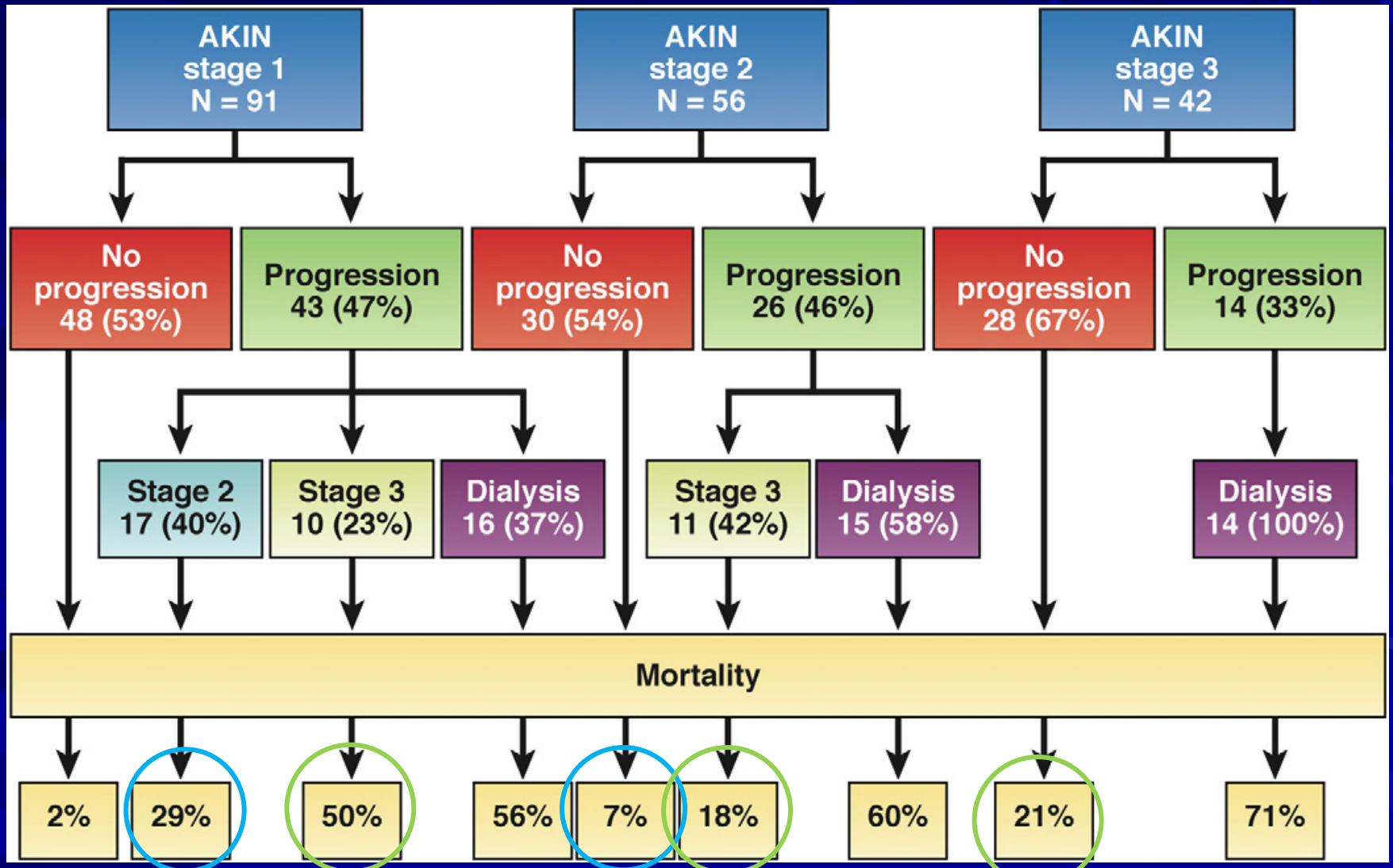


1 (n = 29)	27	23	22
2 (n = 62)	52	45	39
3 (n = 54)	36	33	30
4 (n = 32)	19	9	7

Cirrhotic with HRS has worse prognosis than those with other causes of AKI

Association of AKI with in-hospital mortality in Hospitalized cirrhotics

Belcher JM et al. Hepatology 2013;57:753–762.
Belcher JM et al. Clinical Gastro and Hepatol 2013;11:1550-1558



Association of AKI with in-hospital mortality in Hospitalized cirrhotics

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Initial Stage	Evolution (%)		Mortality (%)
AKI-1 (no HRS)	*No Progression*	*(53%)*	*2*
	Progression to AKI-2	**(19%)**	**29**
	Progression to AKI-3	**(11%)**	**50**
	Progression needing Dialysis	**(17%)**	**56**
AKI-2 (many HRS-2; few HRS-1)	*No Progression*	*(54%)*	*7*
	Progression to AKI-3	**(19%)**	**18**
	Progression Needing Dialysis	**(27%)**	**60**
AKI-3 (many HRS-1)	**No Progression**	**(67%)**	**21**
	Progression needing Dialysis	**(33%)**	**71**

Prevention of HRS-1 in

- Cirrhosis with Infection (SBP)
- Cirrhosis with Ascites and Azotemia
- Advanced Cirrhosis with Ascites
- Alcoholic Hepatitis

SBP & HRS-I

(Sort et al. NEJM 1999;341:403-409)

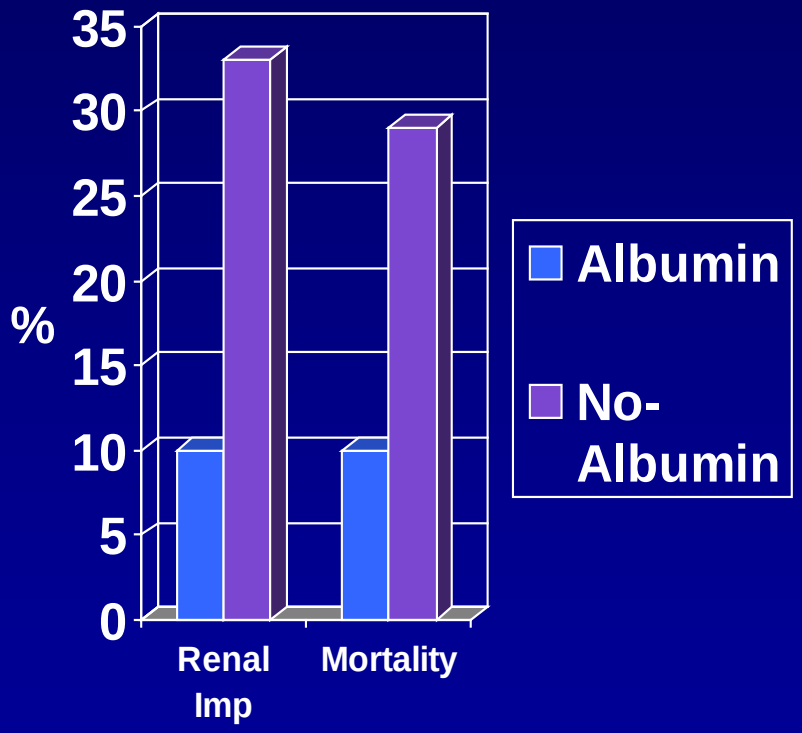
- ***KNOWN POOR PROGNOSIS FACTORS FOR SBP***
  - ***Creatinine > 2.1 mg/dl***
  - ***HRS***
  - Albumin < 2.5 mg/dl
  - Bilirubin > 8 mg/dl
  - PSE
  - UGI bleed

- ***<u>Study</u>: ALBUMIN infusion in SBP***
- Prosp.& Randomized
  - SBP: >250 PMN/mm3
  - Creatinine < 3 mg/dl
- 63 Pts.: Cefotaxime
- 63 Pts.: Cefotaxime + Albumin 1.5gm/kg & 1 gm/kg 3 days later

SBP & HRS-I

(Sort et al. NEJM 1999;341:404-409)

- ***OUTCOMES***
  - **Renal impairment:**
    a) If base Cr > 1.5: > 50% increase of BUN or Cr
    b) If base Cr < 1.5: > 50% increase to Cr >1.5 or BUN>30
  - **Mortality**



SBP & HRS-1
CONCLUSION

- In patients with antibiotic-treated SBP, early volume expansion with IV albumin:
  - decreases risk of HRS, and
  - decreases mortality.

Prevention of hepatorenal syndrome in patients with renal dysfunction in cirrhosis and ascites: pentoxifylline vs. placebo.

Eur J Gastroenterol Hepatol. 2011 Mar;23(3):210-7

- 176 consecutive patients with cirrhosis and ascites.
- Prospective, Randomized pilot study.
- Inclusion criteria:
  - creatinine clearance (CrCl) between 41 and 80 ml/min, and
  - serum creatinine of less than 1.5 mg/dl, and
  - absence of renal disease
- Arms: 6 months of
  - Pentoxifylline (group A) 1200 mg/day, or
  - Placebo (group B).
- Patients were followed monthly for 6 months;
  - kidney function test were done at baseline, 1, 3, and 6 months.
- Primary endpoint:
  - developement of HRS within 6-months of follow-up.

Prevention of hepatorenal syndrome in patients with renal dysfunction in cirrhosis and ascites: pentoxifylline vs. placebo.

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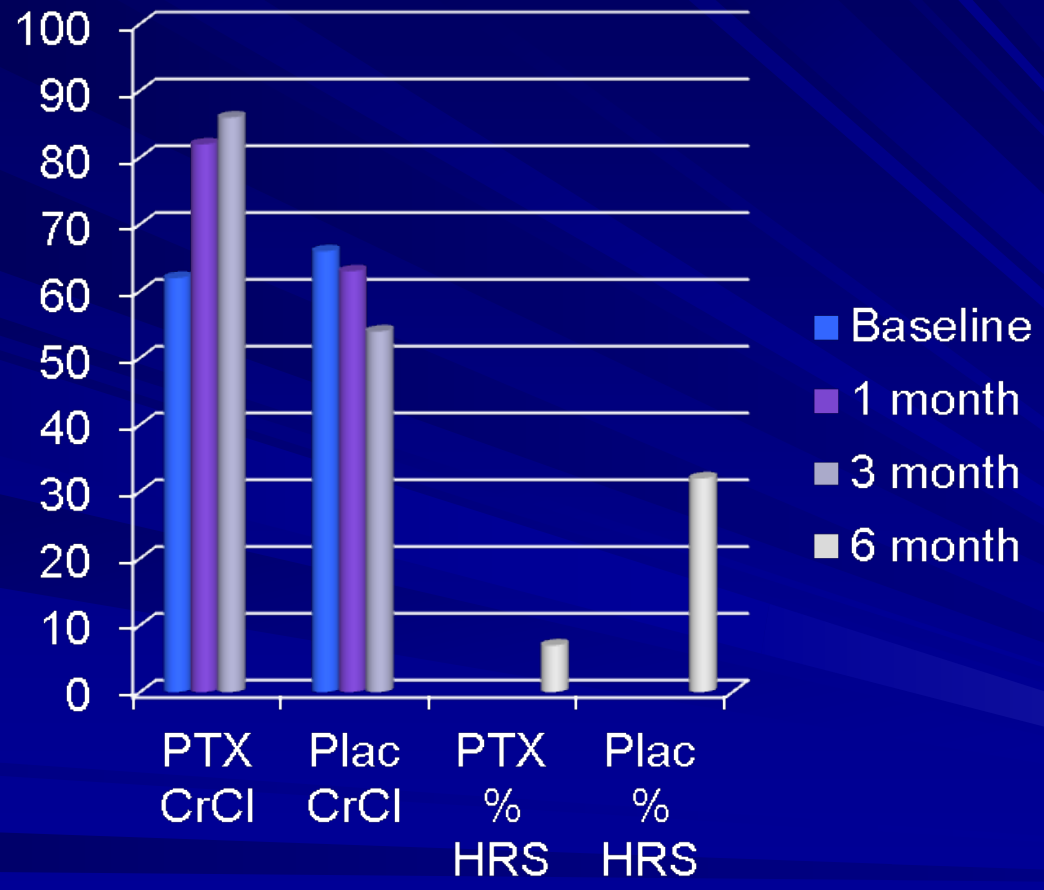


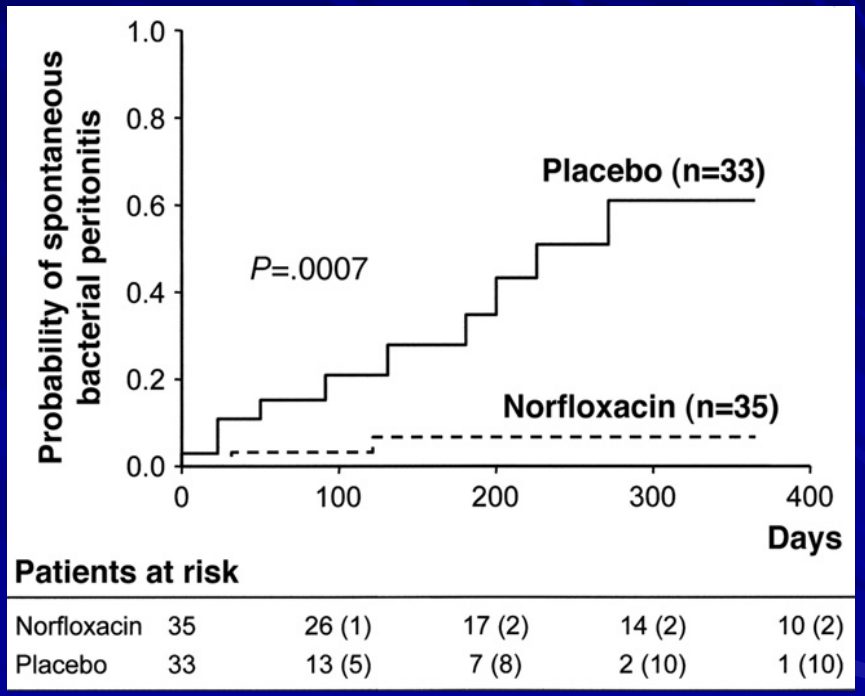
CONCLUSION: Pentoxifylline is effective in preventing HRS in patients with cirrhosis and ascites at risk of HRS.

Primary Prophylaxis of SBP in “advanced” cirrhosis Prevents HRS and Improves Survival

Fernandez J et al. GASTROENTEROLOGY 2007;133:818–824

- Prospective Randomized
- Cirrhotics with low-protein ascites AND
  - Child-Pugh >/=9 with:
    - TB >3 mg/dL, or
    - Cr >/= 1.2 mg/dL, or
    - Na </= 130 mEq/L.
- Group A (N:35): Norfloxacin 400 mg/d x 1 y
- Group B (N:33): Placebo x 1 y
- End-Points:
  - Survival at 3 & 12 months
  - 1-year probability of SBP & HRS
- RESULT: Norfloxacin decreased SBP, delayed HRS, & improved survival.

Probability of SBP



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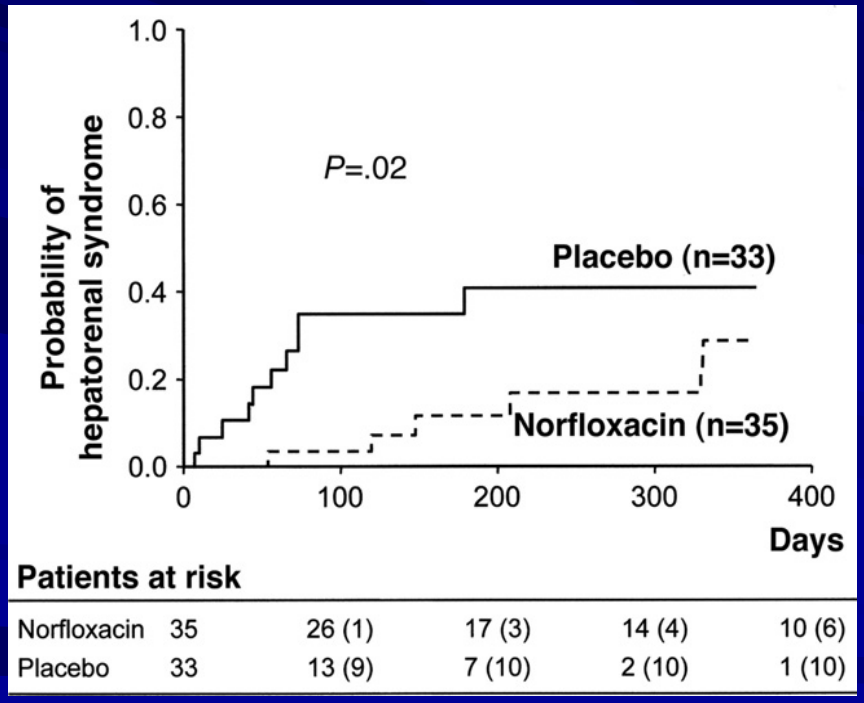
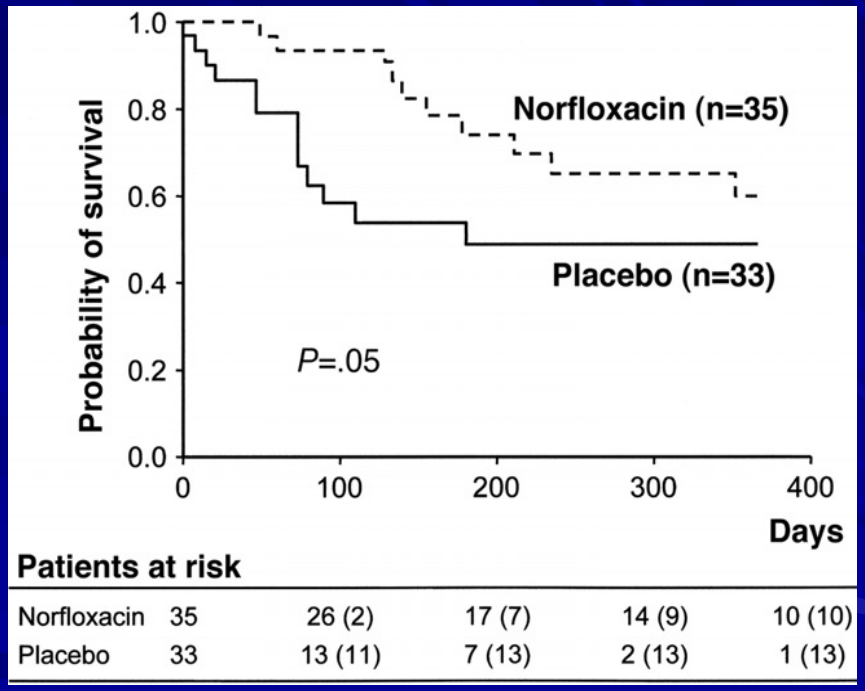
Probability of HRS



Patients at risk

Norfloxacin	35	26 (1)	17 (3)	14 (4)	10 (6)
Placebo	33	13 (9)	7 (10)	2 (10)	1 (10)

Probability of Survival



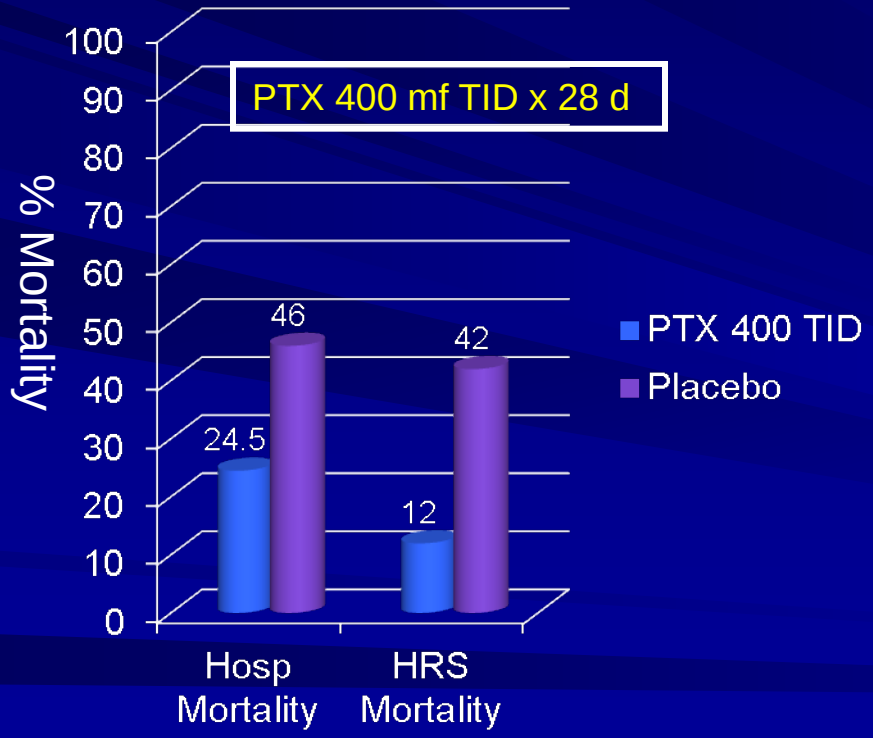
Patients at risk

Norfloxacin	35	26 (2)	17 (7)	14 (9)	10 (10)
Placebo	33	13 (11)	7 (13)	2 (13)	1 (13)

Prevention of HRS in AH

Pentoxifylline in Severe Alcoholic Hepatitis

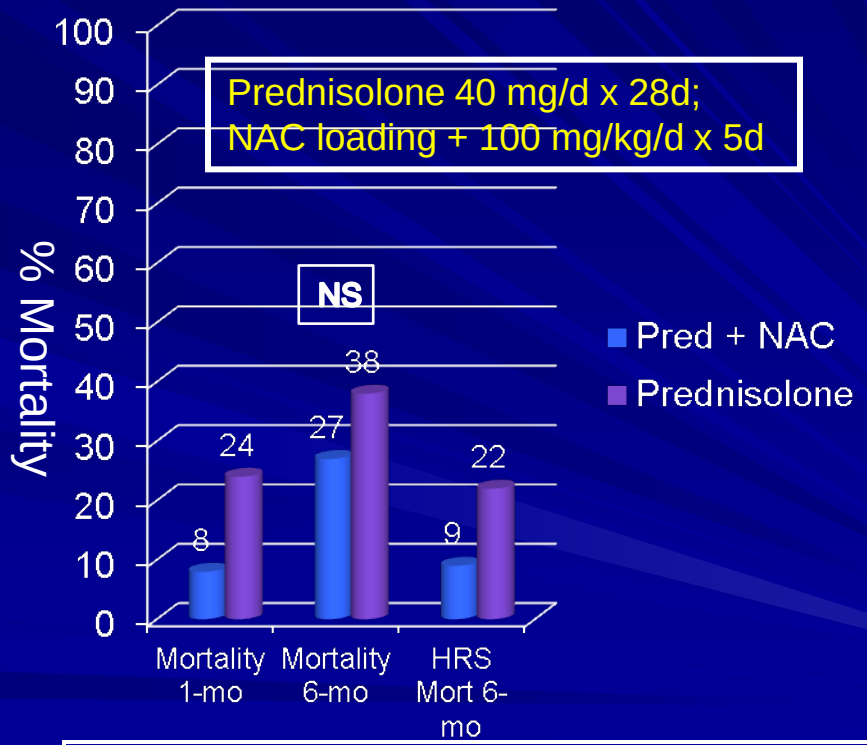
Akriviadis E; Gastroenterology 2000 Dec;119(6):1637-48



In Severe AH, PTX decreases risk of HRS, and 1 & 5 month mortality

Prednisolone + NAC in Severe Alcoholic Hepatitis

Nguyen-Khac E; N Engl J Med 2011; 365:1781-1789



In Severe AH, adding NAC to Prednisolone, decreased risk of HRS, 1 month mortality, and 6 month HRS-related mortality (but not 6-month total mortality)

HRS-Type 1 & 2

MEDICAL THERAPY

HRS-type 1
Medical Therapy

- Ornipressin + Albumin (1998)
- N-Acetylcysteine (1999)
- Midodrine + Octreotide + Albumin (1999)
- Noradrenaline + Albumin (2002)
- Terlipressin + Albumin (2008)
- TIPS (empirical use)

General Principles of Treatment

- Expand intravascular volume with IV albumin (1 g/kg/day up to 100 g, or 2L of 5% albumin), guided by continuous CVP or indirect measures of cardiac indices. (Critical Care 2012, 16:R23)
  - Raise CVP to 10-15
- Use vasopressor to keep MAP of 85-90 mm Hg (Velez JC, Am J Kidney Dis. 2011 Dec;58(6):928-38).
  - Midodrine 10-20 mg po q8h + Octreotide 100-200 mcg SQ q8h or 25 mcg bolus + 25 mcg/h,
  - Norepinephrine IV drip 0.5-3 mg/h (titrate to MAP)
  - Ornipressin IV drip 2 IU/h, or
  - Terlipressin IV 0.5-2 mg q 4-6h (Max 12 mg/d) x max 14 days
- Continue therapy until creatinine is </= 1.3 mg/dL (up to 14 days for IV therapy, and 21 d for Midodrine/Octreotide)

Ornipressin & Albumin

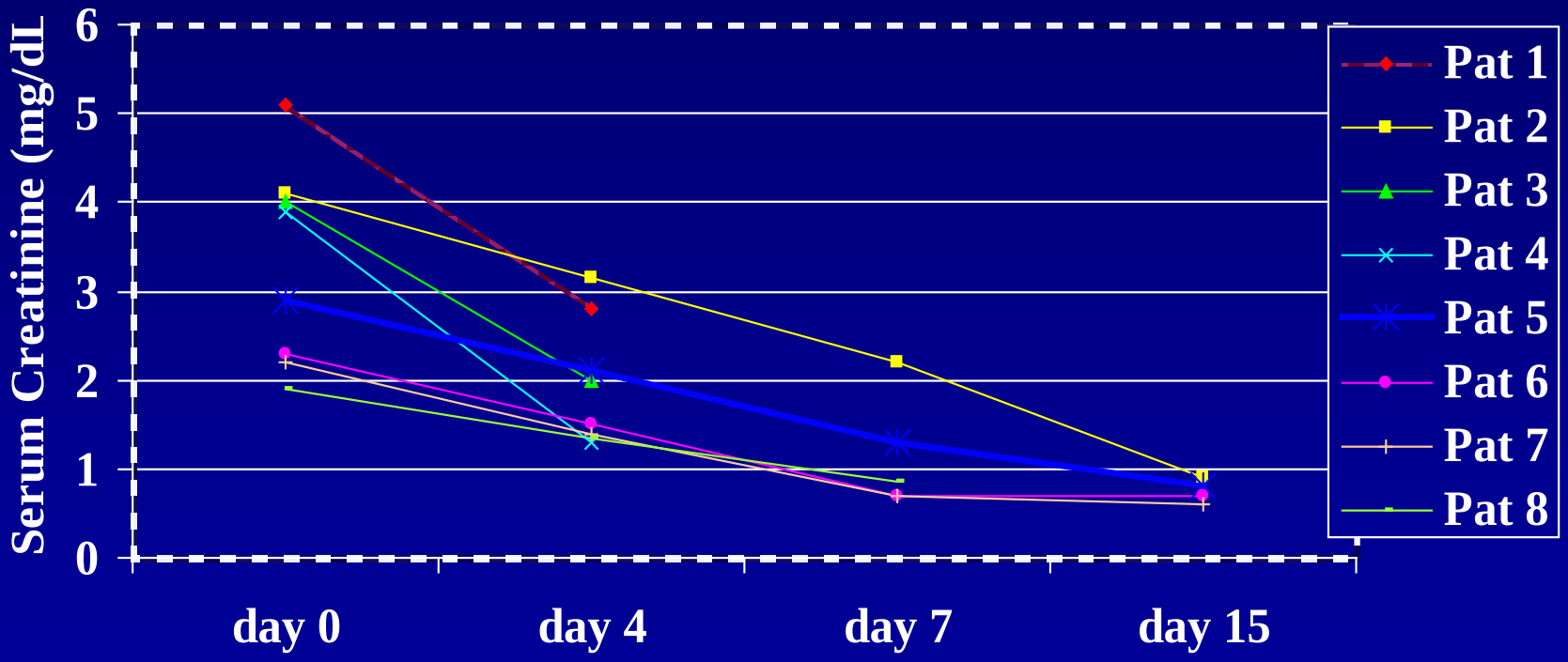
- ***ORNIPRESSIN***
  - Splanchnic vasoconstion
  - Increases SVR
  - Increases Blood Pressure
  - Systemic vasoconstriction
  - Coronary vasoconstriction
  - Decrease Cardiac output
- ***ALBUMIN***
  - Expands intravascular volume
  - Decreases Plasma Renin Activity

Hepatorenal Syndrome-I & Ornipressin + Albumin

HEPATOLOGY 1998;27:35-41

- Patients:
  - 8 with all 5 major HRS-I criteria.
  - Median age=53; M/F=6/2; ascites= 75%
  - Median Cr= 3.2 mg/dL; Inulin Cl=10mL/min
- Intervention:
  - Ornipressin 2 IU/h x 15 d + Albumin (20%) 1g/Kg
  - Goal: to normalize Plasma Renin Activity
- MAP effect: raised from 69+/-3, to 84+/-4 mmHg
- Complications:
  - Four d/c therapy (day 4-9) due to ischemia

Hepatorenal Syndrome-I & Ornipressin + Albumin



N-Acetylcysteine

- Antioxidant
- Improves Renal Function in Experimental Cholestasis/Renal Failure
- Acetaminophen Induced Liver/Renal Failure: trend to improved renal function

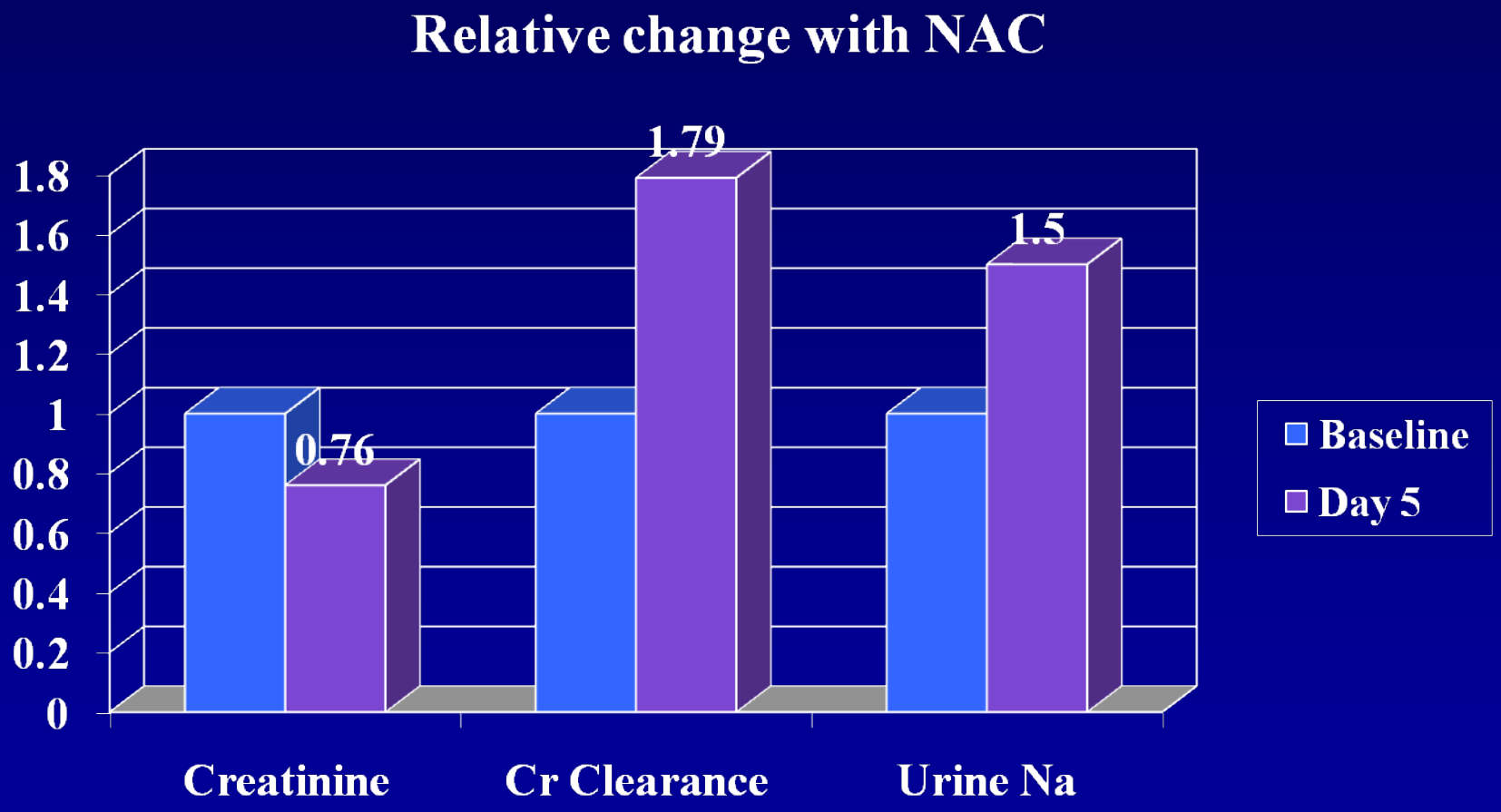
Hepatorenal Syndrome-I & NAC

LANCET 1999;353:294-295

- Twelve pat. with all 5 major HRS-I criteria
- ALD=9, HCV=2, AIH=1
- NAC IV 150 mg/Kg in 2 h +
  100 mg/Kg/d x 5 days

  Base Cr= 2.5mg/dL & CrCl= 24 mL/min
  EOT Cr=1.9mg/dL & CrCl= 43 mL/min
- Survival: 1 month= 67%; 3 months=58%

Hepatorenal Syndrome-I & NAC



Midodrine & Octreotide

- ***MIDODRINE***
  - Alpha-1-adrenergic agonist (arteriolar and venous constriction)
  - Increases renal perfusion
  - Increases blood pressure
- ***OCTREOTIDE***
  - Splachnic arterial vasoconstriction
  - Decreases Portal Pressure
  - Decreases glucagon (vasodilator)
  - Increases GFR

Midodrine + Octreotide vs. Dopamine in HRS-1

Hepatology 1999;29:1690-1697

- Patients:
  - 15 consecutive, Type 1 HRS by 5 major criteria
  - Two excluded: Heart disease & DM
- Treatment Groups:
  - First 8: Dopamine + Albumin
  - Next 5: Midodrine + Octreotide + Albumin

Hepatorenal Syndrome-I
Midodrine + Octreotide

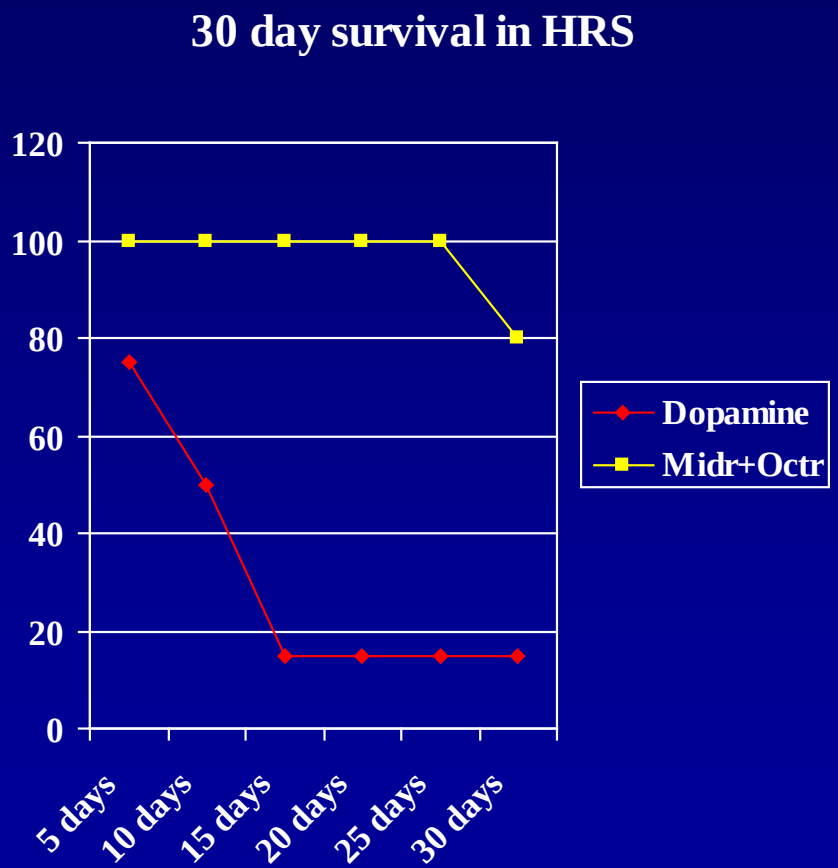
Hepatology 1999;29:1690-1697

- All Patients received:
  - IV albumin to CVP of 12 mm Hg
- Treatment Arms:
  - A) Dopamine 2-4 mcg/kg/min IV infusion, or
  - B) Midodrine 7.5-12.5 mg p.o. TID + Octreotide 100-200 mcg SQ TID
- **Goal**:
  - Plasma Renin Activity reduced > 50% after 3 days of therapy, and/or
  - ***Raise MAP > 15 mmHg***

Hepatorenal Syndrome-I
Midodrine + Octreotide

Hepatology 1999;29:1690-1697

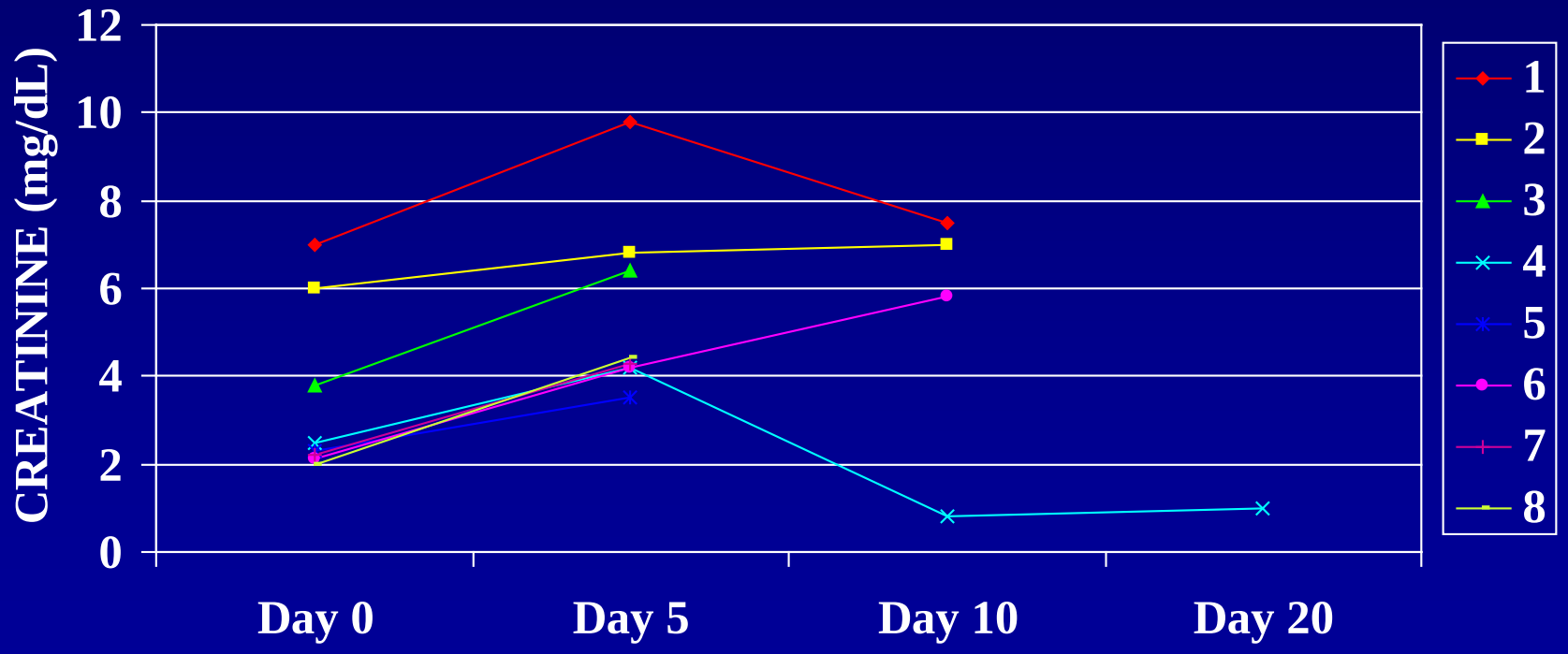
- Ascites + Cr > 2 mg/dl
- Off diuretics 5 days
- IV albumin .8-1.5 L/d x4
- Urine Na <10 mEq/L
- Normal sediment & Renal U/S
- No infection or shock
- MAP effect: M/O/A group increased from 75.9+/-3 to:
  - 90.9+/-5.2 @ 5d, and
  - 96.9+/-6.5 @ day 10



HRS-I + Low Dose Dopamine
Serum Creatinine (mg/dL)

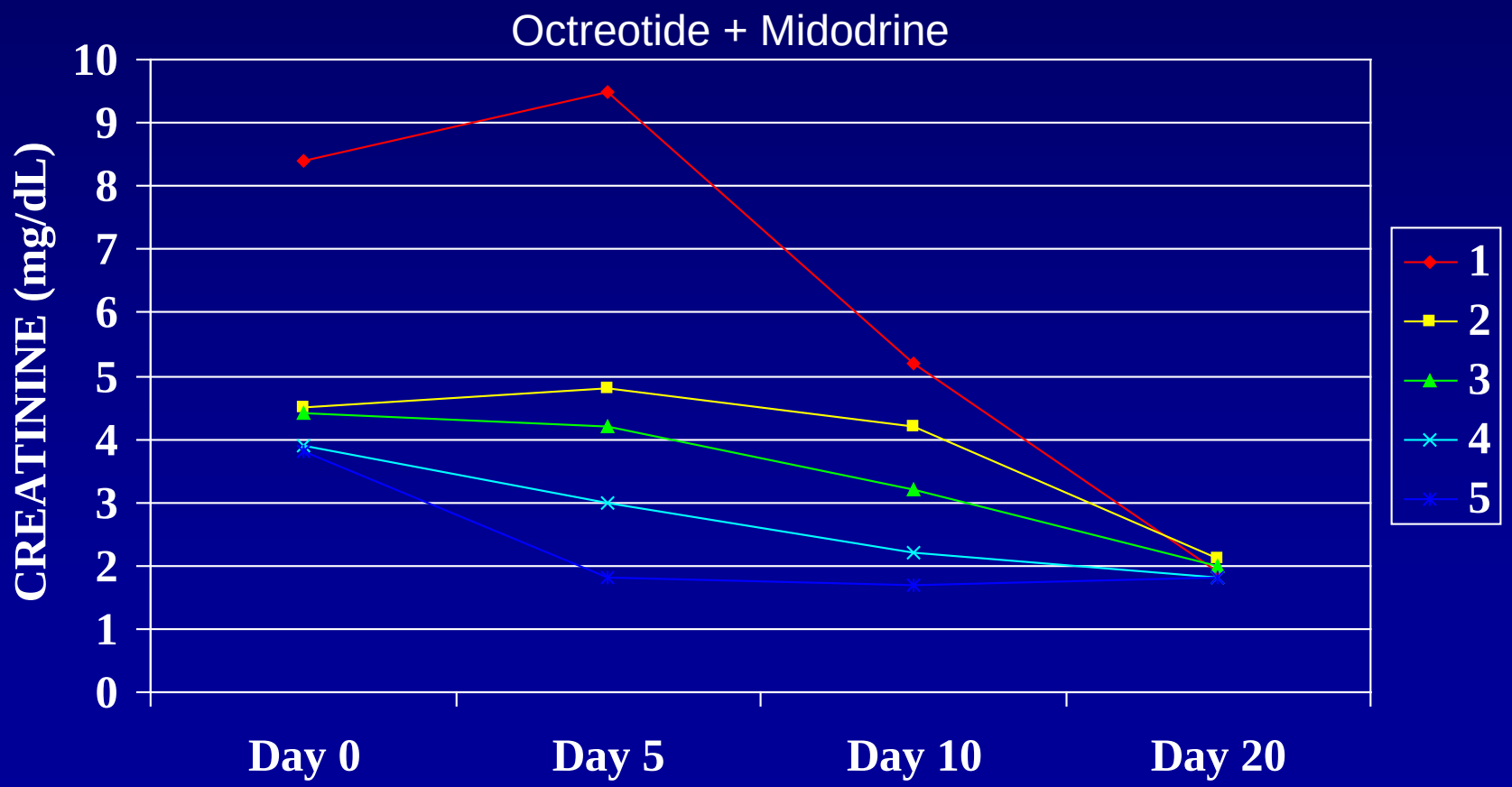
Hepatology 1999;29:1690-1697

Dopamine 2-4 mcg/kg/min



HRS-I + Midodrine & Octreotide
Serum Creatinine (mg/dL)

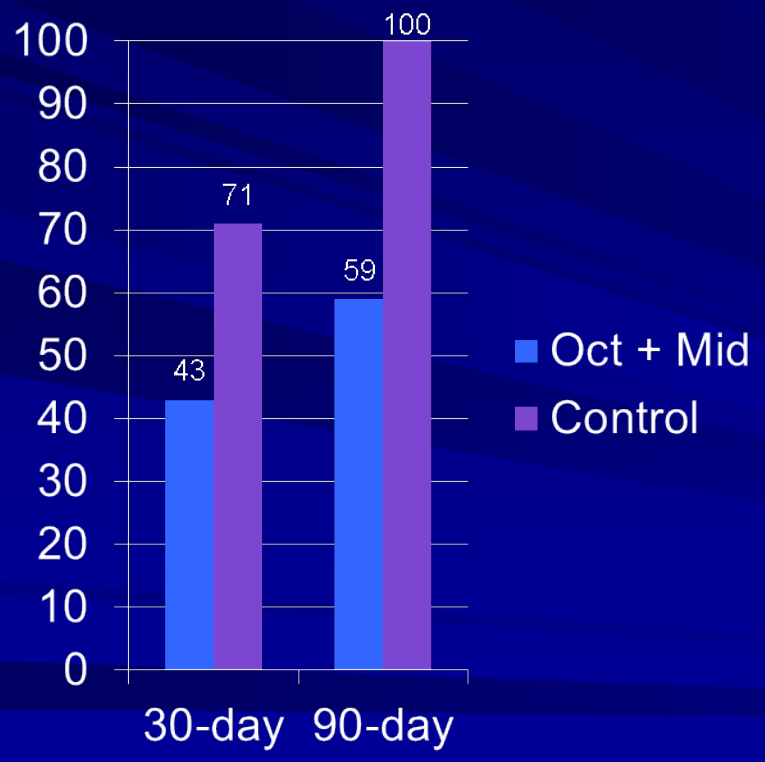
Hepatology 1999;29:1690-1697



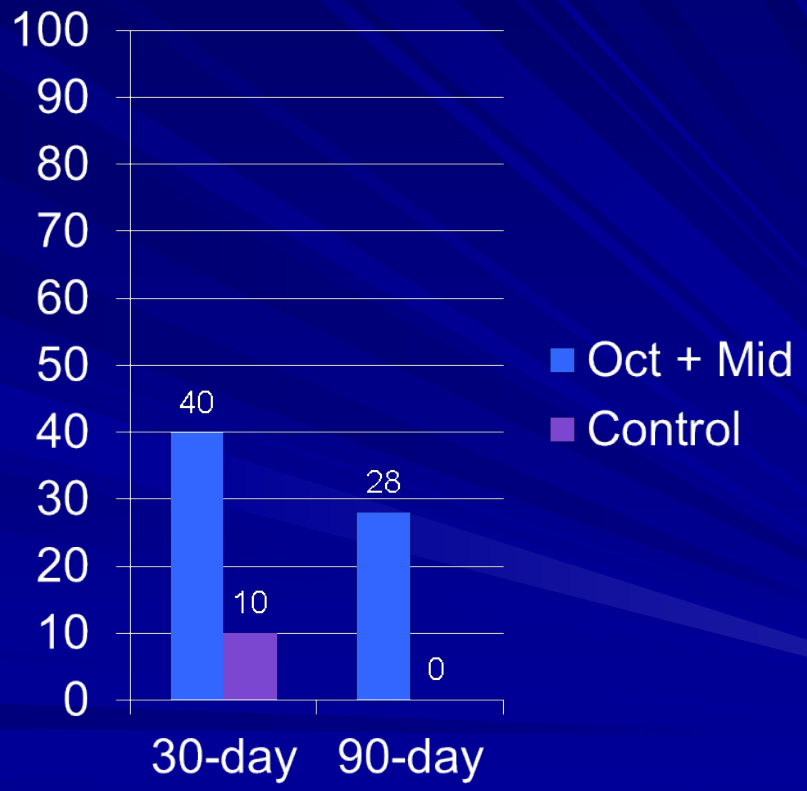
Mortality & Sustained Response Octreotide + Midodrine in HRS

Esrailian E et al. Dig Dis Sci 2007;52:742-748

Mortality



Sustained improved GFR



HRS-I & Noradrenaline + Albumin
(Duvoux et al. Hepatology 2002;36:374-380)

- Prospective study
- Patients:
  - 12 consecutive cirrhotic patients
  - Type-I HRS
- Exclusion criteria:
  - Child-Pugh score > 13,
  - CAD,
  - obstructive cardiomyopathy,
  - ventricular arrhytmia,
  - obliterative arterial disease of lower limbs,
  - infection within last week.

HRS-I & Noradrenaline + Albumin

(Duvoux et al. Hepatology 2002;36:374-380)

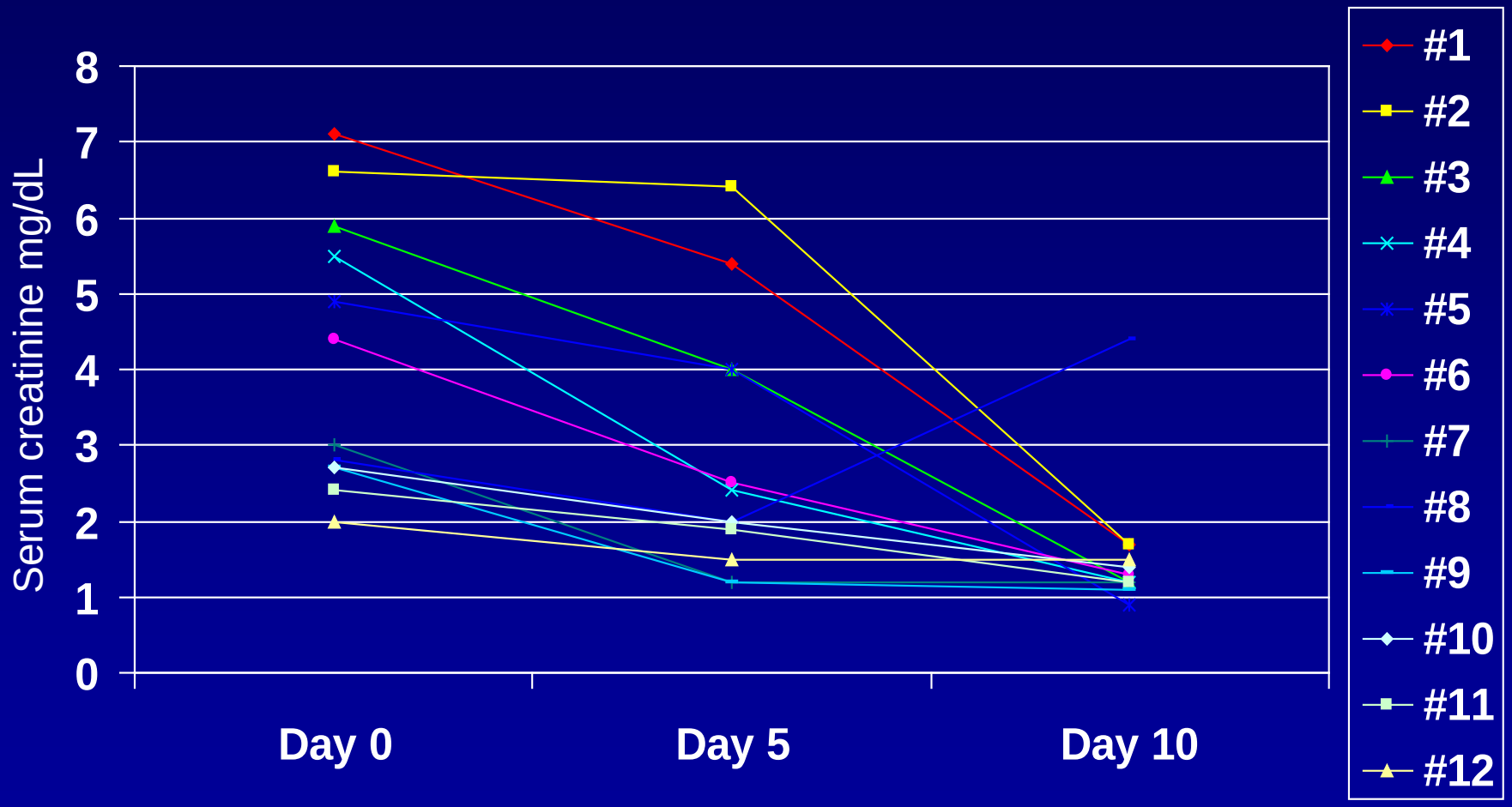
- Age 54+/-11
- Child-Pugh 11.3+/-1.7
- Bili 16.6+/-10.3
- Creatinine 2.7+/-1.1
- Cr Clearance 16.1+/-14
- Serum Na 123+/-6
- Urine Na 10+/-16
- Urine volume 697+/-555

HRS-I & Noradrenaline + Albumin

(Duvoux et al. Hepatology 2002;36:374-380)

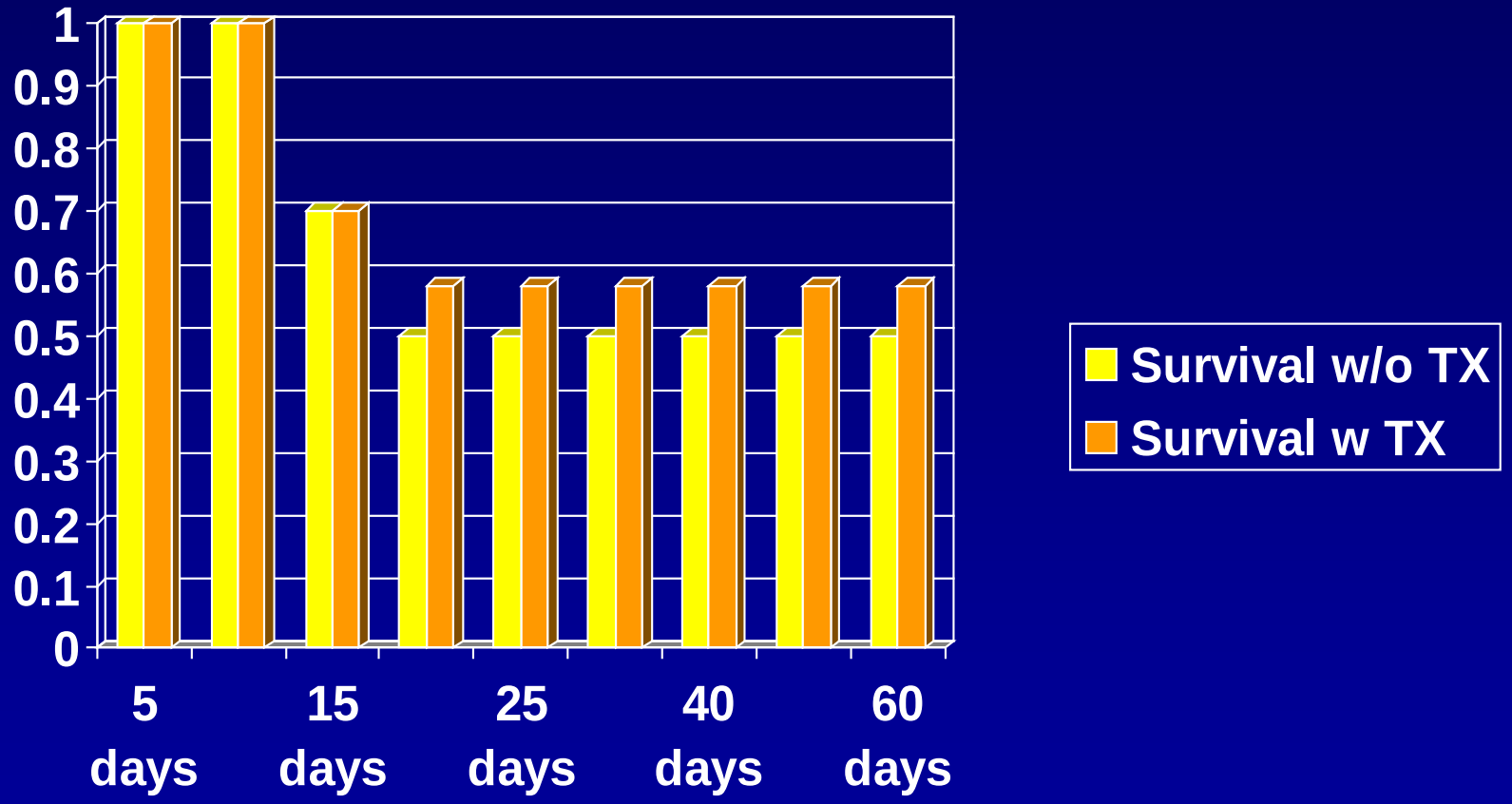
- *Volume Expansion x 48 h*
  -20% albumin infusion to goal CVP > 4
  -Lasix 120mg IV Q4 to goal U/O 25cc/h
- *If creatinine not improved and U/O < 600 cc/d:*
  -Noradrenaline 0.5 mg/h and increased by 0.5mg/h q4h (max 3 mg/h) until MAP increases by > 10 mmHg and U/O to > 50cc/h
- *End point:*
  - resolution of HRS (Cr < 1.5, or CrCl > 40cc/min), or
  - 15 days of therapy.
- **MAP effect**: raised from 65+/-7, to 74+/-7 mmHg

HRS-I & Noradrenaline + Albumin



HRS-I & Noradrenaline + Albumin

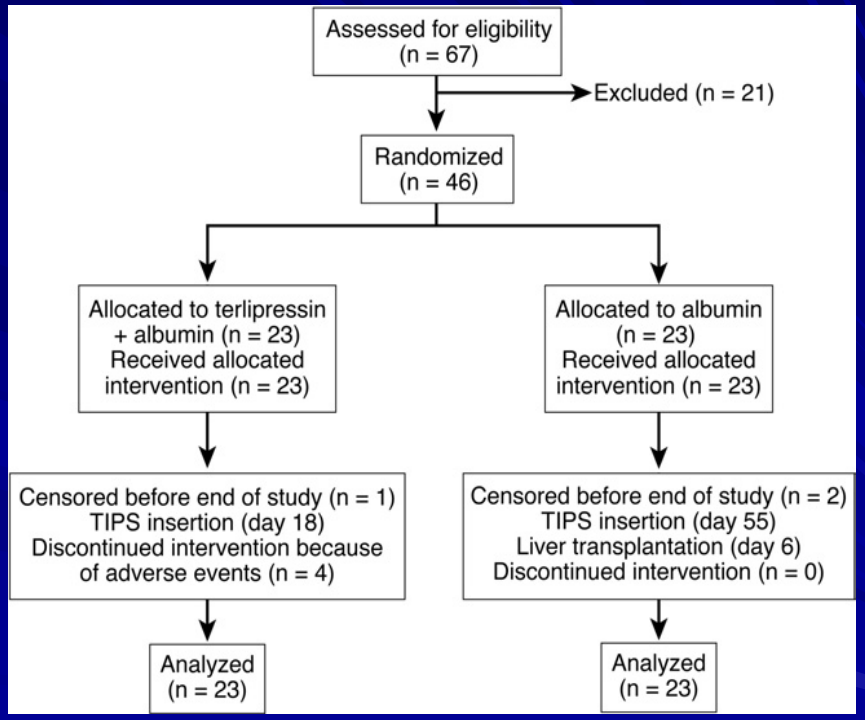
Two-month Survival



Terlipressin + Albumin vs Albumin in HRS

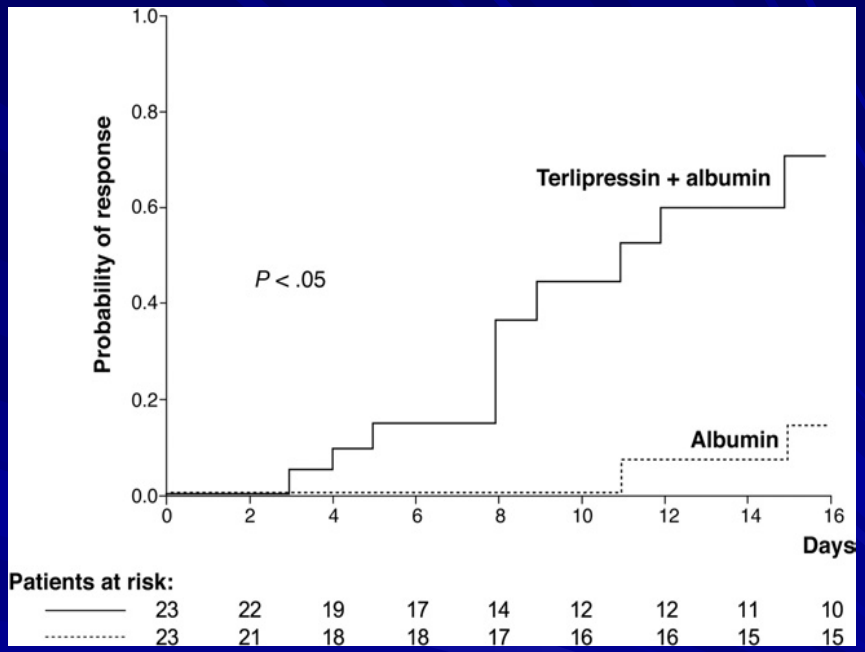
Martin-Llahi, M et al. GASTROENTEROLOGY 2008;134:1352–1359

- Patients with Type I or II HRS (74 & 78% were type I)
- Randomized, prospective.
- All patients:
  - D/C diuretics and received
  - Albumin (20%) 1 g/kg day 1; then 40 g/d.
  - Goal CVP: 10-15
  - Lasix IV if CVP > 18
- Terlipressin:
  -1 mg IV bolus q4h x 3 days;
  -If creat has not decrease by 25%, increased to 2 mg q4h



RESULTS

- Complete response:
  - Creatinine </= 1.5 mg/dL
- Partial response:
  - creatinine drop > 50%, but with final creat > 1.5 mg/dL.
- Response rate:
  - HRS-I: 35%
  - HRS-II: 67%
  - Overall: 43.5%
- MAP effect: in responders increased from 75+/-13 to 84+/-18

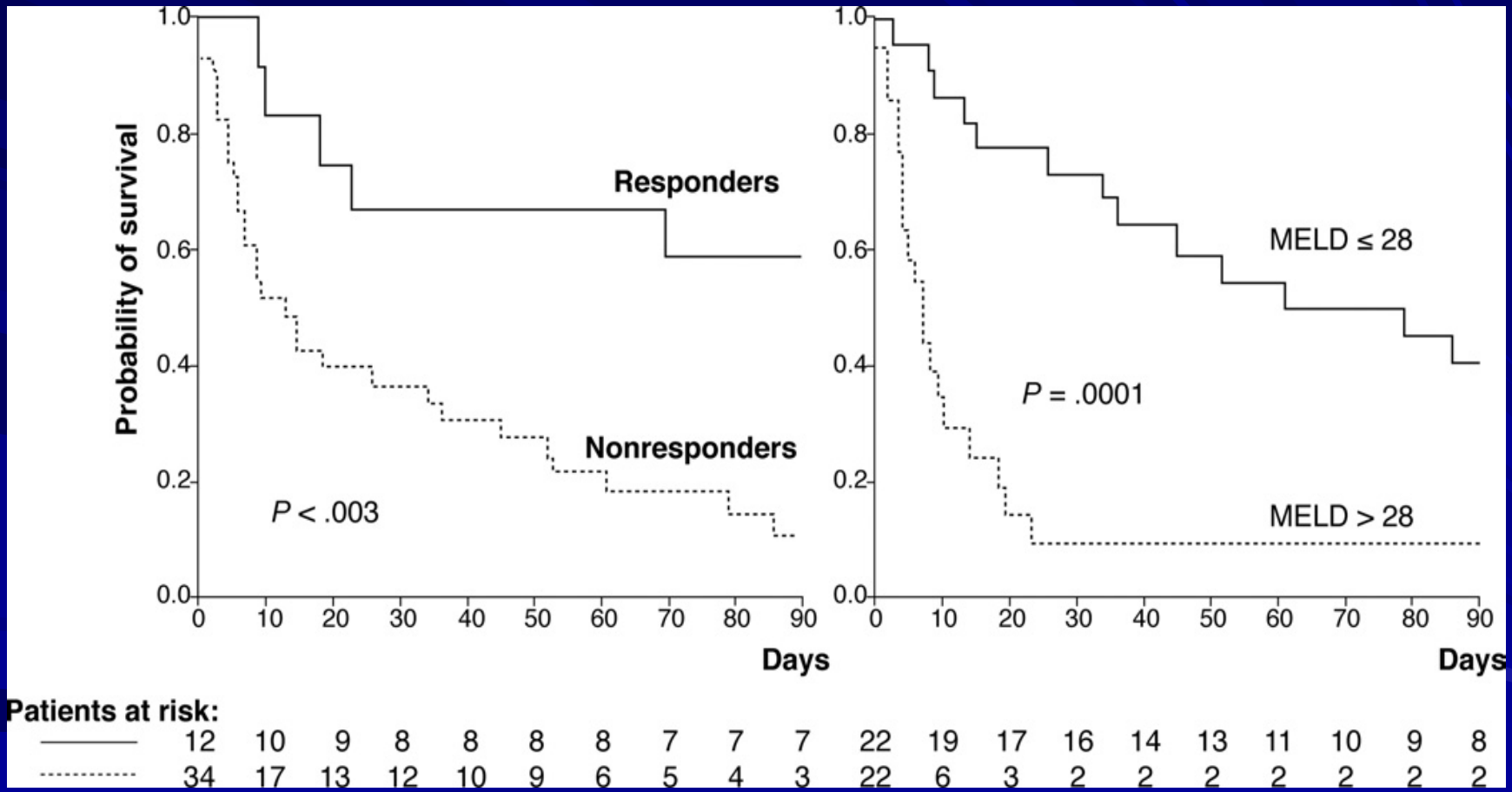


Inverse Kaplan–Meier: cumulative incidence of improvement of renal function.
Median time to improvement of renal function with terlipressin andalbumin was 11 days

Probability of survival at 3 months

By improvement of renal function *(left)*, and
By base-line MELD score (*right graph*).

(MELD score could not be calculated in 2 patients).



Side Effects and Conclusion

	Terlip + Alb (23)	Alb (23)	P value
Encephalopathy	70	70	.538
Bact. Infection	39	55	.23
GI Bleed	17	26	.722
Myocardial Infarct	4	0	1
Intest. Ischemia	13	0	.233
Arrhytmia	9	0	.489
Volume overload	30	17	.187
Arterial HTN	4	0	1
Other	30	9	.135

- **CONCLUSION:**
  - Terlipressin + Albumin is effective in reversing HRS
  - There was no effect on overall survival
  - Responders had improved survival at 3 months: 58% vs 15%.

Terlipressin in Type-I HRS: Effect on MAP in Responders vs Non-Responders

Sanyal et al. AASLD 2008

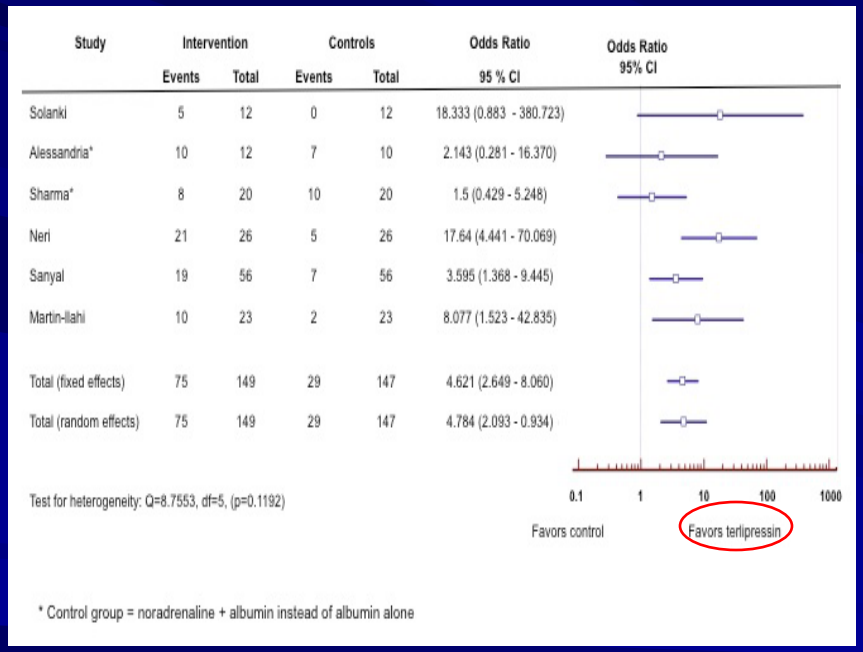
- Population: 111 pts with Type-I HRS;
  - Terlipressin = 56;
  - Placebo = 55.
- Intervention:
  - **Terlipressin** 1 mg q 4-6 h iv +
    Albumin 100 g on day 1, then 25 g/day
  - **Placebo** q 4-6 h iv +
    Albumin 100 g on day 1, then 25 g/day
  - Terlipressin or placebo were increased to double-dose if creat has not decreased 30% by day 3.
- Result:
  - Responders: MAP changed from 72.8 +/- 11.6 to 80.7 +/- 7.9
  - Non-Respon: MAP changed from 76.9 +/- 11.3 to 76.5 +/- 12.4

Meta-Analysis of [Terlipressin plus Albumin] vs Control in HRS

Int J Artif Organs. 2009 Mar;32(3):133-40

Reversal of HRS

(effective)



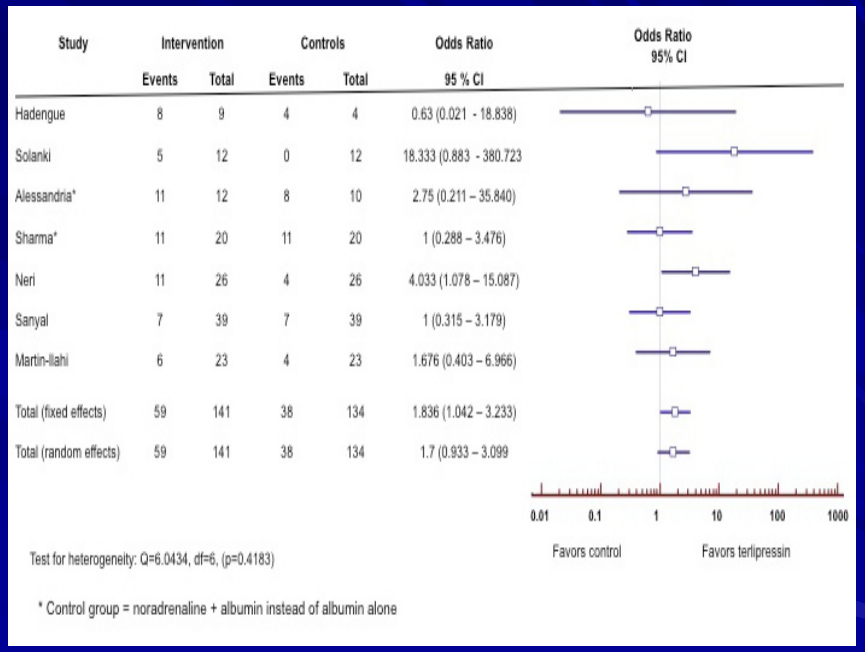
Study	Intervention Events	Intervention Total	Controls Events	Controls Total	Odds Ratio 95 % CI
Solanki	5	12	0	12	18.333 (0.883 - 380.723)
Alessandria*	10	12	7	10	2.143 (0.281 - 16.370)
Sharma*	8	20	10	20	1.5 (0.429 - 5.248)
Neri	21	26	5	26	17.64 (4.441 - 70.069)
Sanyal	19	56	7	56	3.595 (1.368 - 9.445)
Martin-Ilahi	10	23	2	23	8.077 (1.523 - 42.835)
Total (fixed effects)	75	149	29	147	4.621 (2.649 - 8.060)
Total (random effects)	75	149	29	147	4.784 (2.093 - 0.934)

Test for heterogeneity: Q=8.7553, df=5, (p=0.1192)

* Control group = noradrenaline + albumin instead of albumin alone

Survival

(no clear benefit)



Study	Intervention Events	Intervention Total	Controls Events	Controls Total	Odds Ratio 95 % CI
Hadengue	8	9	4	4	0.63 (0.021 - 18.838)
Solanki	5	12	0	12	18.333 (0.883 - 380.723
Alessandria*	11	12	8	10	2.75 (0.211 – 35.840)
Sharma*	11	20	11	20	1 (0.288 – 3.476)
Neri	11	26	4	26	4.033 (1.078 – 15.087)
Sanyal	7	39	7	39	1 (0.315 – 3.179)
Martin-Ilahi	6	23	4	23	1.676 (0.403 – 6.966)
Total (fixed effects)	59	141	38	134	1.836 (1.042 – 3.233)
Total (random effects)	59	141	38	134	1.7 (0.933 – 3.099

Test for heterogeneity: Q=6.0434, df=6, (p=0.4183)

* Control group = noradrenaline + albumin instead of albumin alone

Terlipressin + Albumin is superior to Placebo in reversal of HRS but has no apparent impact in survival

Noradrenaline vs Terlipressin in Type-I HRS

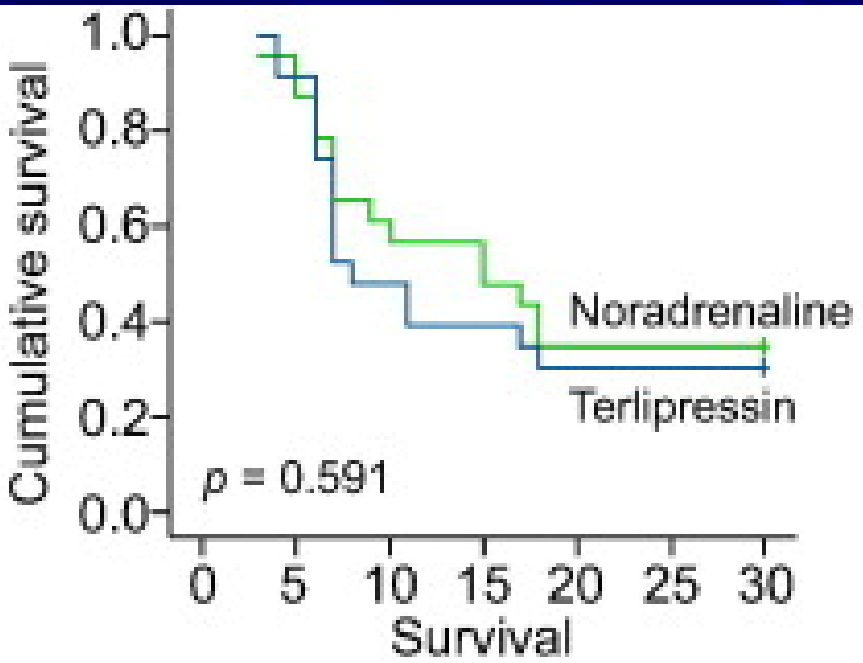
Singh V et al Volume 56, Issue 6, June 2012, Pages 1293–1298

- Design: Prospective, randomized.
- Population: 46 cirrhotics with type-I HRS (60 evaluated)
- Causes for exclusion (14 of 60): severe coronary artery disease (3), sepsis (9), hepatocellular carcinoma (1), diabetic nephropathy (1).
- Arms:
  - A) Terlipressin 0.5 mg IV q 6h increasing q 3d by 0.5 mg up to 2 mg + IV Albumin 20 g/d (hold if CVP >/= 18 cm of saline)
  - B) Noradrenaline 0.5 mg/h to reach MAP increase of 10 mmHg and U.O > 50 mL/h, increasing dose by 0.5 mg/h q 4h until both are reached, up to 3 mg/h + IV Albumin 20 g/d (hold if CVP >/= 18 cm of saline)
- Outcomes:
  - Primary: Creat < 1.5 mg/dL;
  - Secondary: 15 days of therapy or death.

Noradrenaline vs Terlipressin in Type-I HRS

Singh V et al Volume 56, Issue 6, June 2012, Pages 1293–1298

Cumulative Probability of Survival; Kaplan-Meier



Patients at risk	Day					
	5	10	15	20	25	30
Terlipressin group (n = 23)	20	11	9	7	7	7
Noradrenaline group (n = 23)	21	13	11	8	8	8

Noradrenaline vs Terlipressin in Type-I HRS

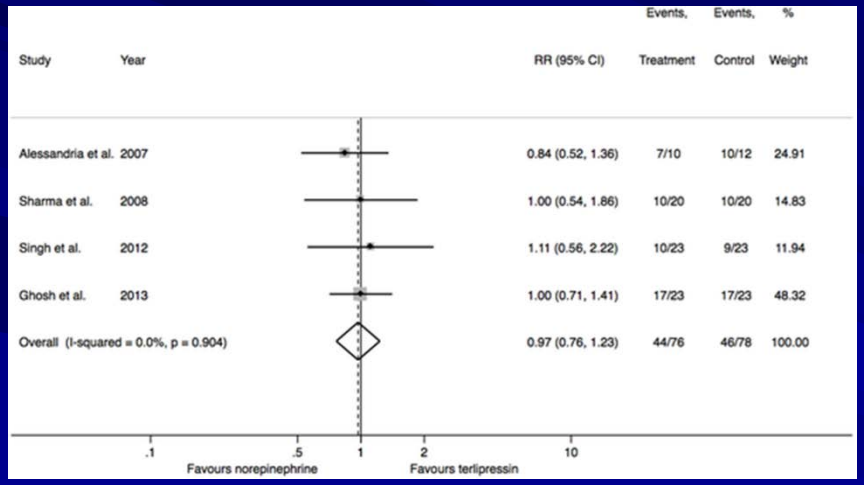
Singh V et al Volume 56, Issue 6, June 2012, Pages 1293–1298

Parameter	Terlipressin group (A)			Noradrenaline group (B)		
	Baseline	Day 15	*p* value (baseline *vs.* day 15)	Baseline	Day 15	*p* value (baseline *vs.* day 15)
Serum creatinine (mg/dl)	3.263 ± 0.81	1.67 ± 0.92	0.002	2.82 ± 0.3	1.55 ± 0.5	0.000
Urinary sodium (mEq/L)	60.6 ± 22.3	72.4 ± 22.6	0.009	46.9 ± 23.5	73.4 ± 33.2	0.069
Urine output (ml/d)	672 ± 194	1084 ± 417	0.034	738 ± 323	1393 ± 529	0.004
Mean arterial pressure (mmHg)	63.2 ± 9.4	70.6 ± 11.2	0.021	70.4 ± 12.5	80.3 ± 5.9	0.036
Plasma renin activity (ng/ml/h)	38.68 ± 15.21	10.21 ± 3.60	0.001	35.23 ± 10.32	8.96 ± 2.21	0.000
Plasma aldosterone concentration (pg/ml)	1755.67 ± 873.44	668.89 ± 310.82	0.012	1757.27 ± 706.14	543.64 ± 269.34	0.001
Number of responders (%)	0	9 (39.1)		0	10 (43.4)[a]	
Cost of treatment for 15 days (€)		945			275[b]	

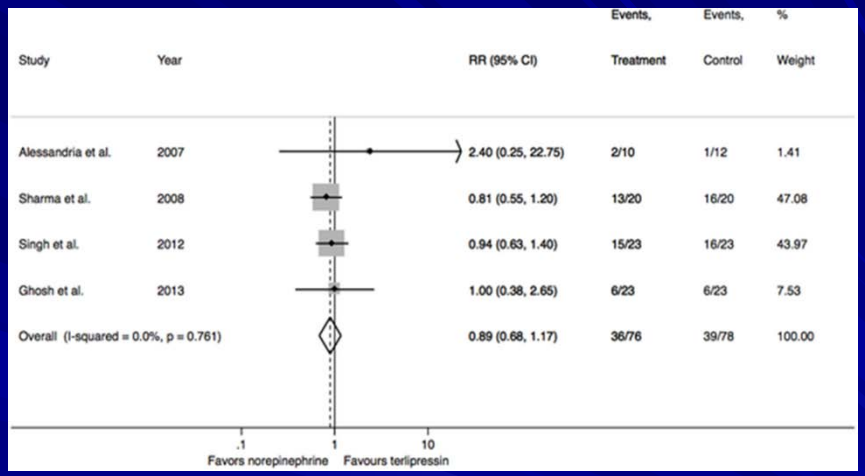
Noradrenaline is as safe and effective as terlipressin, but less expensive in the treatment of HRS-I and baseline CTP score </= 10 is predictive of response.

Meta-Analysis: Terlipressin vs Norepinephrine in HRS

Reversal of Hepatorenal Syndrome.



Mortality Rate at 30 days



No difference in HRS Reversal Rate nor in 30-d Mortality Rate
Adverse events less common with Norepinephrine

Nassar Junior AP, Farias AQ, d' Albuquerque LAC, Carrilho FJ, Malbouisson LMS (2014) Terlipressin versus Norepinephrine in the Treatment of Hepatorenal Syndrome: A Systematic Review and Meta-Analysis. PLoS ONE 9(9): e107466. doi:10.1371/journal.pone.0107466
http://127.0.0.1:8081/plosone/article?id=info:doi/10.1371/journal.pone.0107466

Noradrenaline vs terlipressin in the treatment of type 2 hepatorenal syndrome: a randomized pilot study

Ghosh S et al. Liver International Volume 33, Issue 8, pages 1187–1193, September 2013

- Forty-six patients with type 2 HRS were managed with terlipressin (group A, *N* = 23) or noradrenaline (Group B, *N* = 23) with albumin in a randomized controlled trial.
- HRS reversal could be achieved in 17 (73.9%) patients in group A as well as in group B (*P* = 1.0).
  - In multivariate analysis only baseline serum creatinine, urine output and urinary sodium were associated with the response.
- Eight patients in group A and 9 in group B died within 90 days of follow-up (*P* > 0.05).
- Noradrenaline was less expensive than terlipressin (*P* < 0.05).
- No major adverse effects were seen.

TIPS in HRS Type I and II
and
TIPS After HRS

TIPS for HRS Type I and II

Rossle M et al. Gut 2010;59:988-1000.

- Guevara et al.: seven patients with type-1 HRS had TIPS:
  - TIPS significantly improved serum creatinine, blood urea nitrogen, glomerular filtration rate and renal plasma flow.
  - Three of 7 patients survived by more than 3 months.
- Brensing et al.: 31 nontransplantable patients (14 type-1 and 17 type-2) had TIPS:
  - Renal function improved following TIPS.
  - Survival rates: a) HRS-1: @1y = 20%, and @2y = 20%;
    b) HRS-2: @1y = 70%, and @2y = 45%,
  - Nine patients were excluded from TIPS due to a bilirubin >/= 10 mg/dl.
  - Liver failure was one of the most frequent causes of death following TIPS.
- Testino et al.: TIPS in 18 patients with type-2 HRS and a Child-Pugh score of 10-12 awaiting transplantation:
  - All patients improved with respect to ascites and renal function.

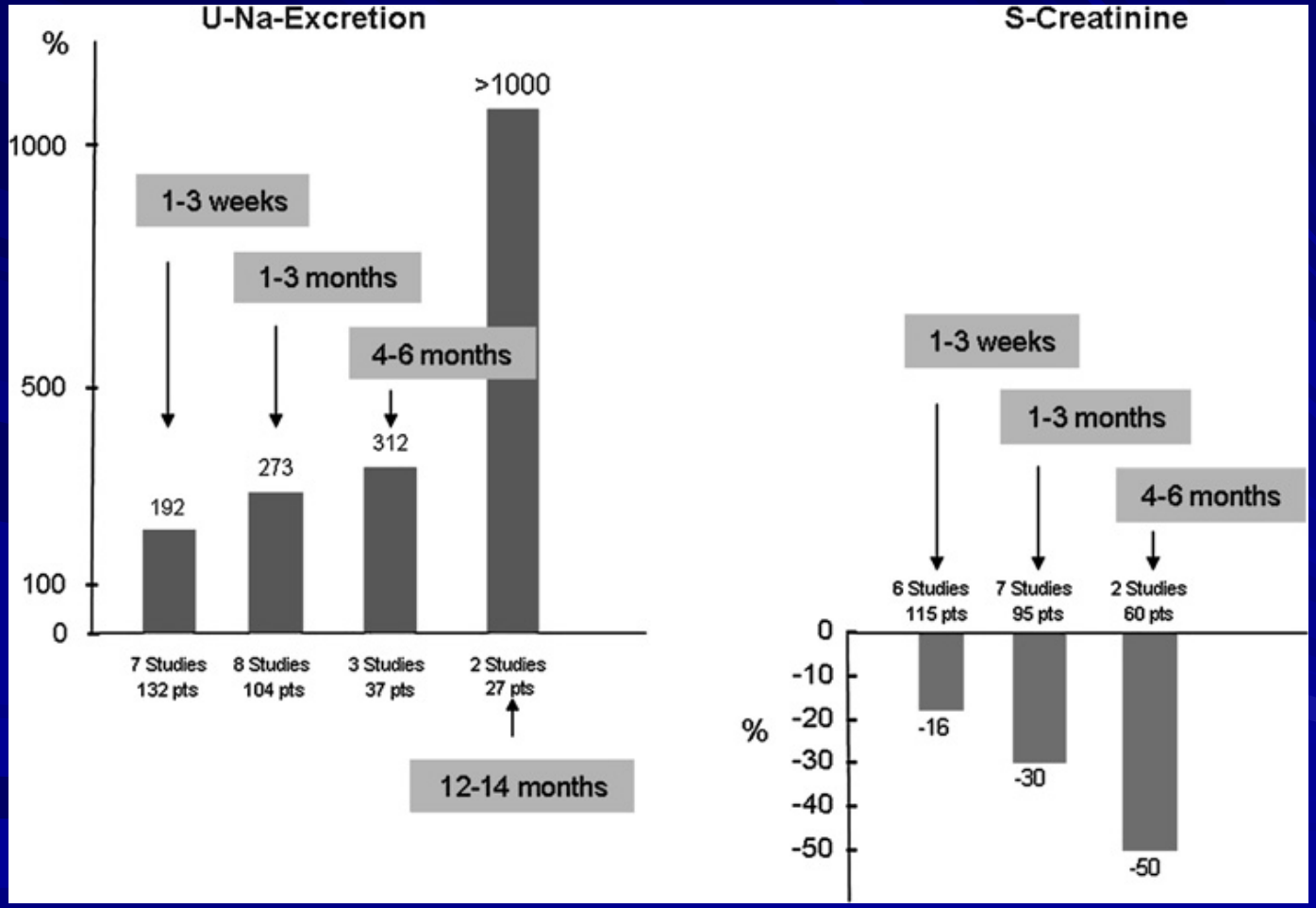
TIPS after Reversal of HRS

Rossle M et al. Gut 2010;59:988-1000.

- Wong et al showed that TIPS may have a role in maintaining patients who initially respond to vasoconstrictor treatment.
  - Fourteen patients with type-1 HRS were treated using a combination of midodrine, octreotide and albumin.
  - Medical therapy for 14 days improved renal function in 10/14 patients with mean serum creatinine significantly decreasing from 233 mmol/l (2.6 mg/dL) to 112 mmol/l (1.26 mg/dL).
  - Five responders were then treated with TIPS and showed further improvement in renal function (mean glomerular filtration rate: 96+/-20 ml/min at 12 months).

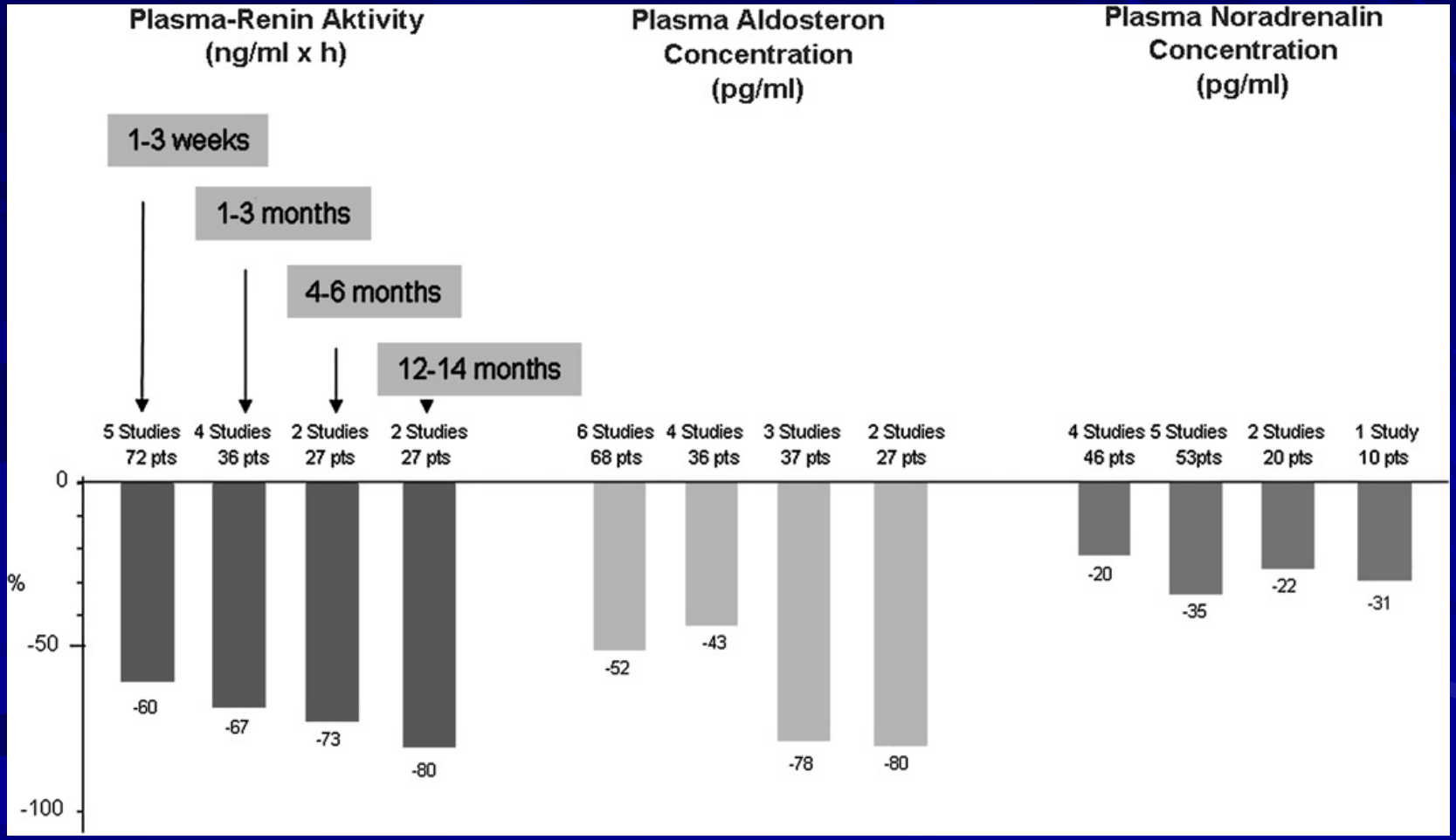
Effect of TIPS in Natriuresis and Azotemia

Rossle M et al. Gut 2010;59:988-1000.



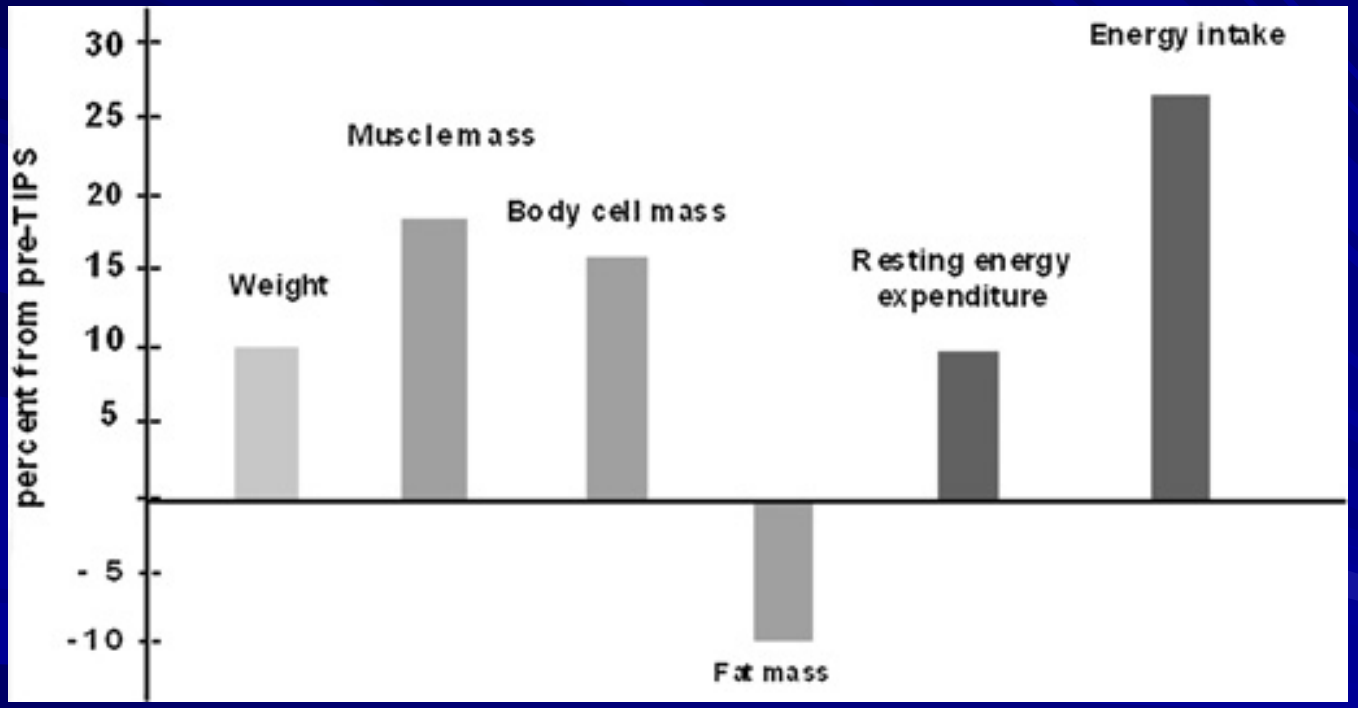
Effect of TIPS on Plasma Renin, Aldosterone & Noradrenaline levels

Rossle M et al. Gut 2010;59:988-1000.



Effect of TIPS in Nutrition after 6 month Follow-up

Rossle M et al. Gut 2010;59:988-1000.



TIPS in HRS

- TIPS can improve renal function in type-1 and type-2 HRS and eliminate ascites.
- Data are limited and survival may not be improved in patients with poor liver function.
- There is insufficient data for the use of TIPS in HRS-1.
- TIPS is indicated in selected patients after rescue from HRS and/or in candidates for liver transplantation.
- If MELD > 15-18, or bili > 4 mg/dL patients should be informed of higher 30 d TIPS mortality and TIPS performed only in the absence of other options.
- TIPS cannot be recommended in patients with:
  - severe liver failure (serum bilirubin >5 mg/dl, INR >2 or Child-Pugh score >11),
  - current hepatic encephalopathy (grade 2 or chronic hepatic encephalopathy),
  - concomitant active infection,
  - progressive renal failure, or
  - severe cardiopulmonary diseases

EASL Practice Guidelines
May 2010

- **Monitoring:**
  - Patients with type 1 HRS should be monitored carefully.
  - Parameters to be monitored include urine output, fluid balance, and arterial pressure, as well as standard vital signs.
  - Ideally central venous pressure should be monitored to help with the management of fluid balance and prevent volume overload.
- **Location:**
  - Patients are generally better managed in an intensive care or semi-intensive care unit (Level A1).
- **Screening for sepsis:**
  - Bacterial infection should be identified early, by blood, urine and ascitic fluid cultures, and treated with antibiotics.
  - Patients who do not have signs of infection should continue taking prophylactic antibiotics, if previously prescribed.
  - There are no data on the use of antibiotics as empirical treatment for unproven infection in patients presenting with type 1 HRS (Level C1).

EASL Practice Guidelines
May 2010

- **Management of type 1 hepatorenal syndrome**
- **Drug therapy of type 1 hepatorenal syndrome:**
  - Terlipressin (1 mg/4–6 h intravenous bolus) in combination with albumin should be considered the first line therapeutic agent for type 1 HRS.
  - The aim of therapy is to improve renal function sufficiently to decrease serum creatinine to less than 133 mcmol/L (1.5 mg/dl) (complete response).
  - If serum creatinine does not decrease at least 25% after 3 days, the dose of terlipressin should be increased in a stepwise manner up to a maximum of 2 mg/4 h.
  - For patients with partial response (serum creatinine does not decrease <133 mcmol/L or 1.5 mg/dL) or in those patients without reduction of serum creatinine treatment should be discontinued within 14 days (Level A1).

EASL Practice Guidelines
May 2010

- **Potential alternative therapies to terlipressin:**
  - Include norepinephrine or midodrine plus octreotide, both in association with albumin, but there is very limited information with respect to the use of these drugs in patients with type 1 HRS (Level B1).
- **Non-pharmacological therapy of type 1 hepatorenal syndrome:**
  - Although the insertion of TIPS may improve renal function in some patients, there are insufficient data to support the use of TIPS as a treatment of patients with type 1 HRS.
- Renal replacement therapy:
  - May be useful in patients who do not respond to vasoconstrictor therapy, and who fulfill criteria for renal support.
  - There are very limited data on artificial liver support systems, and further studies are needed before its use in clinical practice can be recommended (Level B1).

EASL Practice Guidelines
May 2010

- **Management of type 2 hepatorenal syndrome**
- Terlipressin plus albumin is effective in 60–70% of patients with type 2 HRS.
  - More recently, Noradrenaline plus albumin was equally as effective as Terlipressin plus albumin, with 74% response in HRS-2 (Ghosh S et al. Liver International 2013 Sep;33(8):1187-93)
- There are insufficient data on the impact of this treatment on clinical outcomes (Level B1).

EASL Practice Guidelines
May 2010

- **Liver transplantation**

- Liver transplantation is the best treatment for both type 1 and type 2 HRS.
  - HRS should be treated before liver transplantation, since this may improve post-liver transplant outcome (Level A1).
  - Patients with HRS who respond to vasopressor therapy should be treated by liver transplantation alone.
  - Patients with HRS who do not respond to vasopressor therapy, and who require renal support should generally be treated by liver transplantation alone, since the majority will achieve a recovery of renal function post-liver transplantation.
  - There is a subgroup of patients who require prolonged renal support (>12 weeks) (others recommend it if > 8 weeks), and it is this group that should be considered for combined liver and kidney transplantation (Level B2).

EASL Practice Guidelines
May 2010

Prevention of hepatorenal syndrome

- Patients who present with SBP should be treated with intravenous albumin since this has been shown to decrease the incidence of HRS and to improve survival (Level A1).
  - The same is likely true for other infections (Guevara M et al J Hepatol. 2012 Jun 23) but study too small for survival evaluation.
- There are some data to suggest that:
  - Treatment with pentoxifylline decreases the incidence of HRS in patients with severe alcoholic hepatitis.
  - Treatment with norfloxacin 400 mg/d decreases the incidence of HRS in advanced cirrhosis (ascites and C-P >/=9 + [Cr >/=1.2, or Na</= 130, or TB > 3 mg/dL]).
  - Treatment with pentoxifylline in patients with cirrhosis and ascites, with creatinine clearance of 41-80 ml/min, decreases the incidence of HRS.
  - Further studies are needed (Level B2).

EASL Practice Guidelines
May 2010

- **Cautions to terlipressin therapy:**
  - Contraindications include ischemic cardiovascular diseases.
  - Patients on terlipressin should be carefully monitored for:
    - development of cardiac arrhythmias or
    - signs of splanchnic or digital ischemia, and
    - fluid overload;
  - treatment should be modified or stopped accordingly.
- **Recurrence of type 1 HRS after discontinuation of terlipressin therapy:**
  - Is relatively uncommon.
  - Treatment with terlipressin should be repeated and is frequently successful (Level A1).

EASL Practice Guidelines
May 2010

- **Use of beta-blockers:**
  - There are no data on whether it is better to stop or continue with beta-blockers in patients with type 1 HRS who are taking these drugs for prophylaxis against variceal bleeding (Level C1). (but beta-blockers decrease survival in “refractory ascites” and after SBP; Serste T, Hepatology 2010;52(3):1017-1022; Mandorfer M, GASTROENTEROLOGY 2014;146(7):1680-1690)
- **Use of paracentesis:**
  - There are few data on the use of paracentesis in patients with type 1 HRS.
  - If patients have tense ascites, large-volume paracentesis with albumin replacement is useful in relieving patients’ discomfort (Level B1).
- **Use of diuretics:**
  - All diuretics should be stopped in patients at the initial evaluation and diagnosis of HRS.
  - There are no data to support the use of furosemide in patients with ongoing type 1 HRS. Nevertheless furosemide may be useful to maintain urine output and treat central volume overload if present.
  - Spironolactone is contraindicated because of high risk of life-threatening hyperkalemia (Level A1).

Practical Approach to HRS-I

AVOID HRS:

- Strict Na restriction
- Minimize Diuretics
- Avoid intravascular depletion: give albumin after LVP.
- Check for and treat hypothyroidism and adrenal dysfunction.
- No NSAIDs or aminoglicosides
- NAC + Na Bicarbonate for IV contrast
- Albumin in SBP (and other infections)
- Norfloxacine for cirrhosis + ascites & creat >/= 1.2 or Na </=130, or TB >3
- Pentoxifylline for AH,
- Add NAC to Prednisolone in AH.
- Pentoxifylline for cirrhosis + ascites & CrCl 41-80 mL/min

EARLY THERAPY:

- Hold diuretics & give IV albumin/0.9%NaCl until CVP 10-15, [1 g albumin/kg up to 100 g (2L of 5% albumin)], then
- Raise MAP by 15, or to 85 mmHg* with either Octreotide /Midodrine, or Noradrenaline, or Terlipressin (Phenylephrine also works well), until Cr is < 1.3 mg/dL.
- Check for and treat hypothyroidism and adrenal dysfunction when MAP is difficult to elevate or HRS recurs.
- Consider TIPS if MELD falls to </= 15
- NAC + TIPS
- Liver Transplant
- Pentoxifylline or Misoprostol (?)

*An optimal MAP of 90 mmHg or increase of 15 mm Hg has been suggested (Velez JC et al **American Journal of Kidney Diseases** - Volume 58, Issue 6 (December 2011)

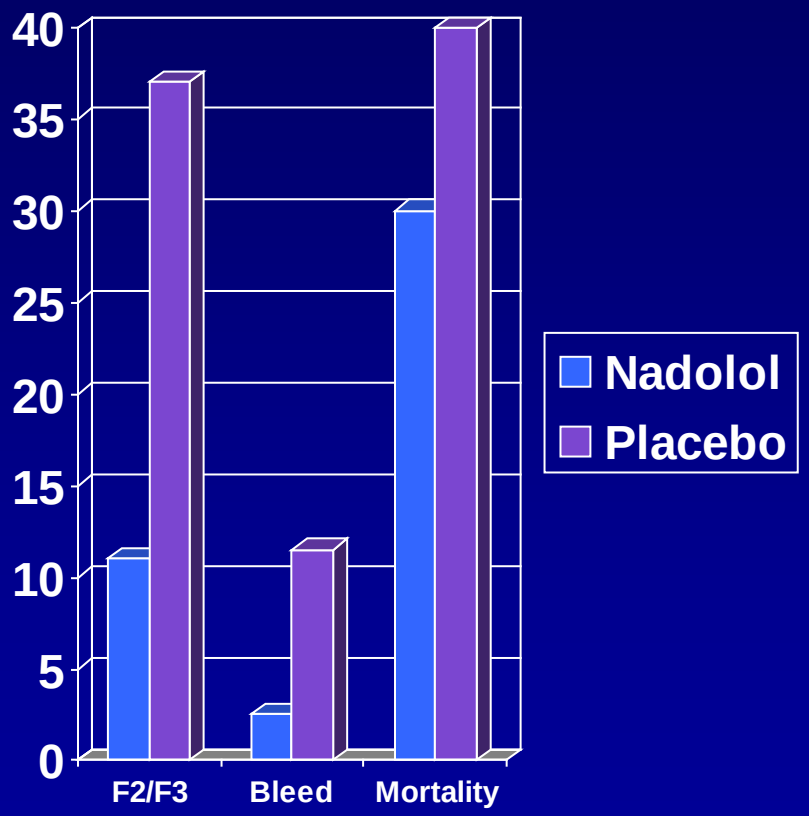
Questions ?

Beta-blockers to Prevent Enlargement of Small (F1) Esophageal Varices (127)

Hepatology 2003;38(4):217A

- Multicenter, prospective, randomized, placebo-controlled.
- 161 cirrhotics with F1 varices (N/P=83/78)
- Matched by age, sex, etiology, severity, time since dx. of cirrhosis and varices.
- EGD q 12 mo. up to 60 months F/U or until development of F2 or F3 varices.
- Nadolol to decrease HR by 25% vs Placebo. After F2/F3 all received Nadolol.

Results (%)

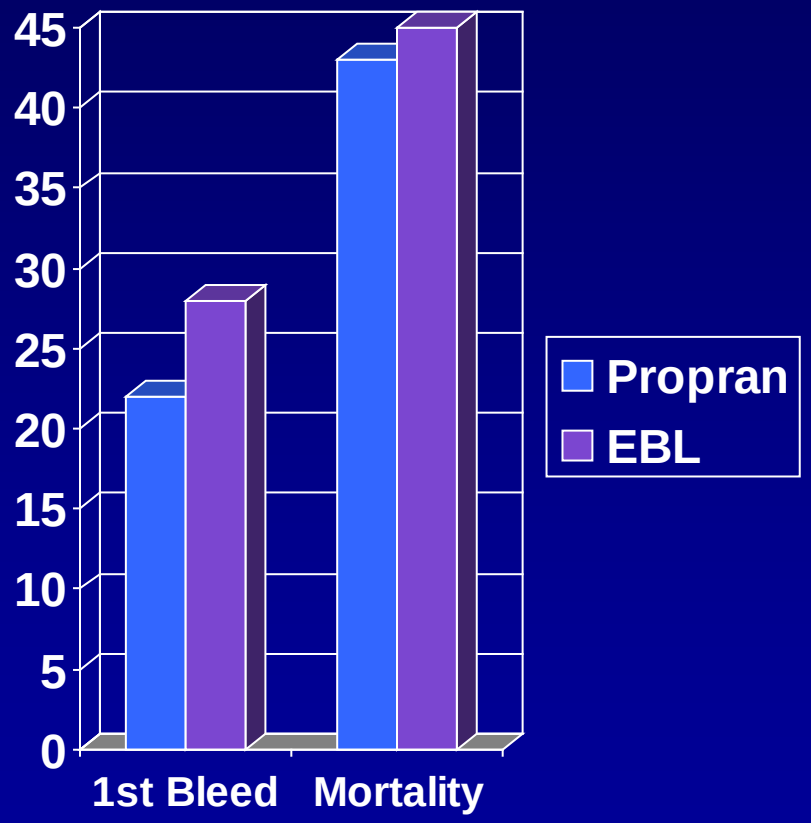


- ***CONCLUSION***
- Nadolol prevents enlargement of small esophageal varices

Propranolol vs Banding as Primary Prevention of Variceal Bleed (128)

- Prospective, randomized, controlled, multicenter.
- 152 cirrhotics with esoph. varices F2/F3 (67/85); Child A/B/C = 71/62/19.
- End-point: bleeding or death (ITT) for up to 2 years.
- Propranolol vs EBL =77 vs 75

Results (%)

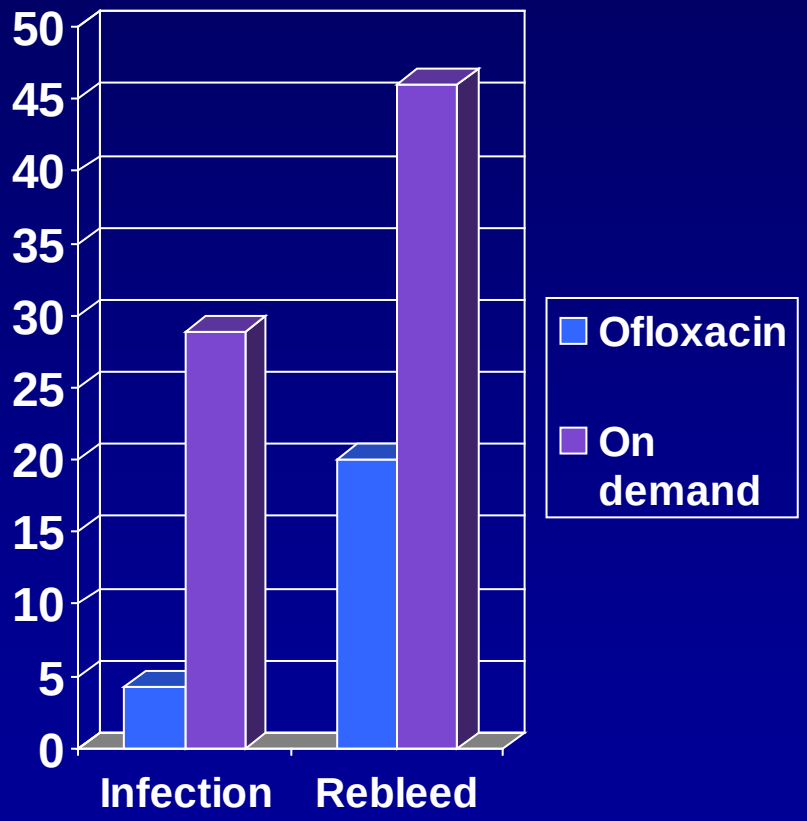


- ***CONCLUSION:***
- EBL is an effective alternative to Propranolol in the prevention of first variceal bleed, in patients with medium or large esophageal varices

Effect of Antibiotic Prophylaxis on Rebleeding rate after Endoscopic treatment of Variceal bleed (283)

- Prospective, randomized.
- 91 cirrhotic patients with variceal bleed receiving endoscopic treatment
- Outcome: rate of rebleeding and infection
- Intervention: Ofloxacin 200mg BIDx 7d vs antibiotic for infection (46 vs 45)
- No difference on: age, sex, etiology, endoscopic finding, time to EGD, hepatoma, severity of bleed.

Results (%)

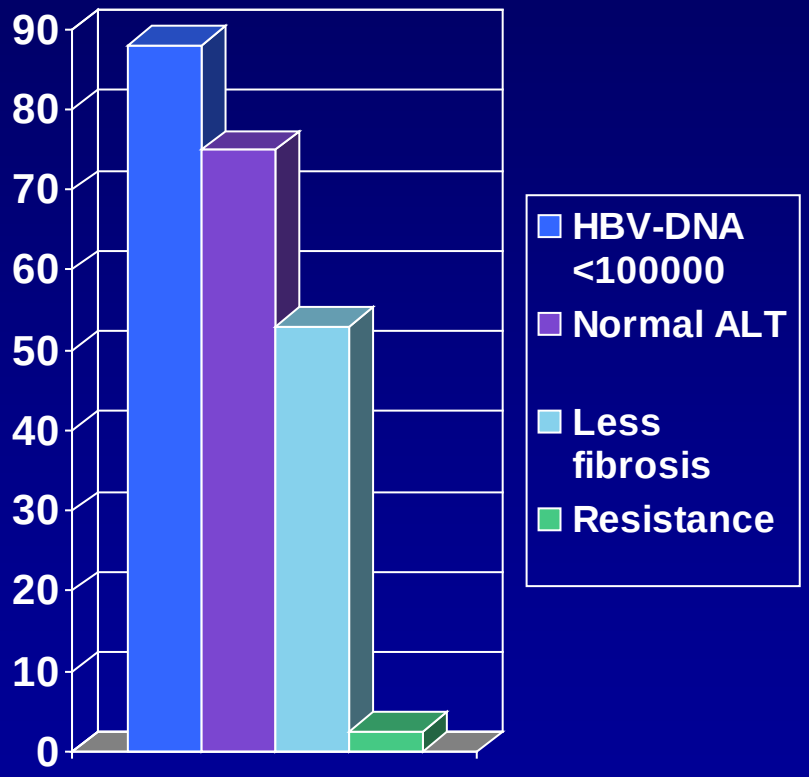


- ***CONCLUSION***
- Prophylactic antibiotics in variceal bleed decrease rebleeding rate and transfusion needs (0.7 vs 2.7 Units)

Long-term (96 wk) Adefovir in HBeAg(-) HBV (241)

- Sub-group analysis of 80 patients enrolled in a prospective, randomized study of Adefovir vs Placebo who received Adefovir for 96 wks.
- All were HBeAg(-) with mean HBV-DNA 10^7 copies/ml and mean ALT 2.3xULN

Results (%)



- ***CONCLUSION***
- Adefovir 10mg/d x 96 weeks reduces HBV-DNA and ALT, and improves histology, with infrequent emergence of resistance

Pegasys +/- Lamuvidine vs Lamuvidine in HBeAg(-)/anti-HBe(+) Chronic HBV (1181)

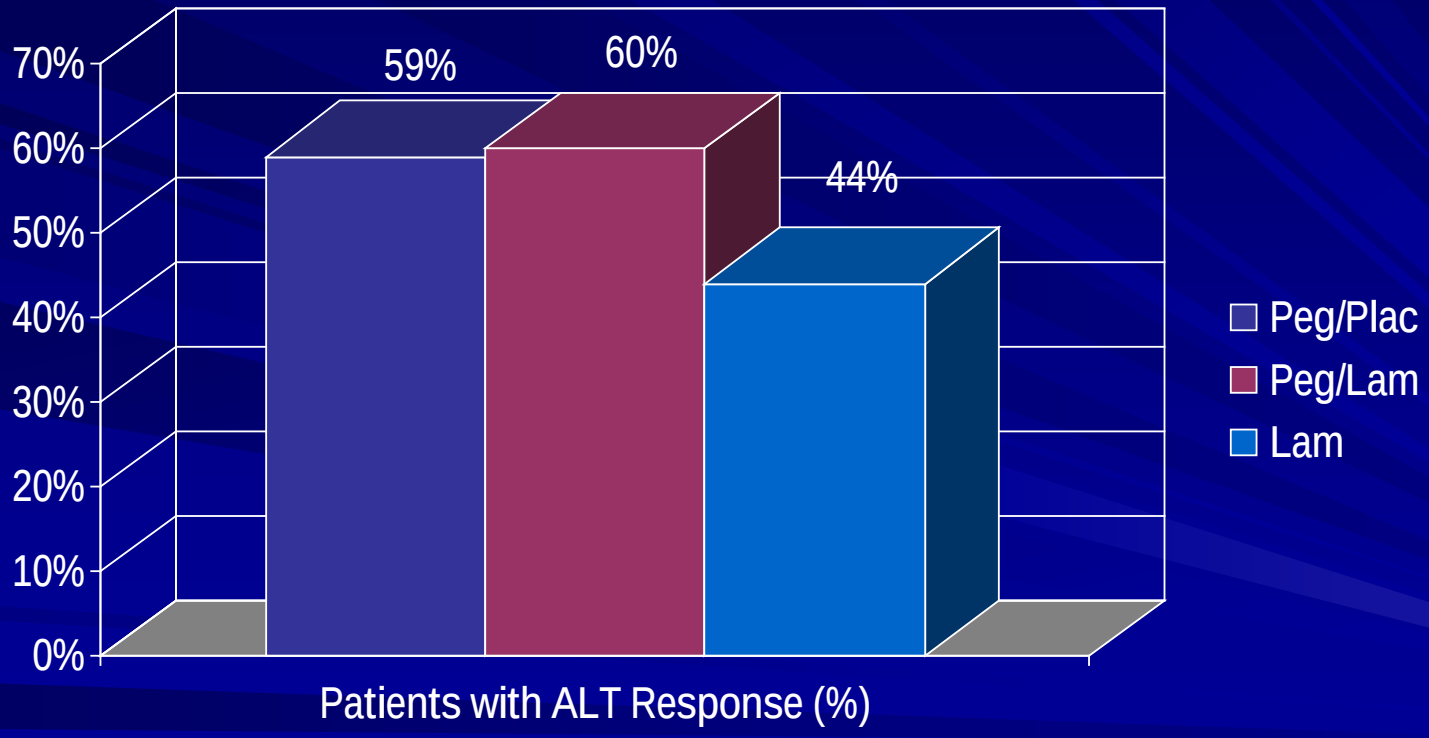
- Multinational, Phase III, Prospective, Partially Double-Blinded.
- 546 patients, HBeAg(-) & anti-HBe(+), HBV-DNA > 10^5 copies/ml, ALT > ULN, necro-inflammation in Bx., compensated liver disease, randomized 1:1:1
- Treatment x 48 wks + 24 wks F/U.
- A) Pegasys 180 mcg/wk, vs
  B) Pegasys 180mcg/wk + Lamuvidine 100mg/d, vs
  C) Lamivudine 100mg/d
- End-Points: HBV-DNA< 20000 copies/ml & Normal ALT @ end-of-follow-up

Patient's Characteristics

- Gender M/F=85/15
- Race Or/Ca=60/39
- Age 40 +/-11
- Weight 70.5 +/- 12
- Mean ALT 96.9
- Advanced fibrosis 27.5%
- HBV-DNA 7.2+/-1.9 lg
- Genotype A/B/C=5/24/34
- Mutations: pre-core 82%, core-promoter 74%, both 58%

HBeAg-Negative/Anti-HBe-Positive Chronic Hepatitis B

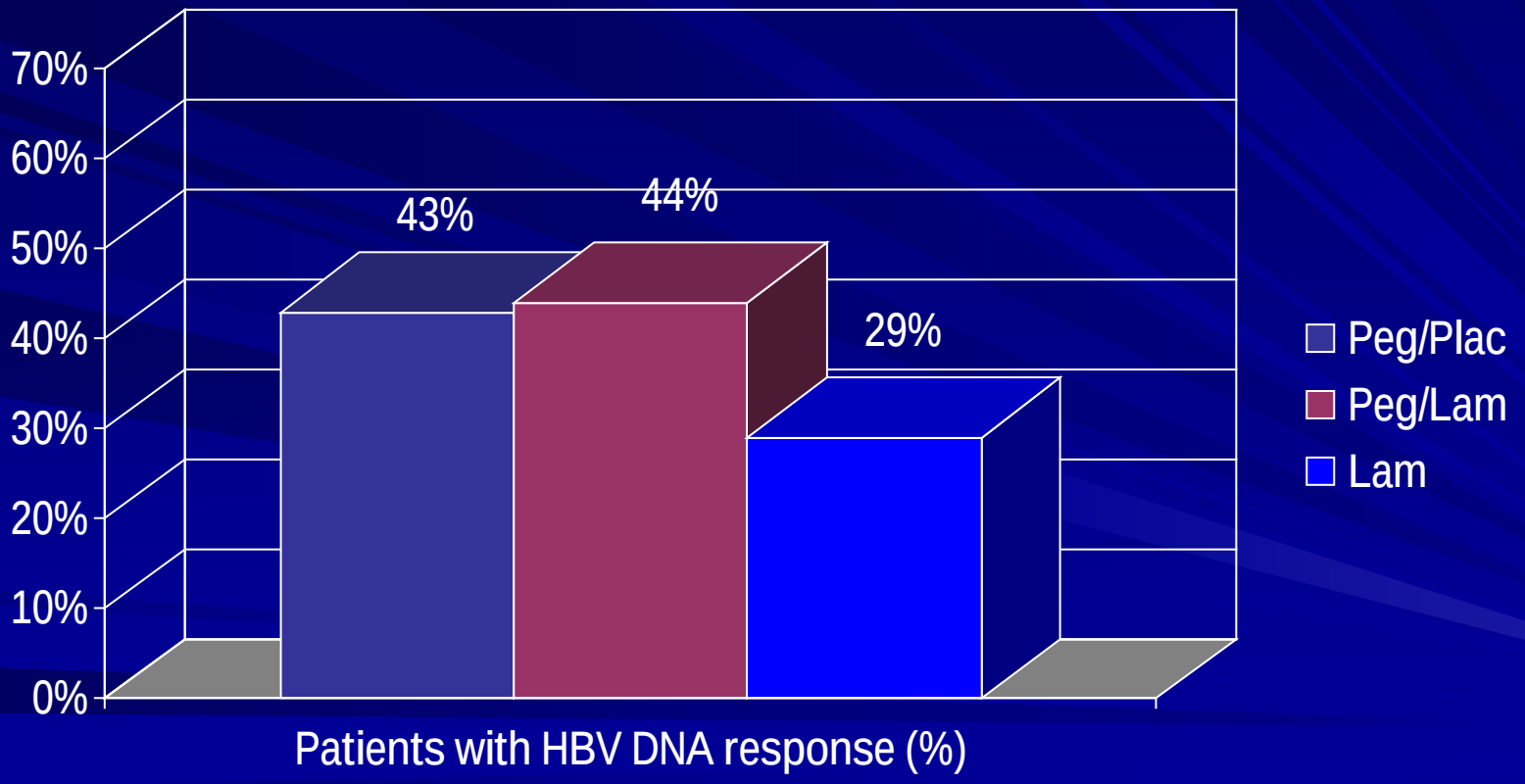
Pegasys, or in Combination with Lamivudine vs. Lamivudine



Marcellin P et al. A Phase III, Partially Double-Blinded Study Evaluating the Efficacy and Safety of Peginterferon Alfa-2A (40 KD) (Pegasys) Alone or in Combination with Lamivudine vs. Lamivudine in 546 Patients with HBEAG-Negative/Anti-HBE-Positive Chronic Hepatitis B (abstract #1181), presented at AASLD, Oct. 24-28, 2003.

HBeAg-Negative/Anti-HBe-Positive Chronic Hepatitis B

Pegasys, or in Combination with Lamivudine vs. Lamivudine



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HBeAg-Negative/Anti-HBe-Positive Chronic Hepatitis B

Pegasys, or in Combination with Lamivudine vs. Lamivudine

Conclusions

- Pegasys monotherapy shows significantly higher response rates at 24 weeks post-treatment for both ALT and HBV DNA than Lamivudine alone.
- **Pegasys + Lamivudine did not improve response rates.**
- No unexpected AEs were reported, and the addition of Lamivudine did not alter the safety profile.

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