



Ascites & HRS
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- Professor of Medicine and Chief of Liver Service at Loma Linda University Medical Center.
- Published 87 peer-reviewed articles (almost entirely focused on ascites), 40 textbook chapters, and fourteen contributions to UpToDate.
- He has been elected to Best Doctors in America 2003-2004, 2005-2006 and 2007-2008. He was elected into America's Top Physicians as well as America's Top Gastroenterologists in 2008.
- He was the first investigator to be asked to write a practice guideline for the American Association for the Study of Liver Diseases (AASLD ascites guidelines).

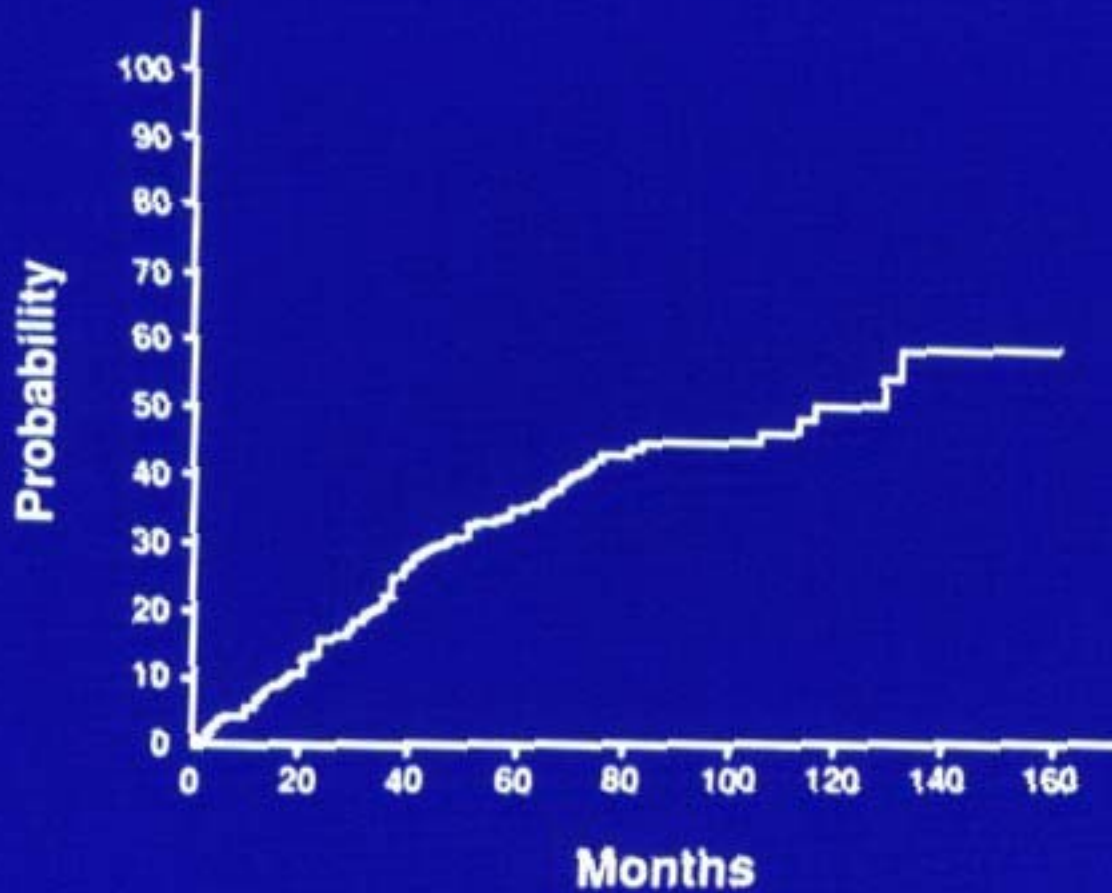


Outline

- Evaluation of the Patient with Ascites
- Tap & Ascitic Fluid Analysis
- Complications of Ascites
- Treatment of Patients with Ascites
- Dx & Rx HRS

Sleisenger and Fordtran 8th Edition
Gastrointestinal and Liver Diseases
2006 pp 1935-64 (9th Coming)
Hepatology 2004;39:841-56
(Update Pending)
UpToDate

CUMULATIVE PROBABILITY OF DEVELOPING ASCITES AFTER DIAGNOSIS OF CIRRHOSIS IN 293 PATIENTS



Hepatology 1987; 7:122-8

Ten-Year Cumulative Probability of Complications of Cirrhosis

- Ascites 47%
- Encephalopathy 28%
- Gut Bleeding 25%

Causes of Ascites

• Cirrhosis	85%
• Mixed	8%
• Heart Failure	3%
• Malignancy	2%
• Tuberculosis	<1%
• Pancreatic	<1%
• Nephrotic	<1%

Differential Diagnosis of Ascites

- Causes of Ascites
 - Special Attention to Curable Diseases: TB, Chlamydia, Pericarditis
- Evaluation
 - History
 - Physical Examination
 - Ascitic fluid Analysis
 - Special Testing

Physical Exam in Ascites Patients

~100% sensitive

- Vascular Spiders
- Palmar erythema
- Abdominal Wall Collaterals
- Jugular Veins
- Umbilical Nodule

Paracentesis

- Routine for New Onset, Admission, or Deterioration
- Diagnostic Tap=22 ga 1.5 inch
- Therapeutic Tap=15-18 ga
- 1% Complication Rate
- ~1/1000 Serious Complication

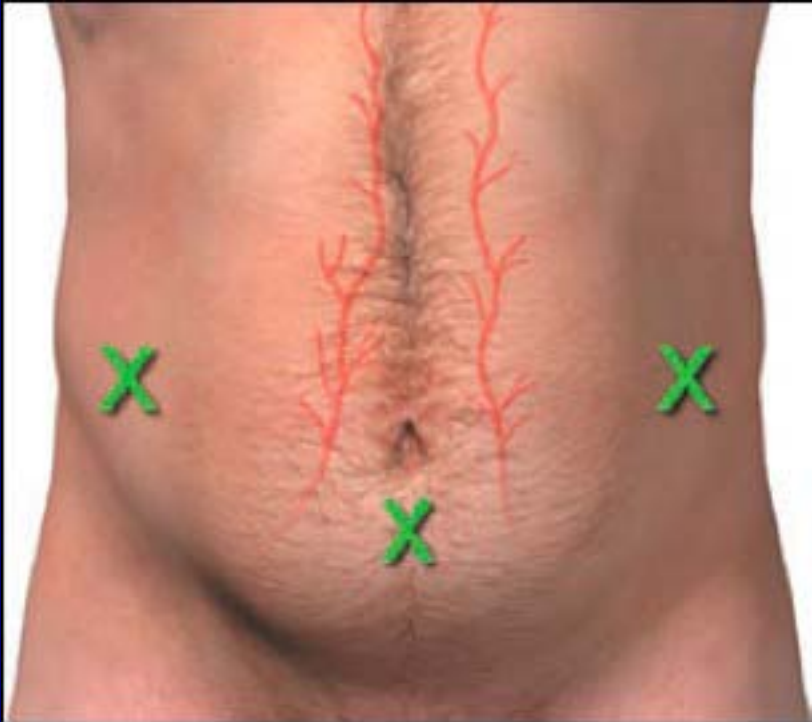
Arch Intern Med 1986;146:2259-61

Transfusion 1991;31:164-71

Hepatology 2004;40:484-8

Video NEJM 2006;355:e21

Tap Site



**I Prefer LLQ 2 FB
Medial & Cephalad to
Ant Sup Iliac Spine**

NEJM 2006;355:e21

Paracentesis

- 1% Abdominal Wall Hematoma
- 70% Coagulopathy
- 1100 LVPs at Mayo Without Transfusions or Complications Despite INR of 8.7, Plt of 19k
- No Need for Transfusions
- Consider DDAVP for CRF

Arch Intern Med 1986;146:2259-61

Transfusion 1991;31:164-71

Hepatology 2004;40:484-8

APT 2005;21:525-9

Ascitic Fluid Tests

Routine	Optional	Unusual	Unhelpful
Cell Count	Glucose	Cytology	pH
Albumin (1 st)	LDH	TB	Lactate
Total Protein	Amylase	Triglyceride	Cholesterol
	Cx in BCB	Bilirubin	Fibronectin
	Gram's stain		

Ascitic Fluid Cell Count

- EDTA Tube="Purple Top"
- Manual Cell Count & Diff
- "Normal" PMN Count Approaches Zero
- Absolute [PMN] ≥ 250 cells/cu mm=Empiric Antibiotics

Rapid Testing for PMNs

- “Dipstick” Testing
 - 90-120 seconds
 - Studies of US Dipsticks Also Positive
 - Ascites Specific Dipstick Coming
- Automated Cell Counting
 - Probably Not Possible

Hepatology 2003;37:745-7

Am J Gastro 2004;99:532-7

Hepatology 2007;45:1275-81

Gastroenterology 2008;134:A792

Serum-Ascites Albumin Gradient (SAAG)

- Not a Ratio
- SAAG ≥ 1.1 g/dL=PHT
- SAAG < 1.1 g/dL=No PHT
- PHT with Peritoneal TB or Ca:
SAAG ≥ 1.1 g/dL
- High vs Low SAAG

Serum-Ascites Albumin Gradient

High (≥ 1.1 g/dL)

Cirrhosis

Alcoholic Hepatitis

Heart Failure

Massive Liver Mets

Fulm. Liver Failure

Budd-Chiari

Low (< 1.1 g/dL)

Peritoneal CA

Tuberculosis

Pancreatitis

Bile Leak

Nephrotic

Lupus Serositis

Other Causes of High SAAG

Portal Vein Thrombosis

Veno-Occlusive Disease

Fatty Liver of Pregnancy

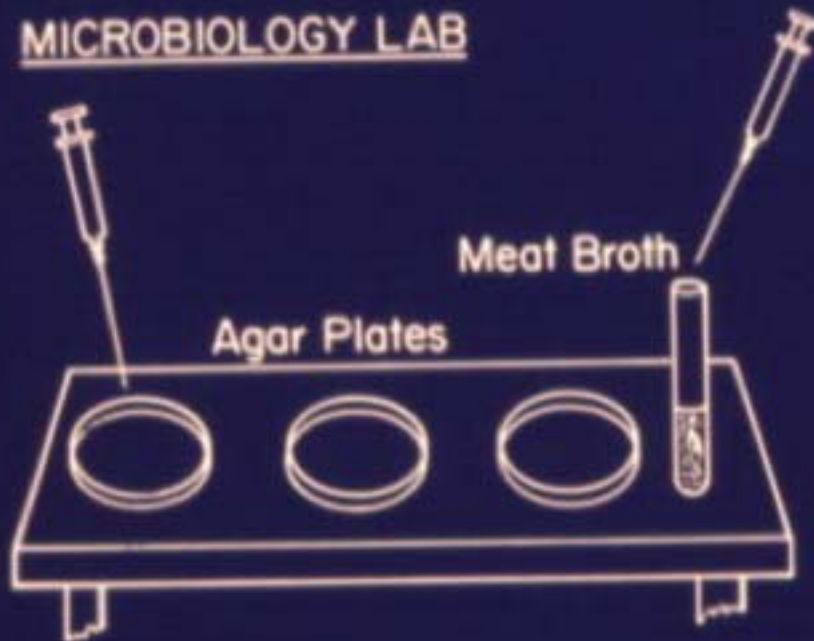
Myxedema

“Mixed”

ASCITIC FLUID CULTURE TECHNIQUES

CONVENTIONAL METHOD

MICROBIOLOGY LAB



LESS THAN 2ml FLUID
INOCULATED IN TOTO
43 % SENSITIVE

BLOOD CULTURE BOTTLE INOCULATION METHOD



WARD



20 ml FLUID INOCULATED
IN TOTO
93 % SENSITIVE

World Literature on Ascitic Fluid Culture

	% Positivity
Conventional Method (136/268)	51%
Blood Culture Bottle (227/277)	82%

Med Chir Dig 1982;11:243-251
Arch Intern Med 1987;147:73-75
Arch Intern Med 1987;147:1849-50
Gastroenterology 1988;95:1351-5
Hepatology 1989;9:662-665
J Clin Micro 1989;27:2145-47
Amer J Gastro 1990;85:1605-8
J Clin Micro 1992;30:667-69

Special Testing

- Abdominal Ultrasound
 - Most Helpful Screening Imaging Study for Liver Patients.
- Cytology for Peritoneal Ca
- TB Smear & Culture

Special testing

- Cardiac Echo
 - Suspected Cardiac Ascites
- Upper GI Endoscopy
 - Screening for Large Varices
 - May Detect H. pylori or Gastric Ca
- Laparoscopy to Rule in TB

Hepatology 2006;44:449A
J Clin Gastro In Press

Large-Volume Paracentesis (LVP)

- LVP Does Not Cause “Vacuum”
- Fluid Forms Slowly, Weeping Across Liver Capsule
- LVP Improves Breathing & Appetite
- Increases Vital Capacity
- Prevents Leaks from Tap Sites

Am J Gastro 1993;88:905-7

Spontaneous Bacterial Peritonitis (SBP)

- Pos AFC, PMN ≥ 250 , No Surg Source
- ~20% Prev. on Adm, Now Lower
- 87% Have Sx, Sn, May Be Subtle
- 77% Due To E. coli, strep, Klebsiella
- Infection Mortality ~0% If Rx Early

Clin Infect Dis 1998;27:669-76

Dig Dis 2005;23:39-46

UpToDate

Empiric Antibiotic Choice

- Single-Agent Third-Gen Cephalosporin
- Cefotaxime: Most Data
- Ceftriaxone: Suboptimal Penetration
- Avoid Nephrotoxic Drugs: 4.0 OR

Hepatology 1985;5:457-62

Dig Dis Sci 1991;36:1782-6

AJG 2001;96:2206-10

Duration of Therapy for SBP

- 100% Penetration of Cefotaxime
- 86% Sterility 6 Hours after 1 Dose
- 5 Days As Good As 10 Days

Dig Dis Sci 1991;36:1782-6

Gastroenterology 1991;100:1737-42

Oral Rx of SBP

- RCT of 123 Patients with SBP
- Exclusions: Shock, Ileus, PSE, Cr >3, GIB
- 61% of SBP Patients Qualified
- Ofloxacin 400 mg po bid vs CTX 2g IV q 6 hr
- No Difference in Response, Duration of Rx, or Survival

Albumin Plus CTX for SBP

- RCT of 126 Pts with SBP: CTX vs CTX +Alb
- 1.5 g/kg in 6 Hrs & 1 g/kg on Day 3
- 29% vs 10% Mortality (p=0.01)
- Lowest Mortality Ever Reported
- Survival Advantage Persisted at 3 Months

NEJM 1999;341:403-9

Prophylaxis

- Norfloxacin 400 mg or Trim/Sulfa 1DS qd for Preventing Recurrence
- Inpatient Daily for AFTP <1 g/dL
- Ceftriaxone 1g IV Daily x 7 Days for GIB
- New RCT c Survival Advantage: AFTP <1.5, Cr \geq 1.2 or BUN \geq 25, C-P \geq 9 c Bili >3
- No Prospective RCTs Regarding Pre-OLT Use

UpToDate: Rx & Prophylaxis of SBP
Gastroenterology 2006;131:1049-56
Gastroenterology 2007;133:818-24

Principles of Evaluation & Treatment Re: SBP

- Tap All Patients With New Onset, On Admission, & for Deterioration
- Bedside Inoculation of BCB
- Treat if PMN ≥ 250 and/or Sn or Sx of Infection
- Avoid Aminoglycosides: CTX is Superior
- Narrow Antibiotic Spectrum When Possible
- Prevention With Norfloxacin or Trim/Sulfa

Rx of Cirrhosis & Ascites

- Abstinence from Alcohol
- Dietary Sodium Restriction: 2g (88 mmol/d)
- Diet Education of Patient & Cook
- Oral Spironolactone & Furosemide
 - Usual Starting Doses 100 mg & 40 mg q AM
- Follow Weight & Urine Sodium

Sodium Balance in Cirrhosis

Skin Na Loss	~5mmol/d
Stool Na Loss	~5mmol/d
<hr/>	
Total Non-Urinary Na Loss	~10mmol/d

JCI 1937;16:729-31
JCI 1950;29:1491-9
JCI 1951;30:1157-70

Sodium Balance

- What Goes In Must Come Out
- Water Follows Na Passively
- Intake-10 mmol=Urinary Output
- Pts on 88 mmol/d Diet Must Excrete
>78 mmol/d or Ur Na>K in Urine to
Lose Weight

J Lab Clin Med 1949;34:1029-38

JCI 1954;33:780-9

Hepatology 1996;24:571A

Hepatology 1996;24:1422-7

Hepatology 2002;36:222A

Diuretics

- Starting Doses
 - 100 mg/d Spiro & 40 mg/d Furosemide
- Follow Wt & Na/K or 24-hr Urine Na
- If No Wt Loss & Ur Na/K <1 or 24-Hr Na $<78/d$, Double to 200 & 80
- Max Doses=400 & 160
- Amiloride Can Be Substituted (10-40 mg/d)

Hepatology 2004;39:841-56

Spiroinolactone

- 5 Day Half-Life of Active Metabolite
- Very Slow as Single Agent
- Once Daily Dosing
- 25 mg, 50 mg and 100 mg Pills
- New Agent: Eplenerone

Gastroenterology 1992;102:1680-5

Avoid IV Furosemide

- IV Furosemide: Reflex in CHF
- Counterproductive in Cirrhosis
- Reduces GFR & Causes Azotemia
- Use IV Furosemide Only Rarely
- LVP Is Preferable

Gastroenterology 1987;92:1859-63

Rx of Patients with Ascites

- Medical Rx: 90% Effective
- Options for Diuretic-Resistant Patients
 - LVP ~q 2 Weeks (8 liters)
 - TIPS
 - Liver Transplantation
 - Peritoneovenous Shunt: LeVeen or Denver

Hepatology 2004;39:841-56

Pseudorefractory Ascites

- High Sodium Intake
 - Non-Compliance
 - No Diet Education
 - Favorite Food
- IV Saline or Medication
- NSAIDs

Tap Equipment

- Tri-Med Caldwell 15-ga 3.25 inch
 - End Hole & Side Holes
- GI Supply RP System
 - Peristaltic Pump 1 L/2 Minutes
 - Longest Needle
- Requires #11 Scalpel Nick

Albumin After LVP

- Study Design is a Problem
- In the 1st Study 31% of Patients Had Not received Diuretics
- Most Pts in these Studies are Diuretic-Sensitive, But Have Tense Ascites
- Albumin Not Needed for Taps <5L
- Albumin Optional for $\geq 5L$, ($\sim 8g/L$)

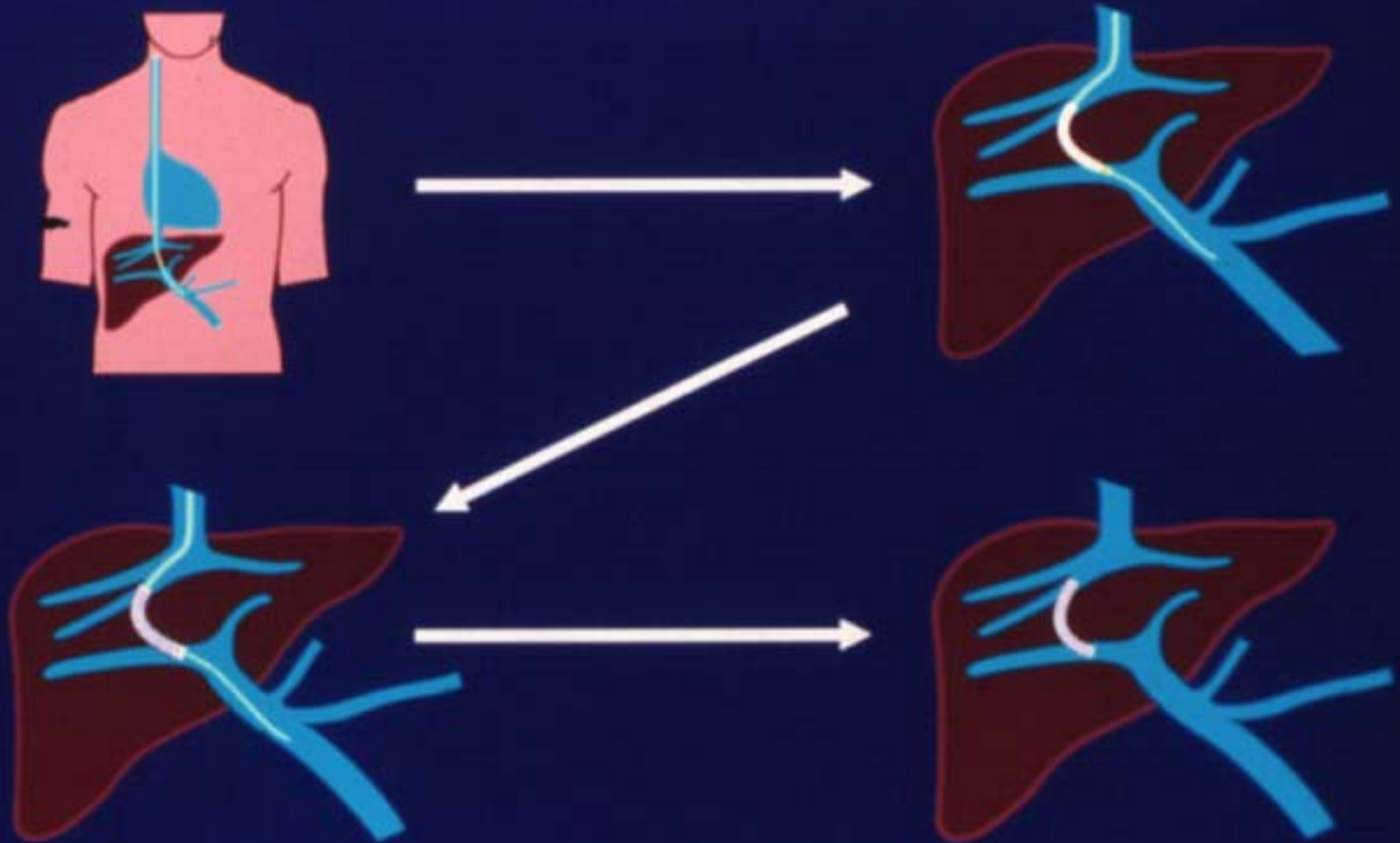
Am J Gastro 1997;92:371-3
Liver Internat—Debate May 09

TIPS

- Transjugular Intrahepatic Portasystemic Stent-Shunt
- Initial Wild Enthusiasm
- Now Much Better Selection

TIPS

Transjugular Intrahepatic Portosystemic Shunt



TIPS for Refractory Ascites

- Side-to-Side Radiologic Shunt
- Usually Converts Diuretic-Resistant to Diuretic-Sensitive
- ~25% Encephalopathy but Treatable
- Much Better Control of Ascites Than Taps
- Possible Survival Advantage

NEJM 2000;342:1701-7

Gastroenterology 2002;123:1839-47

Gastroenterology 2003;124:634-41

TIPS

- Indications
 - Diuretic-Resistant Ascites
 - Multiple Rapid Readmissions for Ascites
 - Refractory Hepatic Hydrothorax
 - Thin Umbilical Hernia

Gastroenterology 2003;124:1700-10
Hepatology 2005;41:386-400

Large-Scale RCTs: Uncoated TIPS for Ascites

Ref	No.	Control	Survival	Enceph
NEJM 2000 342:1701	60	61 vs 18% p=0.006	69% vs 52% p=0.02 mul	58% vs 48% NS
Gastro 2002 123:1839	70	51% vs 17% p=0.003	41% vs 35% NS	All 77 vs 66 NS Sev 60 vs 34 p=0.03
Gastro 2003 124:634	109	58% vs 16% p<0.001	40% vs 37% NS	Mod-Sev 38 vs 12, p=.06
Hep 2004 40:629-35	66	79% vs 42% p=0.0012	77% vs 52% p=0.021	61% vs 39% NS

Goretex TIPS

- Coated: Less Stenosis, No Day 1 U/S
- Vienna Multi-Center Retrospective Study
 - 419 Bare vs 89 Goretex (45 for Ascites)
 - Goretex Had Better Survival: 3 mo, 1 yr & 2 yr
- International RCT
 - 80 Patients (32 Ascites)
 - PPG at 6, 12, 24 Months
 - 13% vs 44% Shunt Dysfunction, $p < 0.001$
 - 8% vs 29% Clinical Relapse, $p < 0.05$
 - No Change in PSE or Survival

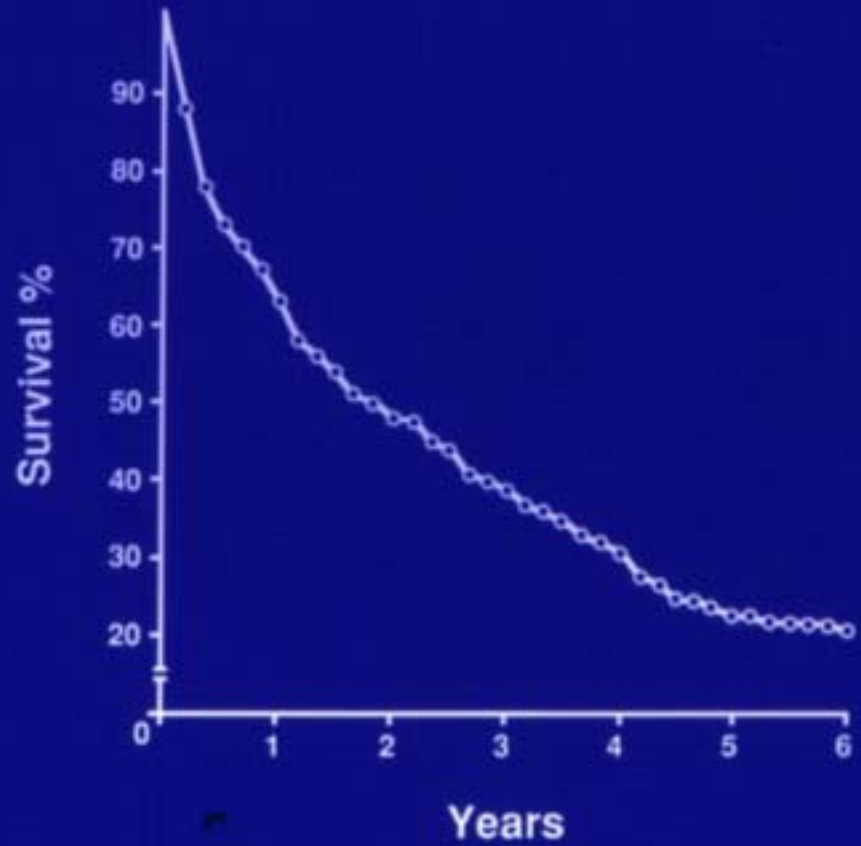
Hepatology 2003;38:1043-50

Gastroenterology 2004;126:469-75

My Personal Tips on TIPS

- It Is Difficult to Show Survival Advantage
- TIPS is Getting Better and Better
- TIPS Improves Hepatologist's QOL & Maybe Pt's
- Choose Patients Wisely
 - <60 y/o, Caregiver in House, Child-Pugh ≤ 12
 - Check MELD for Predicting 3-mo Survival, <18
 - No Alcoholic Hepatitis (80% mort)
 - Ejection Fraction $\geq 60\%$ (nl EF=76% Hep 2002;35:1441-8)
 - Target PPG <8 mm Hg
 - No Severe Spontaneous PSE or 2nd Hit
- Use Diuretics post TIPS
- Goretex Appears To Be a Major Step Forward

SURVIVAL AFTER DECOMPENSATION IN 1155 PATIENTS WITH CIRRHOSIS



DIG DIS SCI 1986; 31: 468-75

PEG in Patients with Ascites

- Ascites is a Contraindication to PEG
- Omentum Cannot Seal a Leak with Fluid Bathing the Surfaces
- I Have Seen No Survivors

Treatment Options

- First Line
 - Abstinence from Alcohol
 - Na-Restricted Diet & Diuretics
 - Consideration of OLT

Treatment Options

- Second Line
 - Q 2 Week Outpatient Taps
 - TIPS
 - Consideration of OLT

Treatment Options

- Third Line
 - Denver Shunt
 - LeVeen Shunt

Hepatorenal Syndrome: Updated Definition in Cirrhosis

- Cirrhosis with Ascites
- Cr >1.5 mg/dL
- No Improvement to Cr \leq 1.5 Despite 2 Days of Diur Withdrawal & 1 g/kg IV Alb Up to 100 g/d
- No Shock or Nephrotoxic Rx
- Ur Prot <500 mg/d, Ur RBC <50/hpf, NI U/S

- 71% of “HRS” is Misdiagnosed

Gut 2007;56:1310-8

Hepatology 2005;42:410A

Hepatorenal Syndrome

- Type 1: Rapidly progressive reduction of renal function: doubling of serum Cr >2.5 mg/dL or 50% reduction in CrCl to < 20 mL/min in less than 2 weeks
- Type 2: Azotemia has a less rapidly progressive course

Hepatology 1996; 23:164-76

Octreotide/Midodrine

- Angeli, et al: Oral Adrenergic Agonist (Midodrine) + Volume Expansion + SC Nonspecific Inhibitor of Endogenous Vasodilators (Octreotide)
- Improvement in Both Systemic and Renal Hemodynamics and Urinary Sodium Excretion
- 5 Treated Patients vs 8 Dopamine Controls

Octreotide & Midodrine

- 20-40 g Albumin Per Day
- Midodrine: 7.5, then 10, then 12.5 mg tid to Achieve MAP \geq 15 mm Hg
- Octreotide: 100 mcg tid, Then 200 mcd tid
- 20 Days Treatment
- 3/5 Survived vs 1/8
- 3 Patients Went Home on Rx

“Good News for Hepatorenal Syndrome”

- Old Days: “Only Complication of Cirrhosis Without Effective Treatment”
 - 15 Day Median Survival
- Vasoconstrictor Rx Very Promising

UA Findings: USC Liver Unit Data on Day of Dx

- 24-hour Volume 465 mL 56% >400
- Na mmol/L 14 38% >10
- Na mmol/d 25
- FENa 0.26
- CrCl 21 mL/min

Rancho HRS Study

- HRS is Usually Non-Oliguric
- Octreotide/Midodrine is Non-toxic
- Can be Delivered on the Ward or Even at Home
- Compared with Non-randomized Controls:
 - Reduction of Mortality from 71.4% → 43.3%
 - Improvement in Serum Cr from 40% vs 9.5%

Nature CPN 2006;2:169-72

Dig Dis Sci 2007;52:742-8

Dosing and Tolerance

- Dosing of midodrine had a statistically significant effect on reduction of serum Cr ($p = 0.029$)
- Among 8 patients who received 15 mg dose, 7/8 (87.5%) had reduction of serum Cr to <1.5

Now I Give 50 mcg/hr if Possible & Increase Mid Dose c Each Dose: 7.5, 10, 12.5, 15 To Increase Sys BP ~10 mm

- Only one patient (age 82) required a reduction of midodrine dose due to hypertension

Terlipressin Treatment of Type I HRS

- US (Plus Germany & Russia) Multi-Center RCT
 - 112 Patient: Creatinine ≥ 2.5 mg/dL (Too High)
 - Terlipressin 1 mg/6 hrs vs Placebo
 - Primary Endpoint: Cr ≤ 1.5 x 48 hrs by Day 14 without dialysis, death or OLT (Silly Endpoint) 25% vs 12.5%, p=0.093
 - Cr ≤ 1.5 , 34% vs 13%, p=0.008
 - Mort at 60 Days, 48% vs 48% (>30% OLT)
 - HRS Reversal Improved Survival at Day 180

Gastroenterology 2008;134:1360-8

Editorial in Gastro 2008;134:1608-11

Terlipressin Treatment of HRS

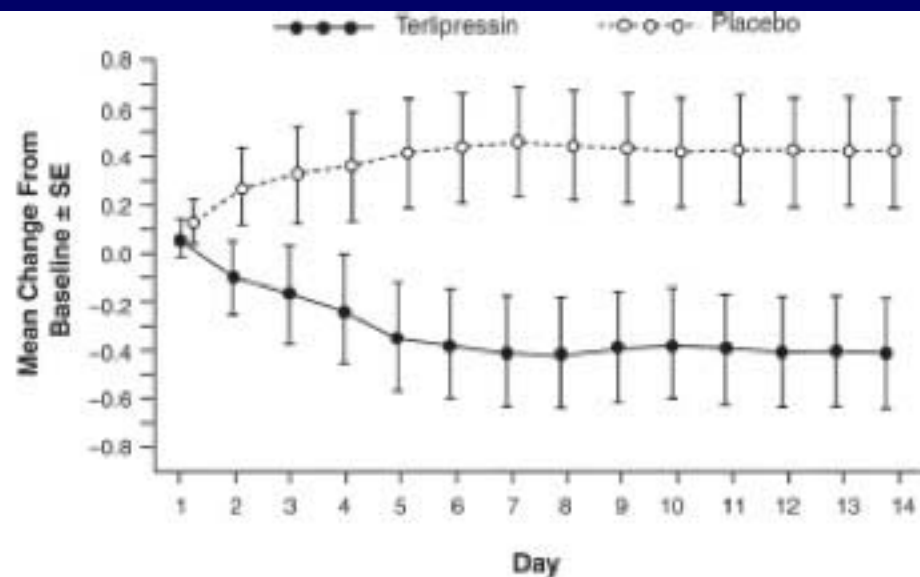
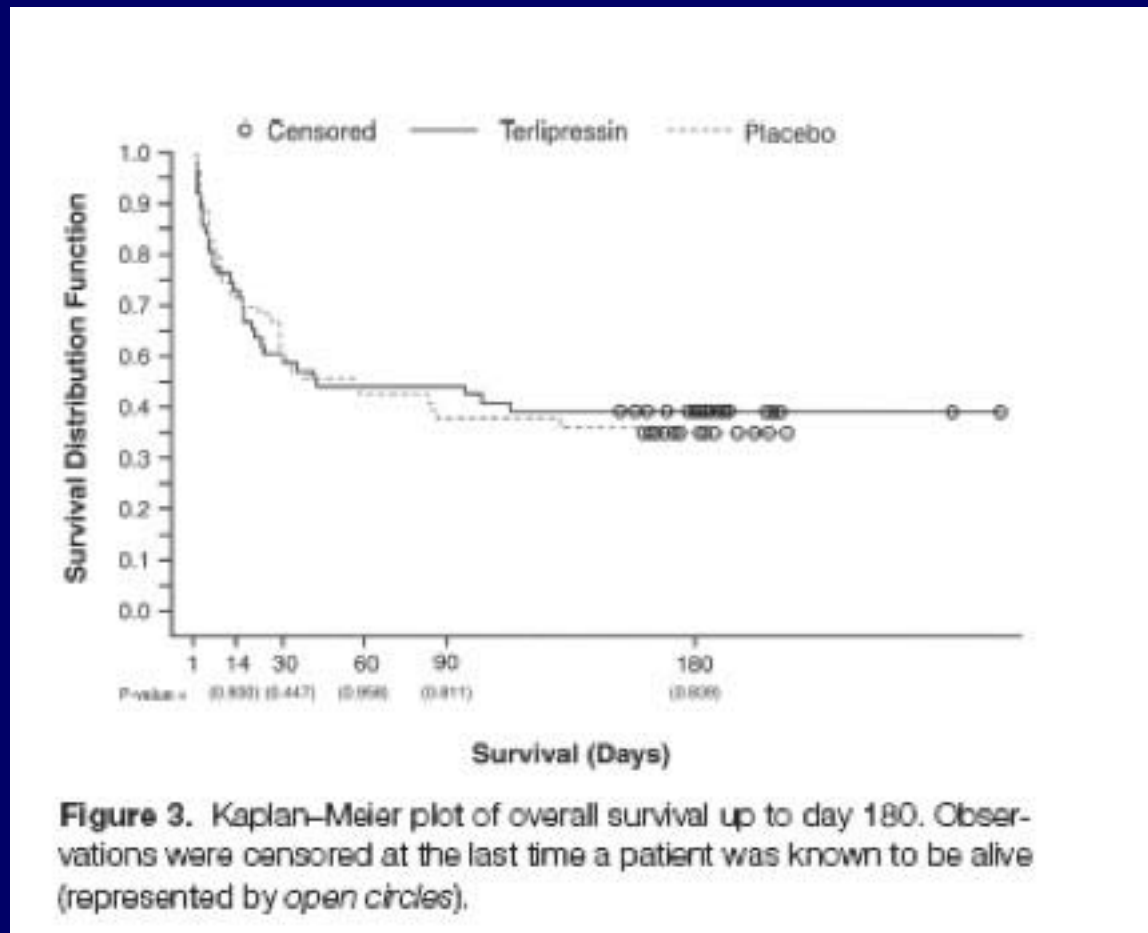


Figure 2. Mean change from baseline in SCr (mg/dL) to end of treatment. Data include all patients in the ITT population at each time point. The mean change from baseline values represents the change from baseline to end of treatment using the last observation carried forward in the ITT population.

Terlipressin Treatment of HRS



Terlipressin Treatment of HRS

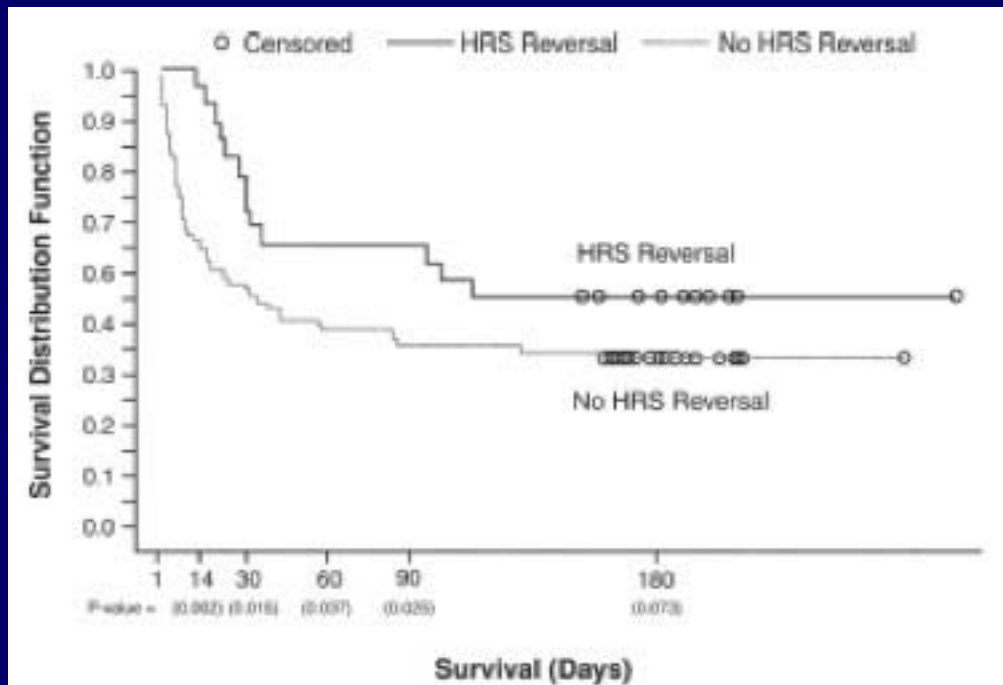


Figure 4. Overall survival for HRS reversal vs no HRS reversal. Observations were censored at the last time a patient was known to be alive (represented by *open circles*). All patients are included irrespective of treatment.

PostHoc Analysis of US Terlipressin RCT

- US Multi-Center RCT
 - HRS Reversal Decreases By 39% for Each 1mg/dL in Serum Creatinine
 - HRS Reversal Decreases By 5.5% for Each MELD Point
 - 0 Reversal If Terli Was Started After Cr >5.6
 - 0 Reversal If Terli Was Given ≤ 3 Days

PostHoc Analysis of US Terlipressin RCT

- If Patients Who Received <3 Days of Rx Were Excluded:
 - Primary Endpoint: 38% vs 18% $p<0.04$
 - HRS Reversal: 53% vs 18% $p<0.02$

Terlipressin Treatment of HRS

- Spanish RCT
 - 46 Patients: Terlipressin 1-2 mg IV q 4 hrs vs Placebo—Non-Blinded. Max Rx 15 Days
 - Alb 1g/kg x 1, Then 20-40 g /d
 - 75% vs 78% Type I, Remainder Type II
 - Primary Endpoint: Survival at 3 Months & Improvement in Renal Function
 - Cr \leq 1.5, 44% vs 9%, p=0.017
 - Survival at 3 Months, 27% vs 19%, p=0.7

My Criticisms of US Terlipressin RCT

- Serum Creatinine ≥ 2.5 mg/dL, Too High
- 1 mg Bolus/6 hr, Wait 3 days, Then Double
- 6 in Terli Group Cr >7 vs 0 in Control Group
- One Third of Patients Received <3 Days of Rx. None Responded
- Only 88% Received Albumin
- “Too Little, Too Late”

Criticisms of Spanish RCT

- Too Small: 46
- Not Double-Blind
- Predicted 3-mo Survival 35% vs 5%--Actual Survival 27% vs 19%
- Included Type II
- Did Not Increase Dose for 3 Days

Vasoconstrictor Rx of Type I HRS

- Seems to Reverse Azotemia
- May Improve Survival
- Terlipressin May/May Not Come To US
- Oct/Mid Is What We Have For Now
- In ICU Consider NE or Vasopressin

HRS: Summary

- Usually in Setting of Advanced Cirrhosis or Alc Hep
- Often Misdiagnosed
- New Definition
- Often Non-Oliguric & with UNa >10
- Rx Type II: Liver Transplant
- Rx Type I: Vasoconstrictors Promising