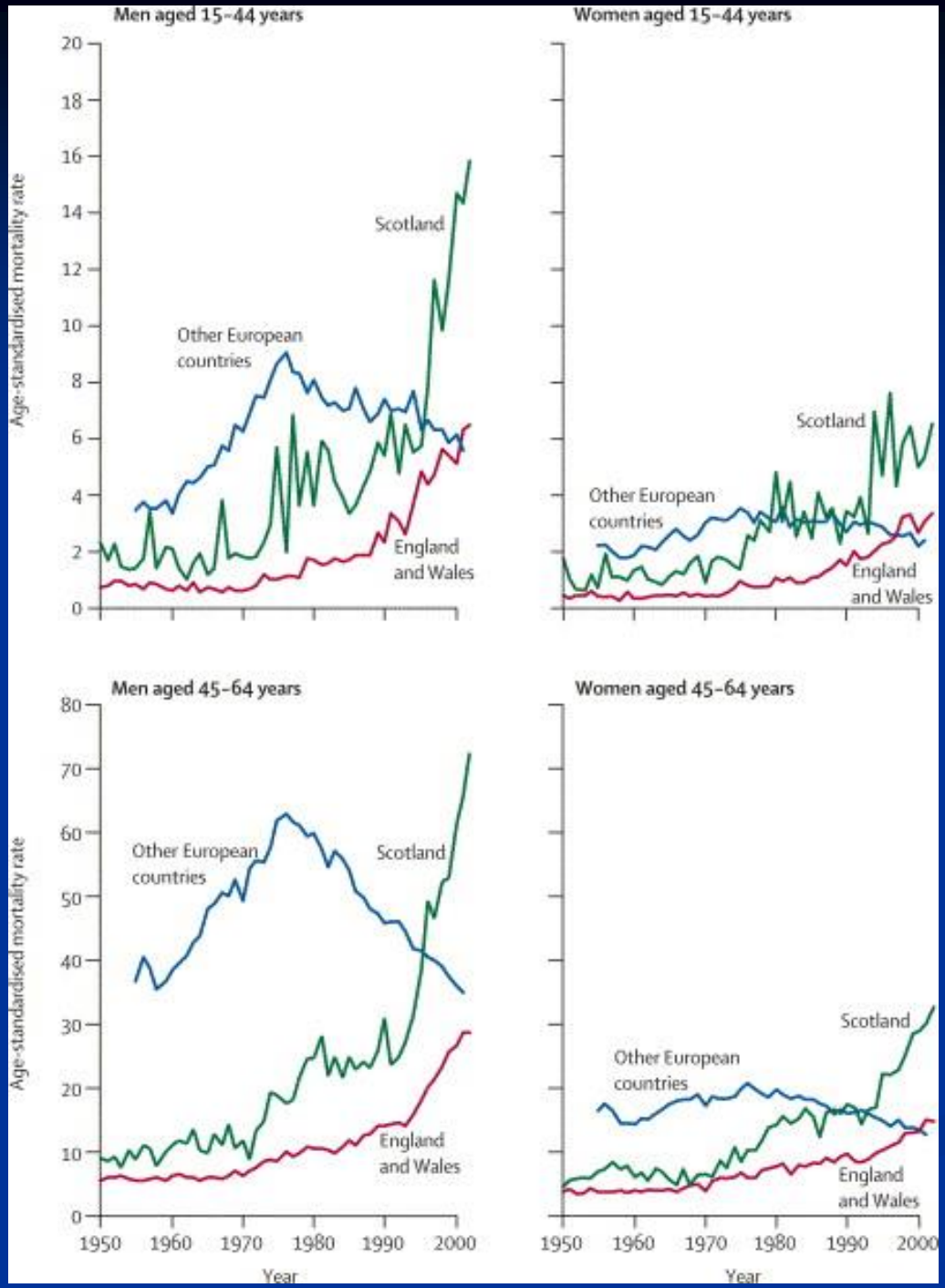
The patient with alcoholic liver disease in ITU

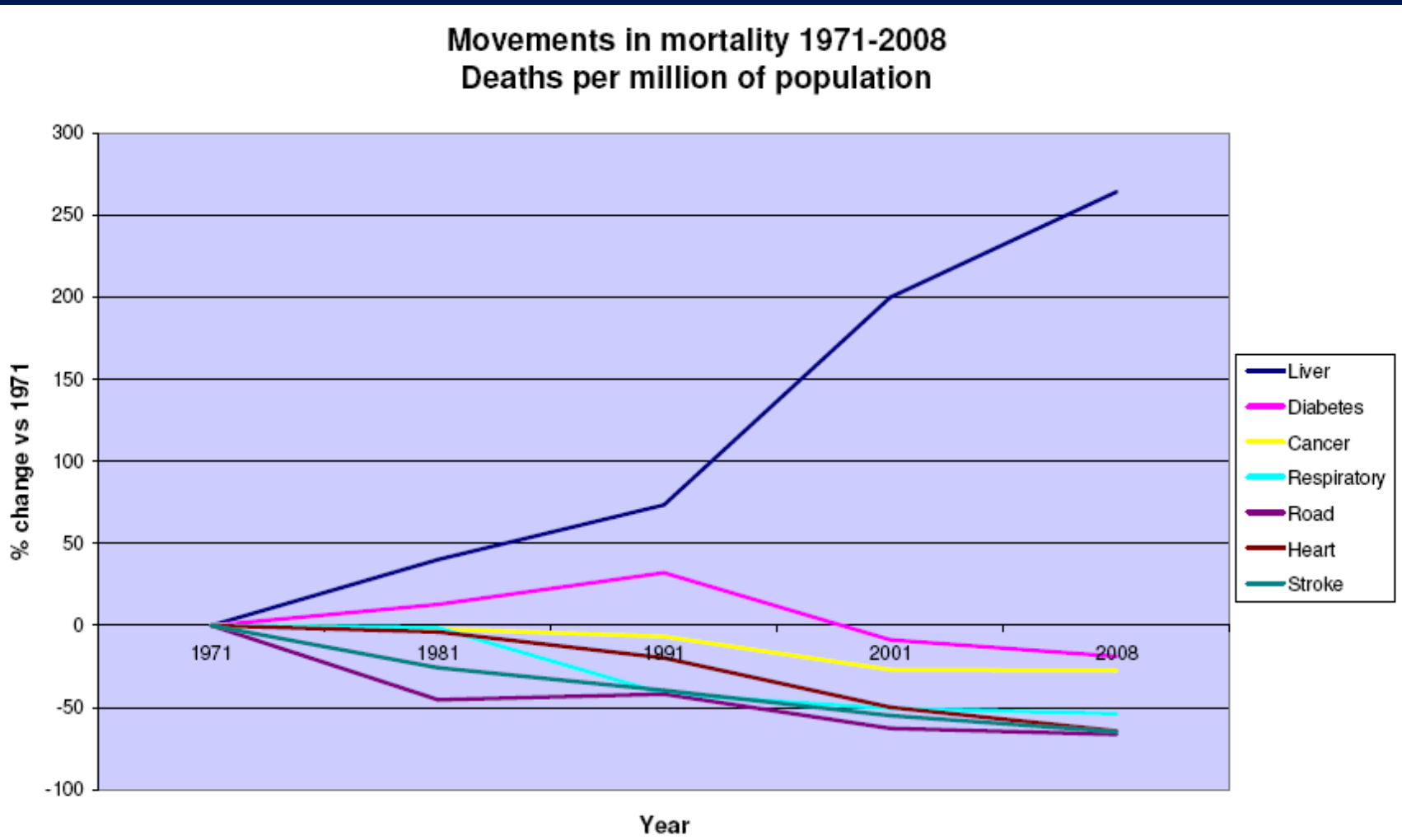
Dr Mark Hudson
Liver Unit, Freeman hospital
Newcastle upon Tyne

Cirrhosis Mortality

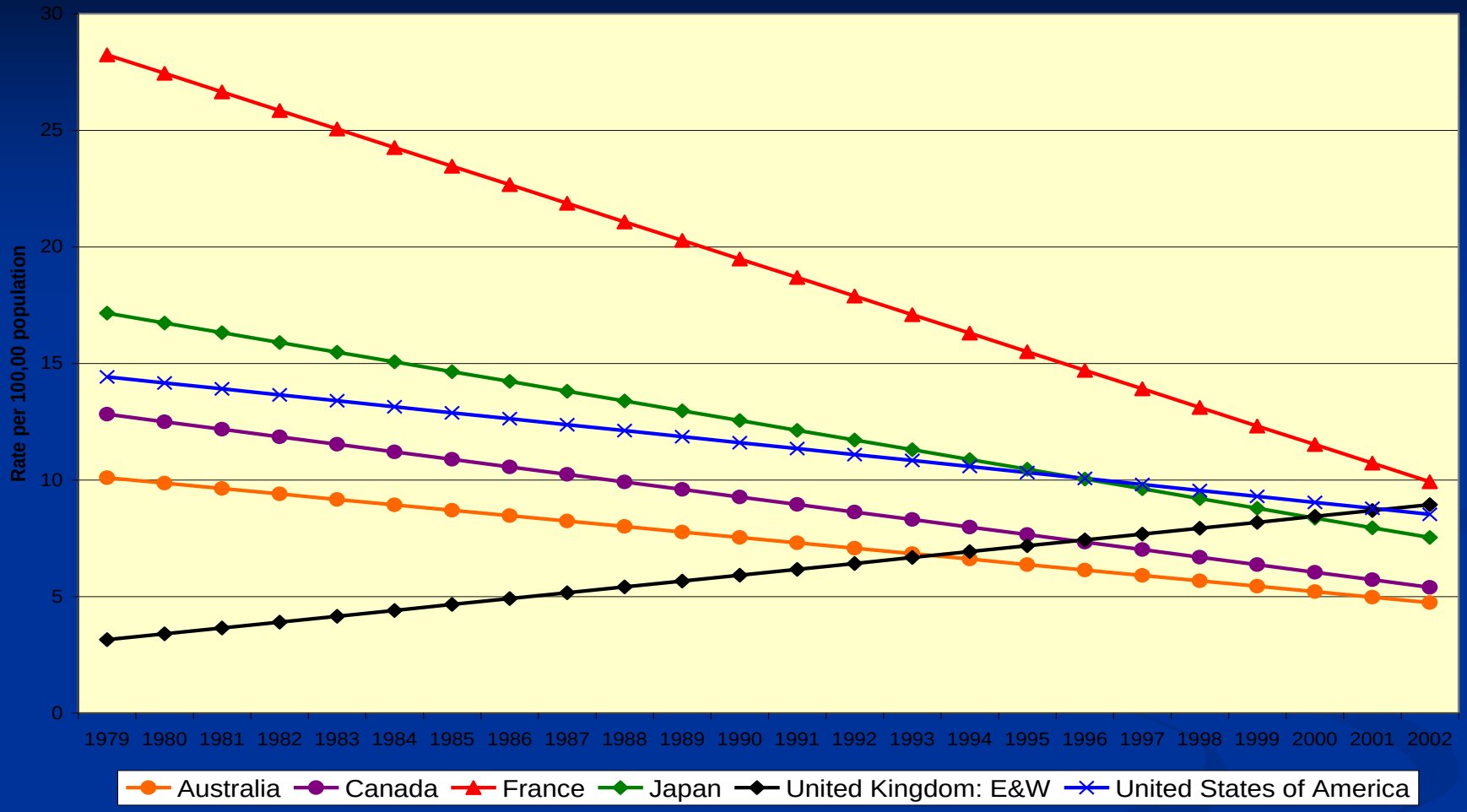
- Rising mortality reflects rising consumption



Leon. *Lancet*, January 2006


Movements in mortality 1971-2008
Deaths per million of population
% change vs 1971
300
250
200
150
100
50
0
-50
-100
1971
1981
1991
2001
2008
Year
Liver
Diabetes
Cancer
Respiratory
Road
Heart
Stroke

Trends in mortality from liver disease in selected countries



If the current trend continues deaths from liver disease in the UK will have overtaken those in France, a country which in 1979 had approximately five times the number of deaths (standardised for age and sex) of England and Wales.

"Patients with cirrhosis are frequently denied access to ITU"

- Grounds of futility
- "Prognostic pessimism"
- Is this pessimism justified ?

Survival of cirrhotics admitted to ITU

Author	Number	Survival	
		ITU	Hospital
Cholongitas et al 2006 (UK)	348	-	35%
Aggarwal A et al 2001 (USA)	240	63%	51%
Wehler et al 2001 (Germany)	143	64%	54%
Arabi et al 2004 (Saudi Arabia)	129	-	26%
Zimmerman et al 1996 (USA)	117	-	37%
Tsai et al 2003 (Taiwan)	111	-	35%
Rabe et al 2004 (Germany)	76	41%	-

King's Liver Unit

- 763 patient admission episodes 2000 -2007
  - 105 excluded due to being elective admissions
  - Further 95 were re-admission episodes
- 563 first admission episodes analysed
- All data non parametric
  - Results reported as median and interquartile range (IQR) or number (%)

Courtesy Jules Wendon

Patient characteristics on ITU admission

Number		563
Age		50 (16-87)
Male		348 (62%)
Aetiology	Alcohol	263 (47%)
	Viral hepatitis	98 (17%)
	Autoimmune	73 (13%)
	Cryptogenic	48 (9%)
	Other	81 (14%)
Reason for admission	Variceal Bleed	196 (35%)
	Non Variceal Bleed	367 (65%)
Scoring System	Child-Pugh	12 (11-13)
	MELD	25 (14-34)
	APACHE II	22 (16-28)
	SOFA	11 (8-13)

Organ Support

Organ Support	Day 1	At any time
Number Requiring Ventilation	349/563 (62%)	405/563 (72%)
Number Requiring Vasopressors	202/563 (36%)	229/563 (41%)
Number Requiring RRT	102/563 (18%)	273/563 (49%)

ITU Survival/Non Survival

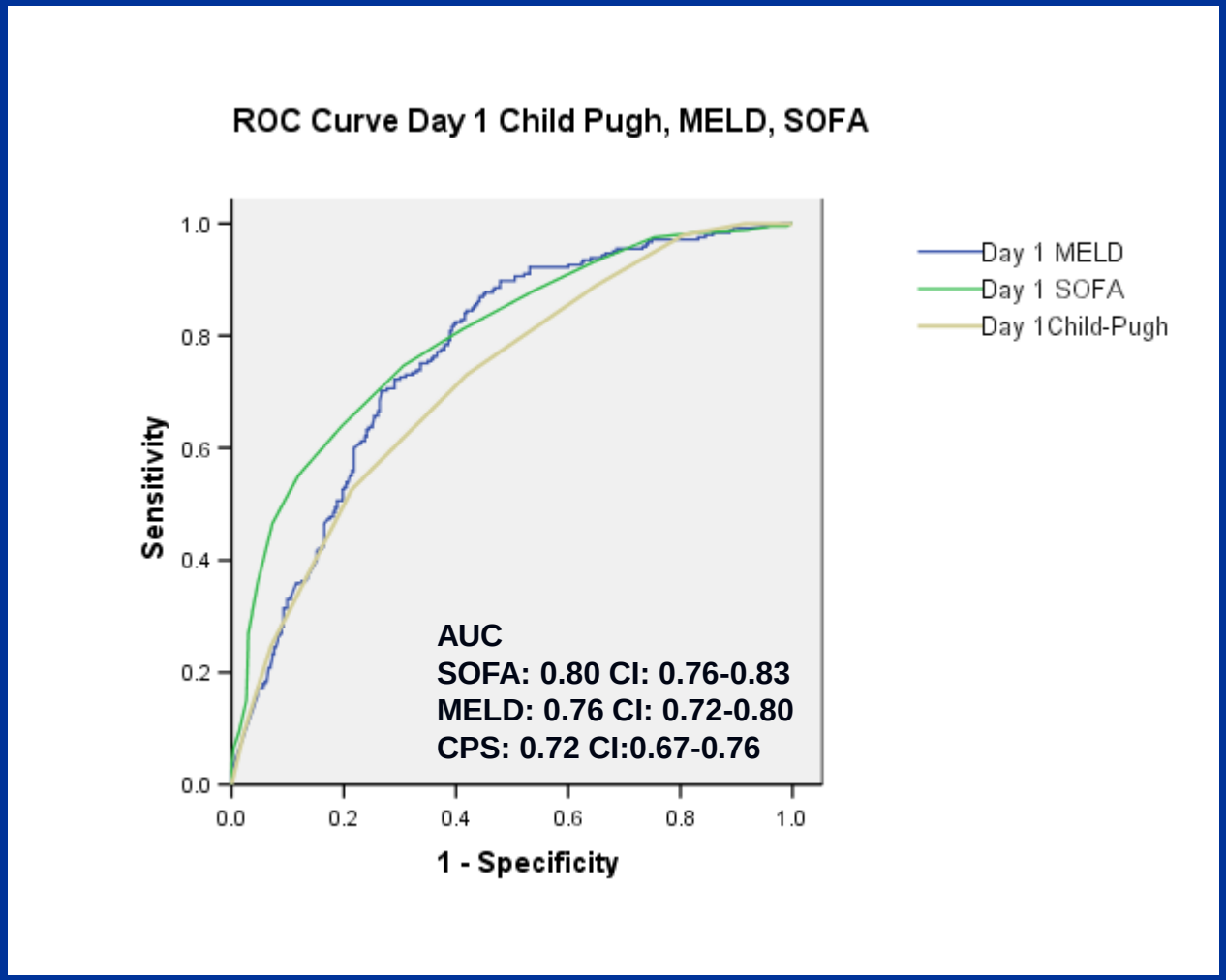
		Survivors	Non-survivors	p value
Number		307 (55%)	256 (45%)	-
Age		49 (30-68)	51 (34-68)	ns
Male : Female		196:111	152:104	ns
Aetiology	Alcohol	146/263 (56%)	117/263 (44%)	ns
	Other	161/300 (54%)	139/300 (46%)	
Reason for Admission	Variceal Bleed	139/196 (71%)	57/196 (29%)	<0.0001
	Non Variceal	168/367 (46%)	199/367 (54%)	

Mortality changes over time

	2000-2004	2004-2007	p value
LITU Survival	128/263 = 49%	179/300= 60%	0.009
Hospital Survival	89/263= 34%	139/300= 46%	0.003
MELD	25	25	0.86
SOFA	11	10	0.009
APACHE II	23	20	0.003

ITU Survival/Non Survival

	Survivors	Non Survivors	p value
Child-Pugh score	11 (10-12)	13 (11-13)	<0.0001
MELD	17 (10-28)	31 (23-37)	<0.0001
APACHE II	17 (14-23)	27 (21-31)	<0.0001
SOFA	9 (7-11)	13 (10-16)	<0.0001
Requirement for RRT	27%	73%	<0.0001
Requirement for Vasopressors	20%	80%	<0.0001
Requirement for Ventilation	44 %	56%	<0.0001



	Day		Survivors		Non Survivors	p value
SOFA	1	ns	9 (7-11)	p<0.0001	13 (10-15)	<0.0001
	3		9 (6-12)		16 (12-18)	<0.001

Hospital Outcomes

- 41% of total cohort survived to hospital discharge
- 122 patients in this cohort were listed for transplantation with 59 (19%) of ITU survivors undergoing liver transplantation

Conclusions

- ITU admission not futile in cirrhotic patients with organ dysfunction
  - 55% survive ITU, 41% to hospital discharge
  - Aetiology not related to outcome
  - Variceal bleeders have better survival
  - Requirement for renal replacement therapy and/or vasopressors strongly linked with mortality
- Outcomes Improving
  - Earlier admission?
  - Early intubation?
- Admit early and assess response

Sequential Organ Failure Assessment (SOFA) Score

TABLE 1. The Sequential Organ Failure Assessment (SOFA) Score

SOFA Score	0	1	2	3	4
Respiration PaO_2/FiO_2	>400	301-400	201-300	101-200 with respiratory support	≤100 with respiratory support
Coagulation					
Platelets, $\times 10^3/mm^3$	>150	101-150	51-100	21-50	≤20
Liver					
Bilirubin, mg/dL	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
(μmol/L)	(<20)	(20-32)	(33-101)	(102-204)	(>204)
Cardiovascular					
Hypotension	MAP ≥ 70 mm Hg	MAP < 70 mm Hg	Dopamine ≤ 5 or dobutamine (any dose)*	Dopamine > 5 or epi ≤ 0.1 or norepi ≤ 0.1*	Dopamine > 15 or epi > 0.1 or norepi > 0.1*
CNS					
Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	>5.0
(μmol/L)	(<110)	(110-170)	(171-299)	(300-440)	(>440)
or urine output				or <500 mL/d	or <200 mL/d

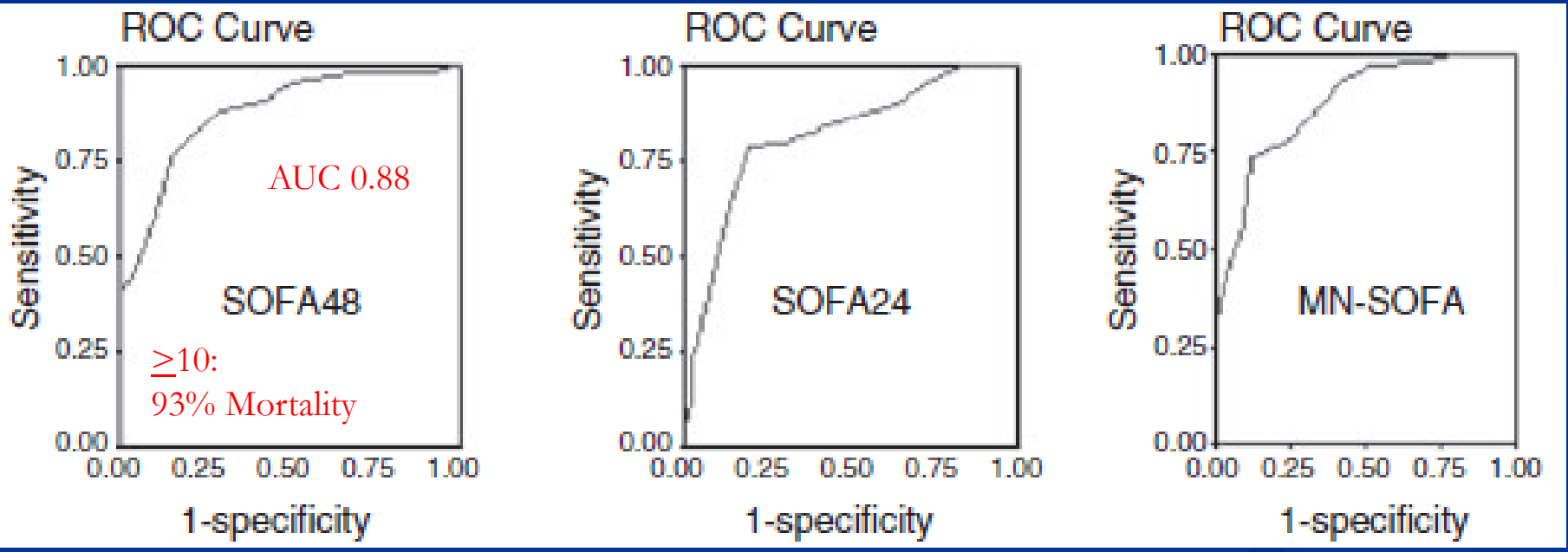
Abbreviations: PaO_2, arterial oxygen tension; FiO_2, fractional inspired oxygen; MAP, mean arterial pressure; CNS, central nervous system; epi, epinephrine; norepi, norepinephrine.

*Adrenergic agents administered for at least 1 hour (doses are given in μg/kg/min).

Vincent et al ICM 1996;22:707-710

HEPATOLOGY

Prognostic models in cirrhotics admitted to intensive care units better predict outcome when assessed at 48 h after admission



Evangelos Cholongitas

Journal of Gastroenterology and Hepatology **23** (2008) 1223–1227

Freeman ICU

Jan 2007 – Dec 2008
119 patients, 134 episodes (of 2203) M:F 72:62

Mean APACHE 2 score 23.8, predicted † 47%
Mean ICNARC score 25.4, predicted † 42%

Actual ICU Mortality 39%, ICU Survival 61%
APACHE 2 SMR 0.8
ICNARC SMR 0.95

55% patients survived to be discharged from hospital

Acute variceal bleeding

MORTALITY

- Varices bleeding † decreased from 42% in the 70's to 15-20% currently.
- Immediate mortality 4-8%.

Predictors of 6 weeks mortality

At admission

Shock	5.8-9.9
HCC	3.1-7.5
HE	2.4-6.9
Active bleeding	5.4
CP score	4.5

Late prognostic factors

Renal failure	17.1-52.1
Bacterial infection	12.6
Early rebleed	3.2-8.7

Initial Management

- Airway protection in the encephalopathic patient
- Prophylactic antibiotics: Reduce rebleeding rate & mortality
- Vasoactive agents: Terlipressin 1 – 2mg IV every 4 – 6 hours (34% RRR †, Ioannou 2002 CHBG)

Antibiotic prophylaxis

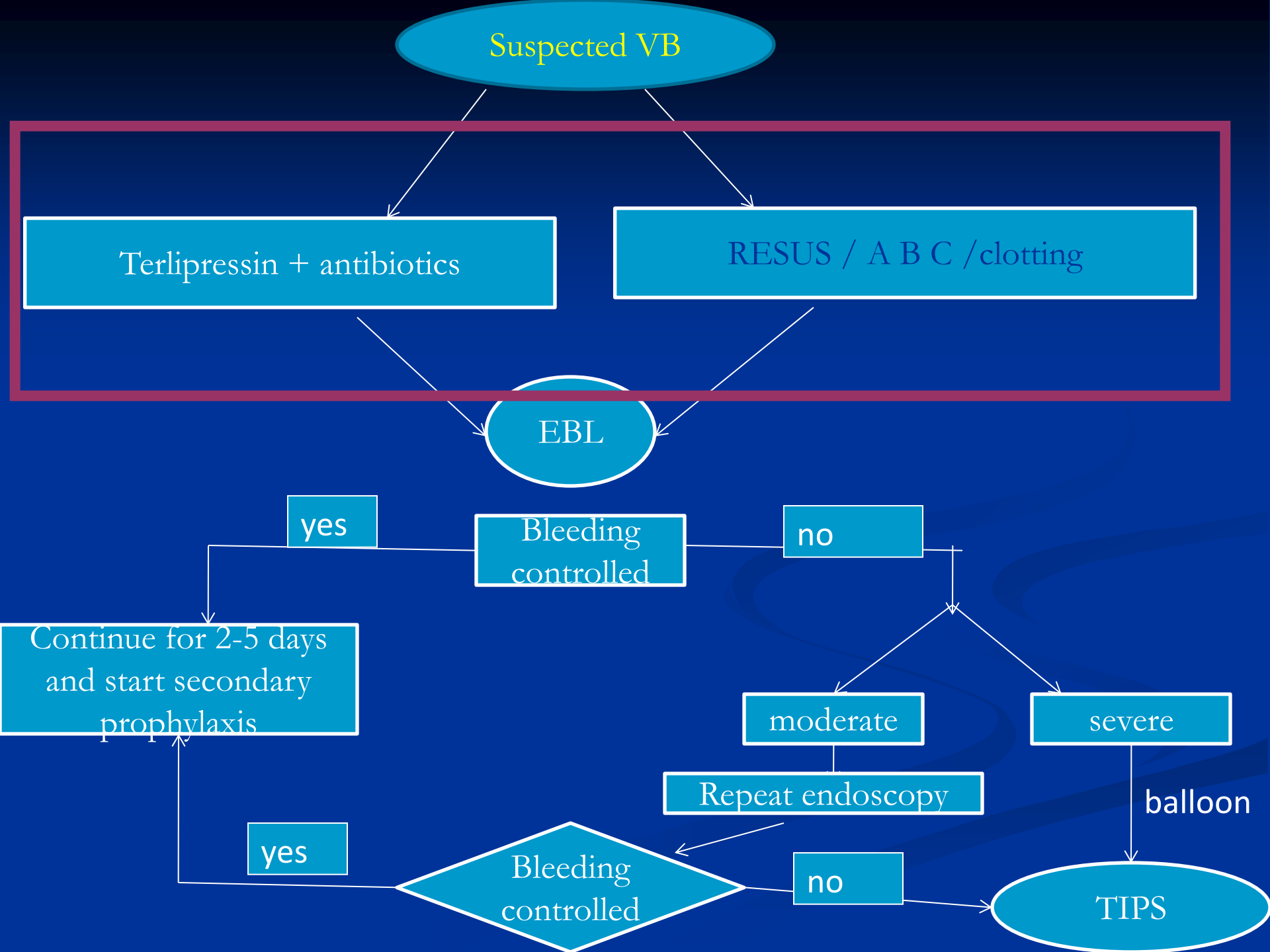
Bacterial infections have been documented in 35 - 66% of patients with cirrhosis who have variceal bleeding

- Bacteria infections are a predictor of early rebleeding (P<0.02 & <0.001)

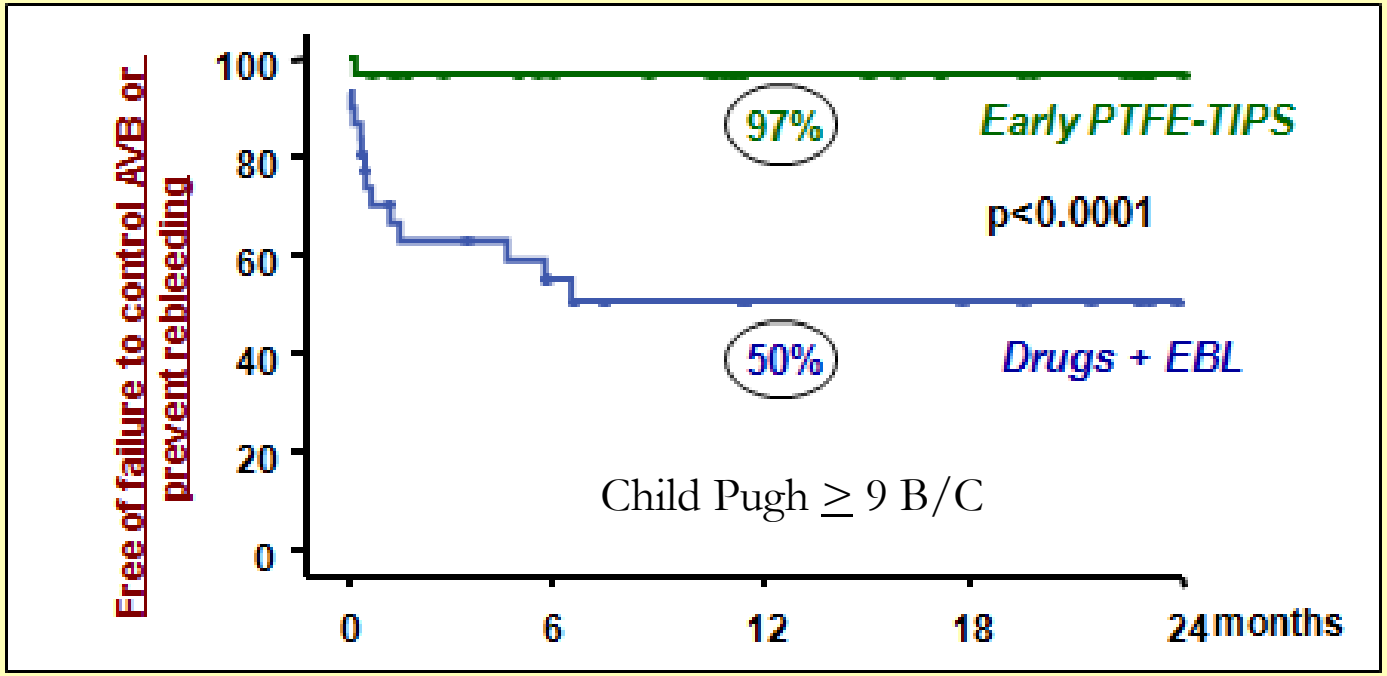
  Bernard et al, Gastro 1995 & Goulis et al, Hepatology 1998

- A recent meta - analysis demonstrates that antibiotic prophylaxis significantly increased mean survival rate (9.1% mean improvement rate; 95% Cl = 2.9 - 15.3; p = 0.004)

  Bernard et al, Hepatology 1999


Suspected VB
Terlipressin + antibiotics
RESUS / A B C /clotting
EBL
yes
Bleeding controlled
no
Continue for 2-5 days and start secondary prophylaxis
moderate
severe
Repeat endoscopy
balloon
yes
Bleeding controlled
no
TIPS

Early PTFE-TIPS vs. Drug+EBL. Composite endpoint: failure to control AVB or to prevent rebleeding



At risk:					
Early TIPS	32	24	15	11	5
Drugs+EBL	31	13	7	7	3

Garcia – Pagan et al, 2008 Hepatology (Abstract)

The New England Journal of Medicine

EFFECT OF INTRAVENOUS ALBUMIN ON RENAL IMPAIRMENT AND MORTALITY IN PATIENTS WITH CIRRHOSIS AND SPONTANEOUS BACTERIAL PERITONITIS

PAU SORT, M.D., MIQUEL NAVASA, M.D., VICENTE ARROYO, M.D., XAVIER ALDEGUER, M.D., RAMON PLANAS, M.D., LUIS RUIZ-DEL-ARBOL, M.D., LLUIS CASTELLS, M.D., VICTOR VARGAS, M.D., GERMÁN SORIANO, M.D., MÓNICA GUEVARA, M.D., PERE GINÈS, M.D., AND JOAN RODÉS, M.D.

Cefotaxime was given daily in doses that varied according to the serum creatinine level, and albumin was given at a dose of 1.5 g per kilogram of body weight at the time of diagnosis, followed by 1 g per kilogram on day 3. Renal impairment was defined as

Renal impairment developed in 21 patients in the cefotaxime group (33 percent) and 6 in the cefotaxime-plus-albumin group (10 percent) ($P=0.002$). Eighteen patients (29 percent) in the cefotaxime group died in the hospital, as compared with 6 (10 percent) in the cefotaxime-plus-albumin group ($P=0.01$); at three months, the mortality rates were 41 percent (a total of 26 deaths) and 22 percent (a total of 14 deaths), respectively ($P=0.03$). Patients treated with cefotaxime had higher levels of plasma renin activity than those treated with cefotaxime and albumin; patients with renal impairment had the highest values.

NEJM 1999

Terlipressin Therapy With and Without Albumin for Patients With Hepatorenal Syndrome: Results of a Prospective, Nonrandomized Study

Rolando Ortega,[1] Pere Ginès,[1] Juan Uriz,[1] Andrés Cárdenas,[1] Blas Calahorra,[1] Dara De Las Heras,[1] Mónica Guevara,[1] Ramón Bataller,[1] Wladimiro Jiménez,[2] Vicente Arroyo,[1] and Juan Rodés[1]

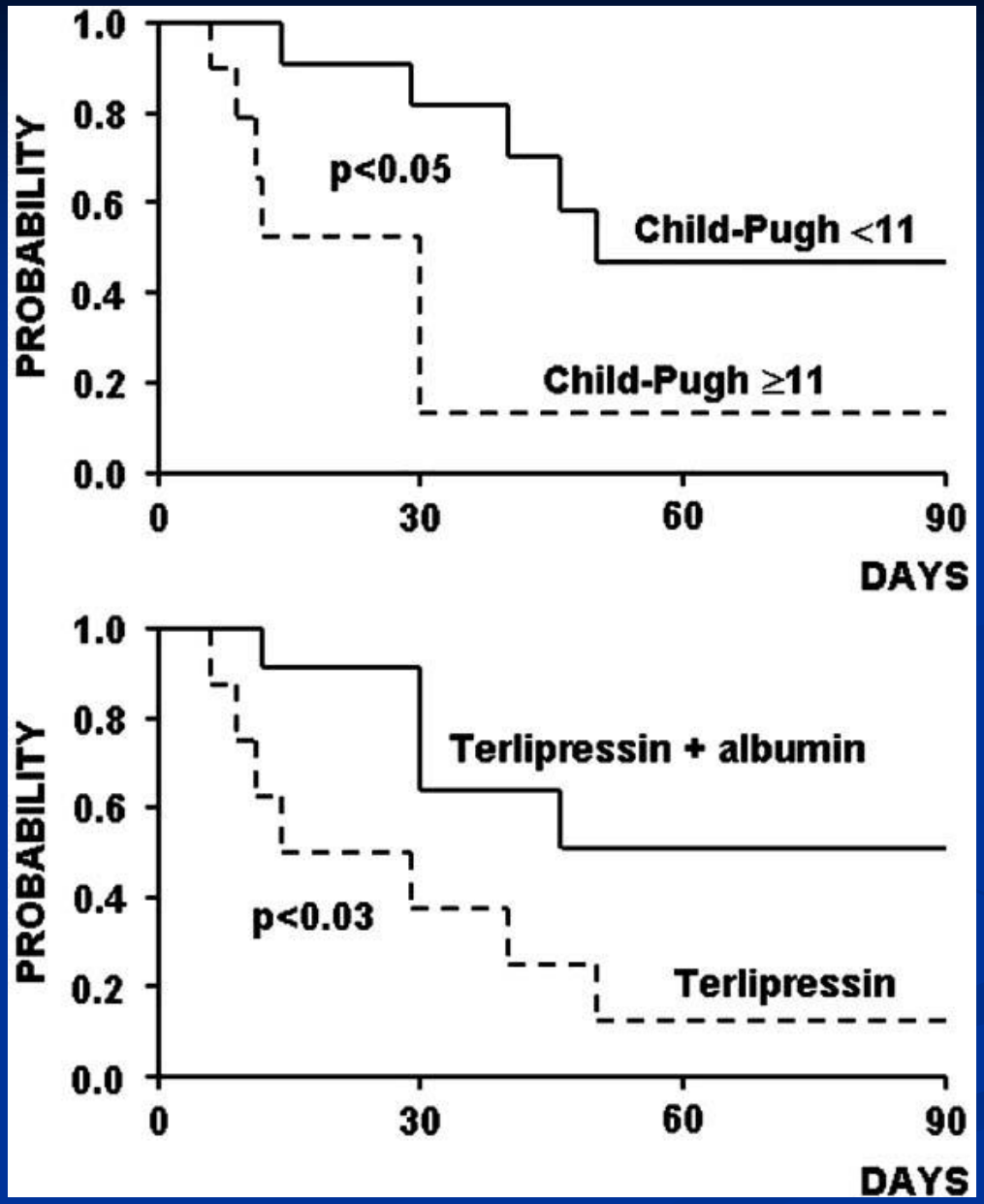
Hepatology 2002

GASTROENTEROLOGY 2002;122:923–930

Terlipressin in Patients With Cirrhosis and Type 1 Hepatorenal Syndrome: A Retrospective Multicenter Study

Gastro 2002

Survival in HRS



A Randomized Unblinded Pilot Study Comparing Albumin Versus Hydroxyethyl Starch in Spontaneous Bacterial Peritonitis

Javier Fernández,[1] Joan Monteagudo,[2] Xavier Bargallo,[3] Wladimiro Jiménez,[4] Jaume Bosch,[1] Vicente Arroyo,[1] and Miguel Navasa[1]

Treatment with albumin was associated with a significant increase in arterial pressure and a suppression of plasma renin activity, indicating an improvement in circulatory function. This occurred in the setting of a significant expansion of central blood volume (increase in cardiopulmonary pressures and atrial natriuretic factor) and an increase in systolic volume and systemic vascular resistance. In contrast, no significant changes were observed in these parameters in patients treated with hydroxyethyl starch. Von Willebrand–related antigen

albumin on endothelial function. In conclusion, albumin but not hydroxyethyl starch improves systemic hemodynamics in patients with spontaneous bacterial peritonitis. This effect is due not only to volume expansion but also to an action on the peripheral arterial circulation. (HEPATOLOGY 2005;42:627-634.)

Hepatology 2005

Prognostication And Management Of Acute Alcoholic Hepatitis

PRINCIPLES OF MANAGEMENT?

- Prognosticate
  - Score the patient
    - DF 1989
    - GAHS 2005
    - MELD 2005
    - Lille 2007
- Are they going to die without treatment?

PROGNOSTICATION

DF = 4.6 (PT - Control PT) + Bi/17

DF > 32 = 35% 28 day mortality

DF > 32 got benefit from steroid treatment

Glasgow Alcoholic Hepatitis Score (GAHS)

Score Value	1	2	3
Age	<50	≥50	-
WCC (10^9/l)	<15	≥15	-
Urea (mmol/l)	<5	≥5	-
Bilirubin (μmol/l)	<125	125 - 250	>250
PT (ratio)	<1.5	1.5 - 2.0	>2.0

AAH Score	28d mortality	84d mortality
< 9	13%	21%
≥ 9	54%	60%

- Score 5-12
- Derived from 241 patients with ASH
- Verified in 195 patients
- GAHS correctly predicted 28 day outcome in 81%
- DF only 51%

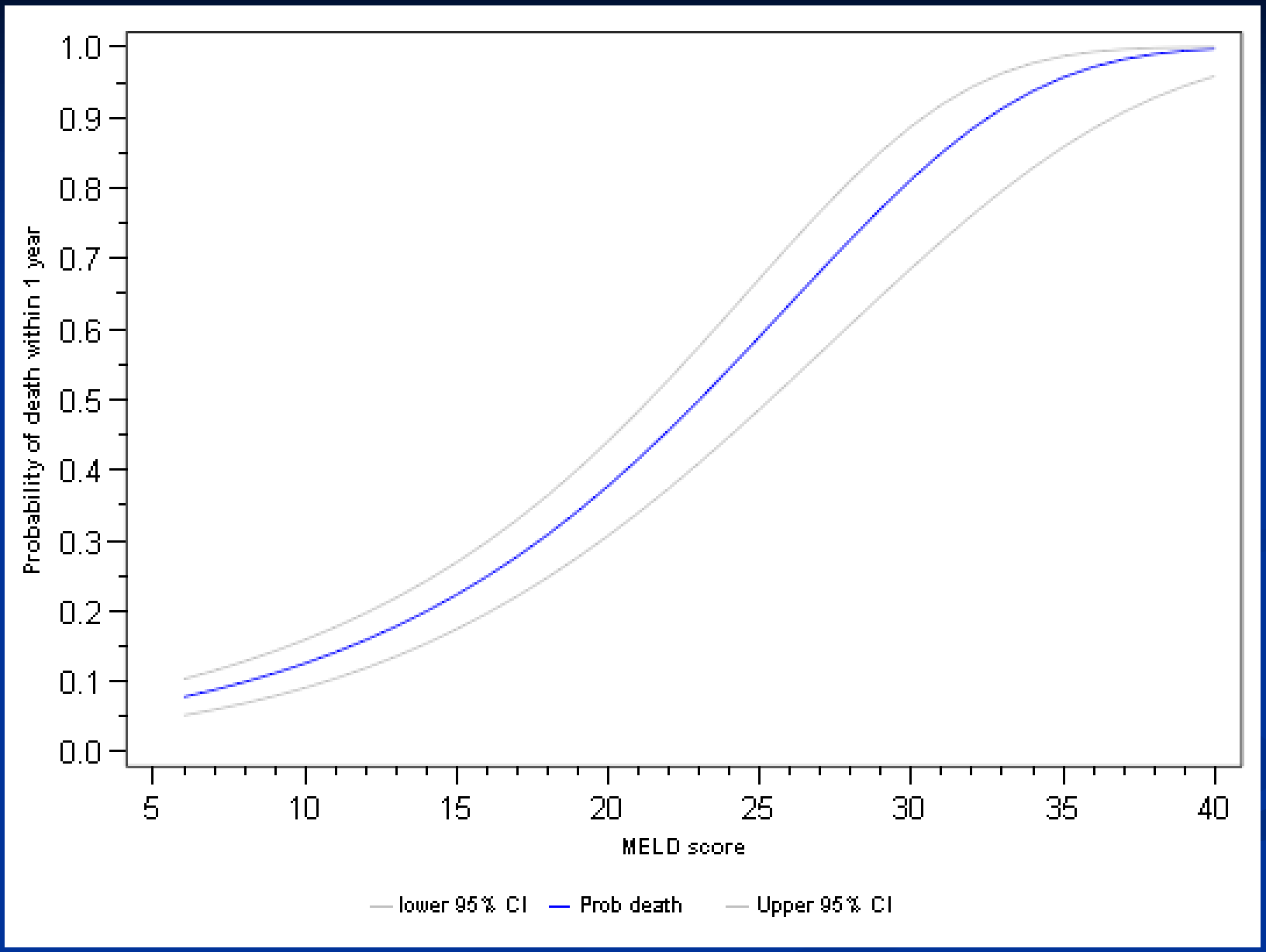
Forrest et al 2005

MELD Accurately Predicts Mortality in Patients With Alcoholic Hepatitis

Winston Dunn,[1] Laith H. Jamil,[1] Larry S. Brown,[2] Russell H. Wiesner,[1] W. Ray Kim,[1] K. V. Narayanan Menon,[1] Michael Malinchoc,[2] Patrick S. Kamath,[1] and Vijay Shah[1]

MELD Score = ((0.957 x Cr) + (0.378 x Bi) + (1.120 x INR) + 0.643) x 10

UKELD = 5 x {(1.5 x INR) + (0.3 x Creat) + (0.6 x Bi) – (13 x Na) + 70}

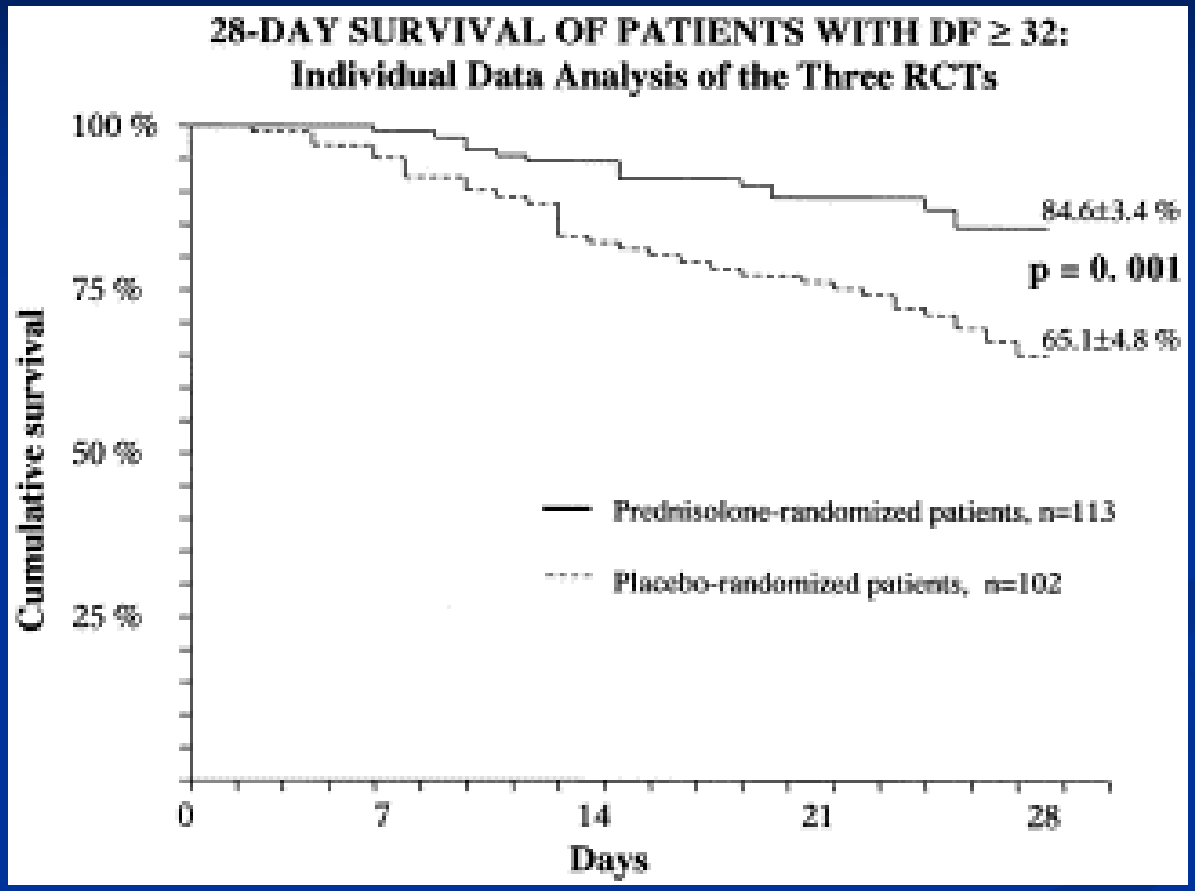

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Probability of death within 1 year
5
10
15
20
25
30
35
40
MELD score
lower 95% CI
Prob death
Upper 95% CI

THERAPEUTIC OPTIONS FOR ACUTE ALCOHOLIC HEPATITIS

1. Pentoxifylline
2. Enteral nutrition
3. Steroids

MATHURIN'S NOVEL META-ANALYSIS

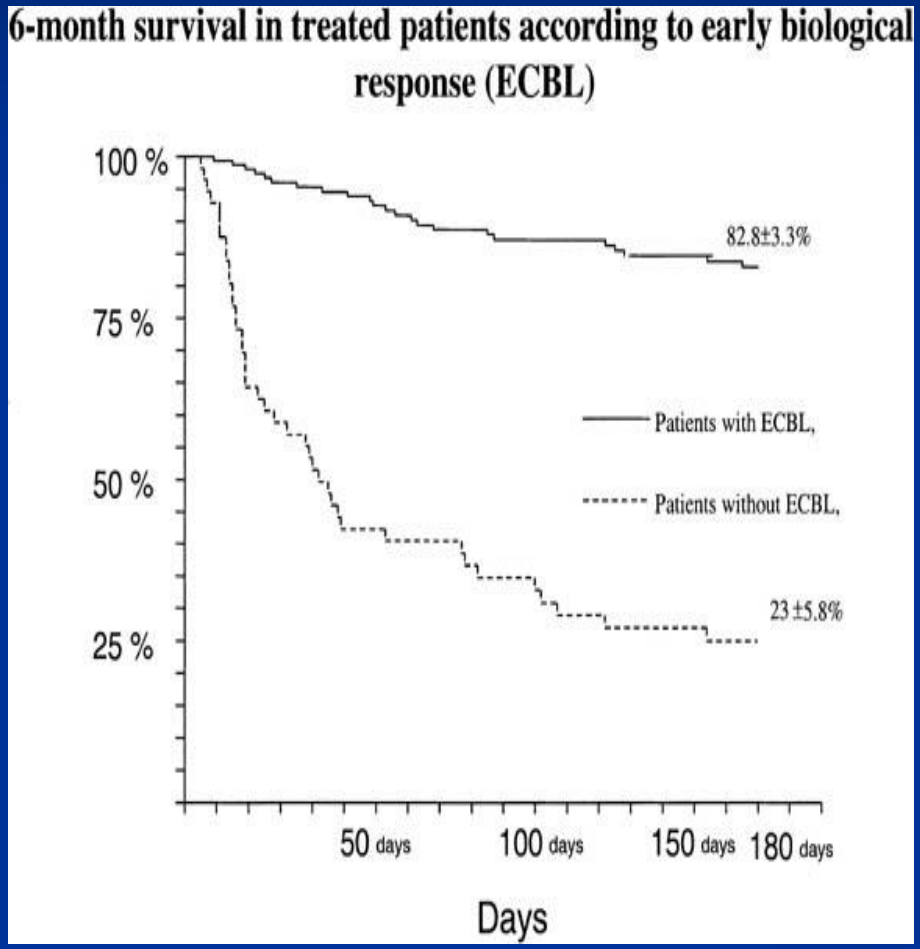
- Individual patient data from last 3 RCTs
- 102 on placebo, 113 steroids
- All: DF >32, not infected, not bleeding


28-DAY SURVIVAL OF PATIENTS WITH DF ≥ 32:
Individual Data Analysis of the Three RCTs
100 %
75 %
50 %
25 %
Cumulative survival
84.6±3.4 %
p = 0. 001
65.1±4.8 %
Prednisolone-randomized patients, n=113
Placebo-randomized patients, n=102
0
7
14
21
28
Days

MATHURIN'S NOVEL META-ANALYSIS

- Individual patient data from last 3 RCTs
- 102 on placebo, 113 steroids
- All: DF >32, not infected, not bleeding
- 28 day survival 85 vs 65% ($p<0.001$)
- Beneficial effect at up to 1 year
- NNT to prevent one death - 5

CAN WE PREDICT OUTCOME ON STEROIDS? (ECBL)



- 238 patients, all DF>32
- All treated with steroids
- ECBL = any fall in bilirubin at 7 days (73%)
- Highly predictive of 6 month outcome
- ? Stop steroids at 7 days

Mathurin Hepatology 2003

SO WHAT IS THE MESSAGE?

We are getting better at predicting mortality in acute alcoholic hepatitis, including on treatment.

An early change in bilirubin is a good prognostic indicator

A rise in bilirubin is a bad prognostic indicator as there are no other treatments to switch to

WHEN HAVE WE LOST THE GAME?

Beware the very high DF, GAHS, MELD score

Limited options in those that are not candidates for steroids

Poor survival in steroid non-responders and limited alternative treatments

HRS not responding to albumin and terlipressin

Beware the patient with "terminal addiction"

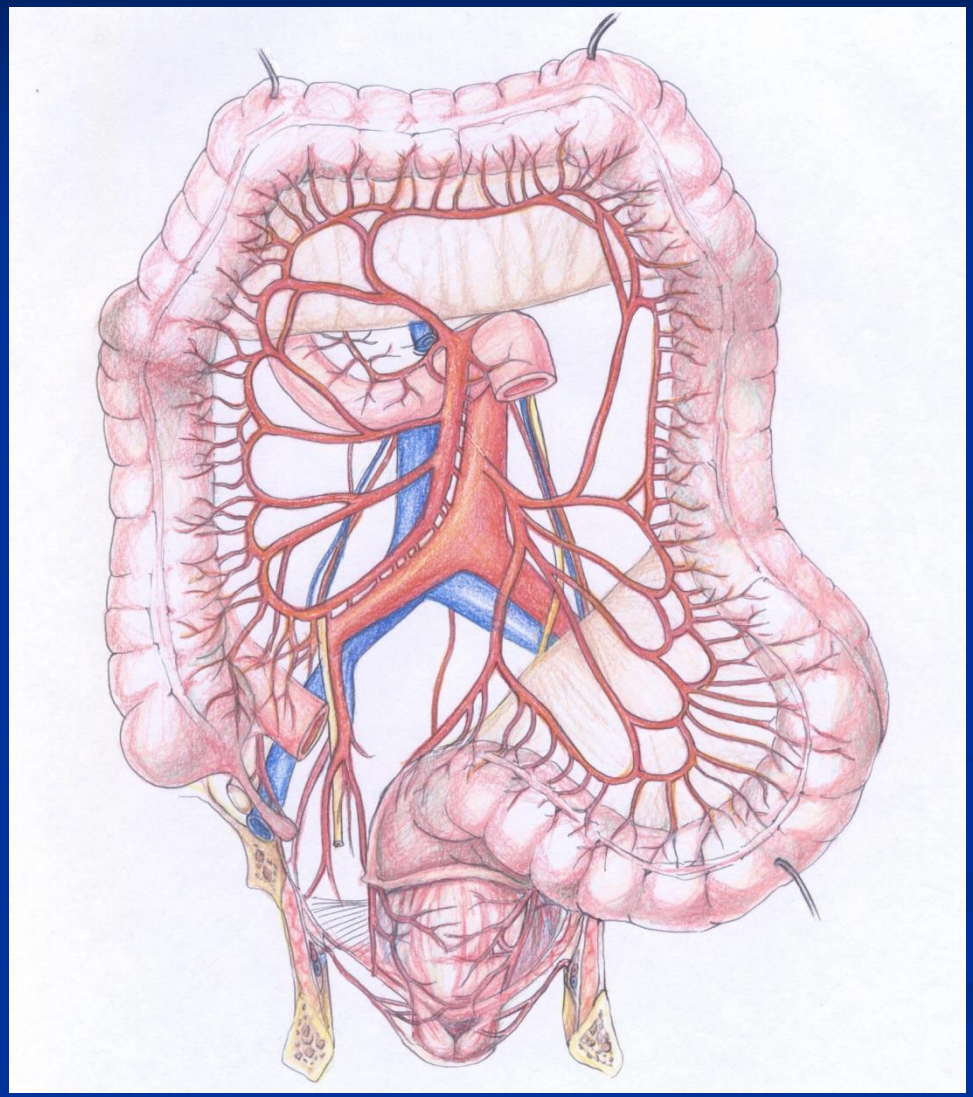
SUMMARY

- Splanchnic vasodilatation in cirrhosis drives ascites formation, hyponatraemia and HRS
- Recognition of precipitants and volume expansion are at the heart of treatment
- Albumin (+/- terlipressin) are the agents of choice
- Transplantation is the only long term treatment

TWO COMMON PROBLEMS

- Fluid management in chronic liver disease (Hyponatraemia and HRS)
- How to manage acute alcoholic hepatitis (and when to withdraw treatment)

SPLANCHNIC VASODILATATION

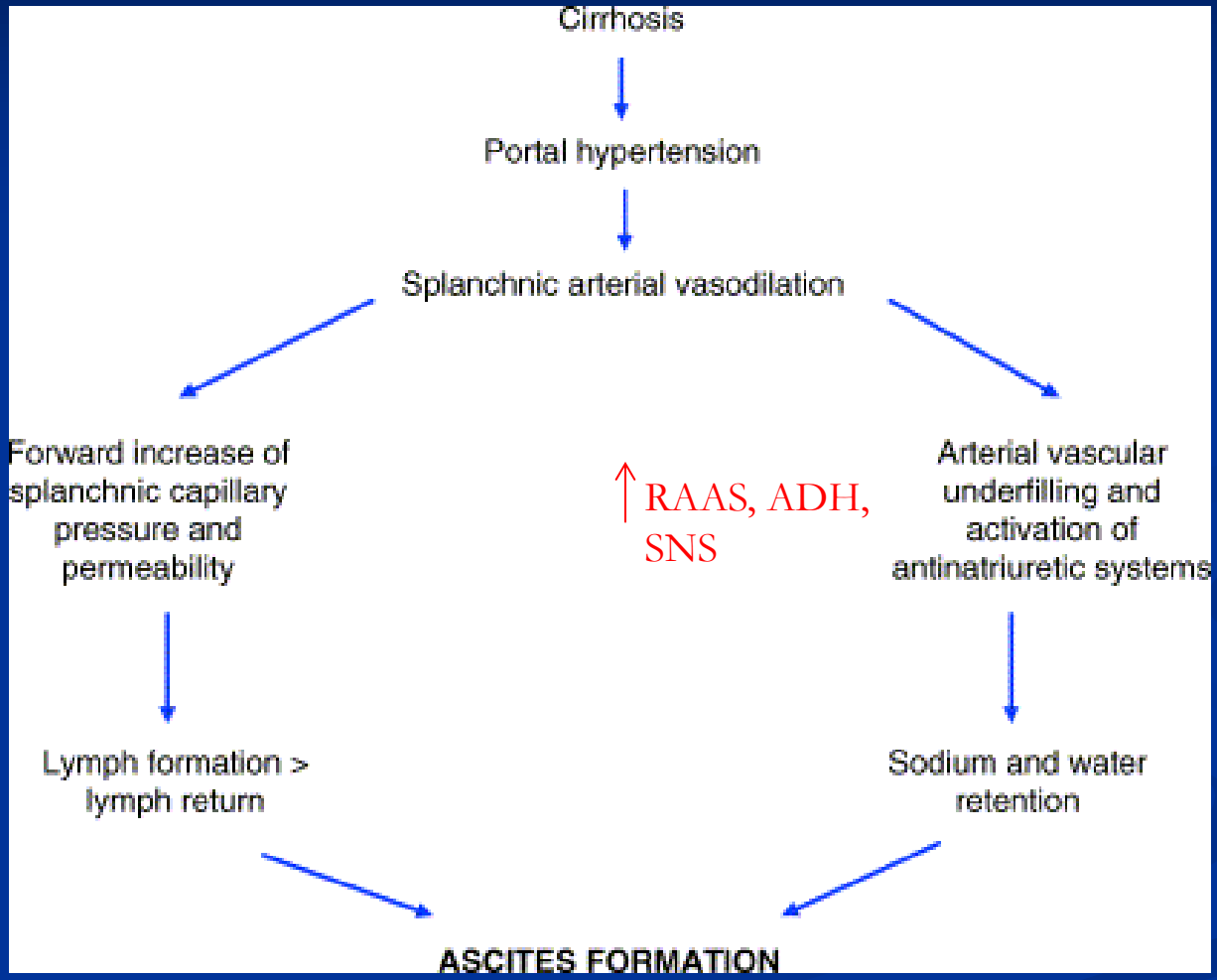


SPLANCHNIC VASODILATATION

- A prominent feature of portal hypertension
- The mechanism is still unclear
- Possibly local NO in response to ?LPS ?portal hypertension
- Seems to be responsible for many of the complications of cirrhosis…
  - Ascites
  - Hyponatraemia
  - Renal impairment

…through sequential stimulation of RAAS, ADH (AVP) and SNS

THE FORWARD THEORY OF ASCITES FORMATION



HYPONATRAEMIA

1. Hyper dynamic circulation – no ascites
2. Mild/moderate sodium retention – diuretic responsive ascites
3. Severe sodium retention – diuretic resistant ascites
4. ADH secretion – hyponatraemia

HYPONATRAEMIA MANAGEMENT

Ignore

Discontinue diuretics – Na < 125

Volume expansion

Water restriction

- Severe
- Euvolaemic
- Not on diuretics
- Normal renal function

HEPATORENAL SYNDROME

1. Hyper dynamic circulation – no ascites
2. Mild/moderate sodium retention – diuretic responsive ascites
3. Severe sodium retention – diuretic resistant ascites
4. ADH secretion – hyponatraemia

5. Acute precipitant – SNS over activation – type 1 HRS
6 Progressive increasing portal hypertension – type 2 HRS

HEPATORENAL SYNDROME

- Occurs on the background of ascites (and usually hyponatraemia)

HEPATORENAL SYNDROME TREATMENT

- Preventative – treat SBP with high dose albumin
- Identify precipitant for type 1 HRS
- Vasoconstrictors and albumin to combat vasodilatation
- Liver transplantation
  - With TIPSS as a potential bridge

The Lille Model: A New Tool for Therapeutic Strategy in Patients with Severe Alcoholic Hepatitis Treated with Steroids

Alexandre Louvet,[1,8] Sylvie Naveau,[2,9] Marcelle Abdelnour,[1,2] Marie-José Ramond,[3] Emmanuel Diaz,[4] Laetitia Fartoux,[5] Sébastien Dharancy,[1,8] Frédéric Texier,[1] Antoine Hollebecque,[1,8] Lawrence Serfaty,[5] Emmanuel Boleslawski,[6] Pierre Deltenre,[1] Valérie Canva,[1] François-René Pruvot,[7] and Philippe Mathurin[1,8]

3.19 - 0.101 x (age in years) + 0.147 x (albumin day 0 in g/L) + 0.0165 x (evolution in Bi) - 0.206 x (renal insufficiency) - 0.0065 x (Bi day 0) - 0.0096 x (PT)

Hepatology 2007

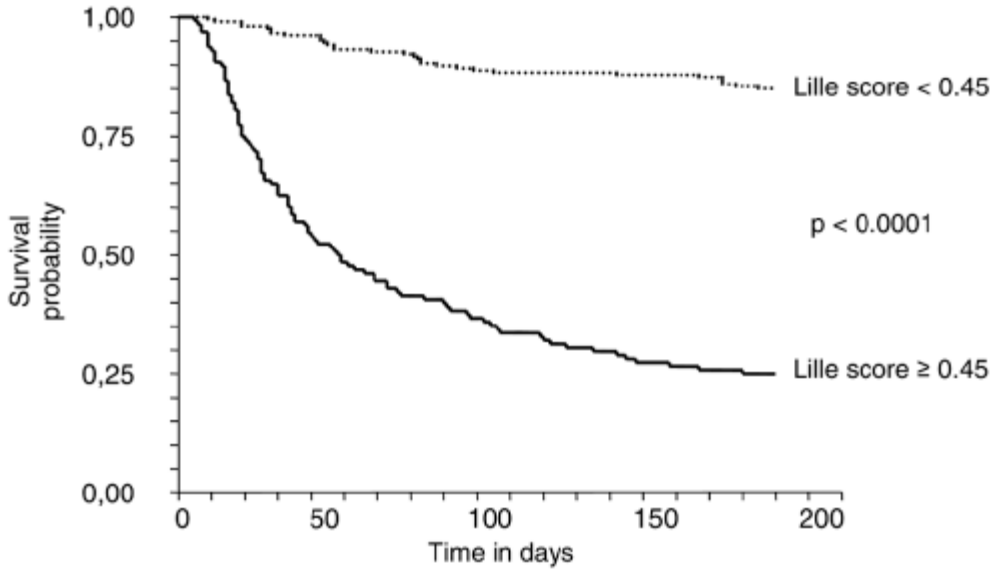
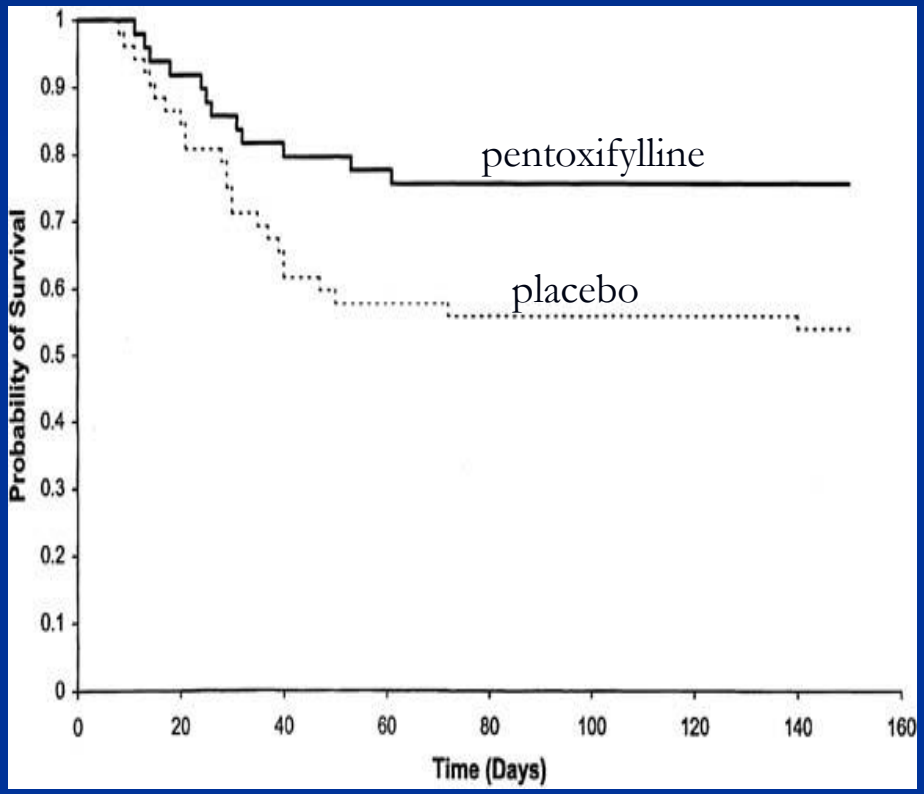


Fig. 4. Kaplan-Meier survival analysis according to 0.45 cutoff of the Lille model.

PLAN OF TALK

A. How can we prognosticate in acute alcoholic hepatitis?
B. How should we treat alcoholic hepatitis?
C. How do we prognosticate on treatment?

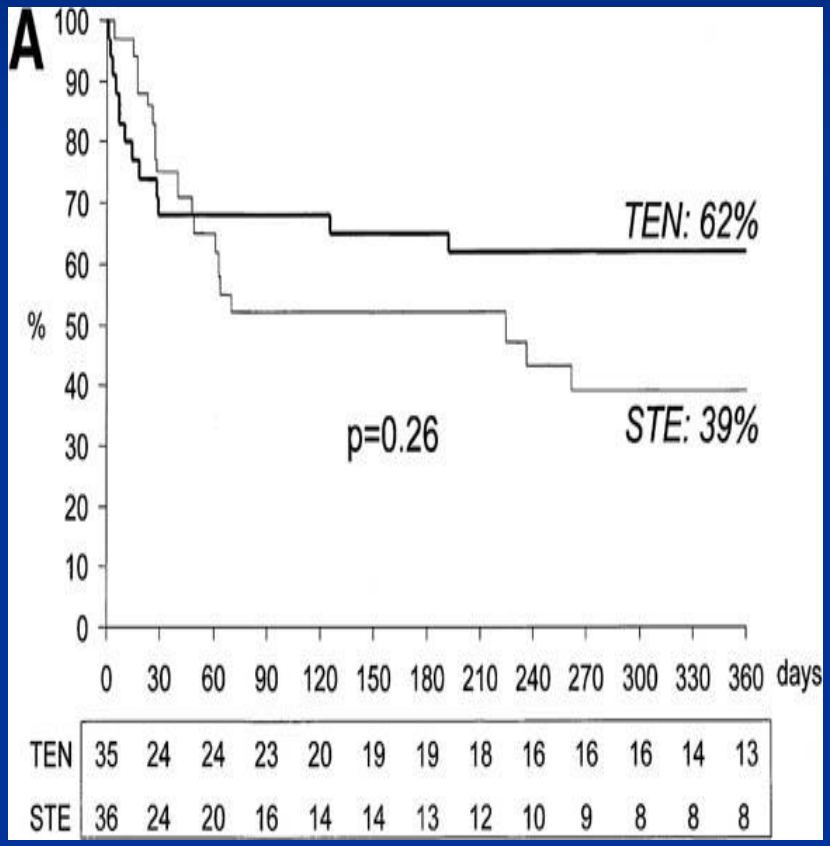
OPTION 1 - PENTOXIFYLLINE



- 101 patients with DF >32
- Sepsis and bleeding excluded
- 4/52 PTX 400[3] vs placebo
- Death in hospital: 24% vs 46%; RR 0.59 [0.35-0.97]
- Improved mortality due to reduction in HRS deaths *Akriviadis et al 2000*
- Needs replication

- Large multicentre UK study funded

OPTION 2 – ENTERAL NUTRITION



- Steroids v TEN for 28 days
- 28d mortality similar; 9/36 v 11/35
- Earlier in TEN; 7d v 23d

- BUT FU mortality higher on steroids
- 10/27 v 2/24; p=0.04
- 9/10 related to infection.

- ?Short course steroids and TEN
- Pilot of combination therapy; 12 month mortality 3/13 (23%)
  - *Alvarez 2004*

OPTION 3 – STEROIDS METANALYSES

- Imperiale 1990 (11 trials)
  - 6/12 mortality reduction: 37% [20-50%]
  - Restricted to those with encephalopathy
  - Only if bleeding and septic patients excluded

- Christensen & Gluud 1995 (12 trials)
  - No effect RR 0.78 [0.51-1.18]
  - Possible beneficial effect in females

WHAT DO WE DO WHEN STEROIDS FAIL?

- Pentoxifylline?
  - 29 switched at day 7. No better survival than matched retrospective cohort
    - *Mathurin J Hep 2008*
- MARS?
  - RCT 19 v 19; no benefit
    - *Mathurin AASLD 2007*
- Transplantation?
  - RCT 18 v matched controls
  - 6/12 survival 83% v 44% (p = 0.009)
    - *Mathurin AASLD 2009*

CASE

- 51 years old male admitted with haematemesis.
- Resident from homeless shelter
- No PMH, never been in hospital before
- BUT Heavy alcohol dependence, 60 units per week for years
- No family with patient.
- Evidence of self neglect and poor nutrition.

O/E

- Clinically jaundiced, spider naevi, palmar erythema, confused.
- BP 80/40 mmHg HR 120 / min.
- Ascites, mild to moderate.
- Evidence of self neglect and poor nutrition.

WORKING DIAGNOSIS

- Likely variceal bleed.
- Decompensated cirrhosis.

HB	8	UR	9
PLT	90	CR	70
PT	20	ALB	23
WCC	9.6	BIL	65
NA	128	ALT	60
K	3.3	ALP	350

NUMBERS

- 30% of patients with compensated cirrhosis, and 60% of those with decompensated cirrhosis have GOV at time of presentation.
- In cirrhotics without varices the incidence is 4.5 % per year. (D'Amico)
- Among patients with cirrhosis and varices the incidence of the first bleed ranges between 20% and 40% within 2 years.
- Only 1/3 of patients with GOV bleed from them in their life time.

NUMBERS

- Variceal bleeding is the cause of acute UGIB in 70% of portal HTN cases.
- Variceal bleeding is spontaneously controlled in 40% of cases (Bosch 2008).
- 30%-40% re-bleed in 6 weeks, 40% of those within 5 days.
- Early re-bleeding is a strong predictor of mortality.
- Available treatments control the bleed within 5 days in 80% of cases.

Glypressin/Terlipressin

- Reduces the variceal blood flow.
- Dose up to 2mg every 4 hours SHOULD be started as soon as VB suspected for the first 48 hours.
- The only medical treatment to be shown to improve prognosis in RCTs and meta-analysis.
- Reduce dose after that and stop over 5 days.

Glypressin/Terlipressin

- First-line treatment of **variceal bleeding** in cirrhosis is with vasoactive drugs, which control **bleeding** in 83% of patients. Thereafter endoscopic therapy added.(D'Amico, Gastroenterology, May 2003)

- On the basis of a **34% relative risk reduction** in mortality, terlipressin should be considered to be effective in the treatment of acute variceal haemorrhage. (Ioannou 2002 CHBG)

- Serious side effects occur in < 3% of patients.

Predictors of treatment failure

FACTOR	ODDS RATIO
HVPG > 20 mm Hg	5.4-11.4
Bacterial infection ★	4.6-9.7
Active bleeding at endoscopy	2.1-3.7
Portal vein thrombosis	3.1
CP score/class	2.7
Shock ★	4.9

A month later

- Patient admitted with encephalopathy and unwell (not been drinking).
- Febrile, Chest clear
- Noted to have significant ascites.
- Blood tests:

ALB	23	Na	124
ALT	70	K	4.1
ALP	350	Urea	7
BIL	200	Cr	65
Hb	9.5	PT	24
WCC	17	Plt	105

Diagnosis

- An ascitic fluid diagnostic tap contained neutrophils of 450/mm3.
- A diagnosis of Spontaneous bacterial peritonitis (SBP) made.
- Negative culture of blood and fluid.

Spontaneous Bacterial Peritonitis

- The prevalence of SBP in unselected cirrhotic patients with ascites admitted to a hospital ranges between 10% and 30% (Navasa 2004).
- Diagnosis of SBP is established by a PMN cell count in ascitic fluid equal to or higher than 250 cells/mm3.
- Mortality is 10-30% mainly due to renal impairment and GI bleeding.

- Culturing the fluid straight into blood culture bottle at bed-side results in positive culture in 40-80% of cases.
- Many can have positive blood cultures.
- If haemorrhagic tap take 1 PMN for every 250 red cells in the fluid.

Treatment of SBP

- Antibiotics should be started immediately.
- 3rd generation cephalosporines are the gold standard, but Augmentin is also effective.
- Always refer to local guidelines.
- Recent evidence support use of more broad spectrum antibiotics.

IV Albumin

Albumin in SBP

- Randomized multi-centre controlled trial assessed the use of IV Albumin in SBP.
- Cefotaxime versus cefotaxime + Albumin infusion.
- A dose of 1.5g/kg at the time of diagnosis and 1 g/kg on day 3 was given.
- Renal impairment 33% vs. 10%.
- Mortality 29% vs. 10%.
- More benefit in patients with renal impaiment or low bilirubin.

Sort P, Navasa M, Arroyo V et al. (1999) Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 5, 403–409.

Hepatorenal Syndrome (HRS)

- Ascites and Hyponatraemia are harbingers of doom…..
- 40% of patients with cirrhosis and ascites develop HRS during the natural history of their disease
- Type 1
  - rapid and progressive renal impairment
  - most commonly precipitated by SBP (25% of patients)
  - characterized by diuretic resistant ascites
  - most patients **die within 10 weeks**
- Type 2
  - Moderate and stable reduction in the GFR
  - median survival of 3-6 months

Practical notes

- Diagnostic tap should be done on all cirrhotic patients when admitted to hospital to allow early diagnosis of SBP.
- It should also be done if patients became unwell during admission.
- Secondary prophylaxis should be considered, but this depends on the local guidelines.
- As renal dysfunction is a result of an aggravation in vasodilatation and a decrease in effective arterial blood volume, procedures that lead to a decreased effective blood volume should be avoided, such as the use of diuretics and large-volume paracentesis (discuss with hepatologist).

conclusion

- Antibiotics + Albumin for SBP.
- Avoid diuretics and ?paracentesis during the episode.
- If patient did not show improvement in 48 hours re-tap the ascites for PMN and cultures.

HRS Diagnosis

- Creatinine > 130 µmol/L that progresses: days to weeks
- Absence of another cause for renal disease, inc:
  - shock
  - sepsis
  - acute tubular necrosis and other causes of prerenal disease
  - nephrotoxic drugs
  - absence of obstruction
  - no known parenchymal renal disease
- Must exclude spontaneous bacterial peritonitis, which is complicated by acute renal failure that may be reversible in 30% patients
- No improvement in renal function after volume expansion with i.v. albumin for at least 2d and withdrawal of diuretics

Alcohol History

- 1unit = 8g/alcohol
  - 1 glass of wine (125mls)
  - 1 short of whisky (25mls)
  - ½ pint beer (standard 3.5%)

→ Acute hepatitis + Chronic damage leading to cirrhosis

‘ 8 pints a night—3.5%’

16 units/day

Units : Volume of drink x % Alc. By Volume

1000mLs

Alcohol history

- History of alcohol excess
  - Overt
  - Not admitted (CAGE or PAT questionnaire)
  - Family/GP
- Assessment of amount/duration – day to day record of 1 week's drinking - Alone ? Through the night ? On waking ?
- Enviromental factors in drinking
- Risk of withdrawl
- Specific questions to indicate organ damage

Short-term "in-hospital" prognosis:

- Maddrey's discriminant function
  - Bilirubin (mg/dl) + 4.6 x PTT prolongation
  - > 32 indicates severe disease with high early (28 day) mortality ~ 35%

Maddrey 1978

Child-Pugh Classification

	Points		
	1	2	3
Bilirubin (µmol/l)	<34	34-50	>50
Albumin (g/L)	> 35	28 – 35	< 28
Prothrombin time (seconds ↑)	<4	4 – 6	> 6
Ascites	None	Slight	Moderate
Encephalopathy	None	Minimal	Advanced
Grade A, <7 points; Grade B, 7-9 points; Grade C, >9 points			

Points	Class	1yr survival	2yr survival
<7	A	100%	85%
7-9	B	81%	57%
>9	C	45%	35%

Acute variceal bleeding

Resuscitation (and factors that may compromise outcome)

- A Airway - aspiration
- B Breathing - encephalopathy
  - endoscopy
  - tense ascites
- C Circulation - blood loss
  - vasodilation - cirrhosis
    - secondary to sepsis
  - sedatives (eg propofol)

Transfer to high nursing dependency-bed

Terlipressin for acute variceal bleeding

20 studies identified (n = 1609)

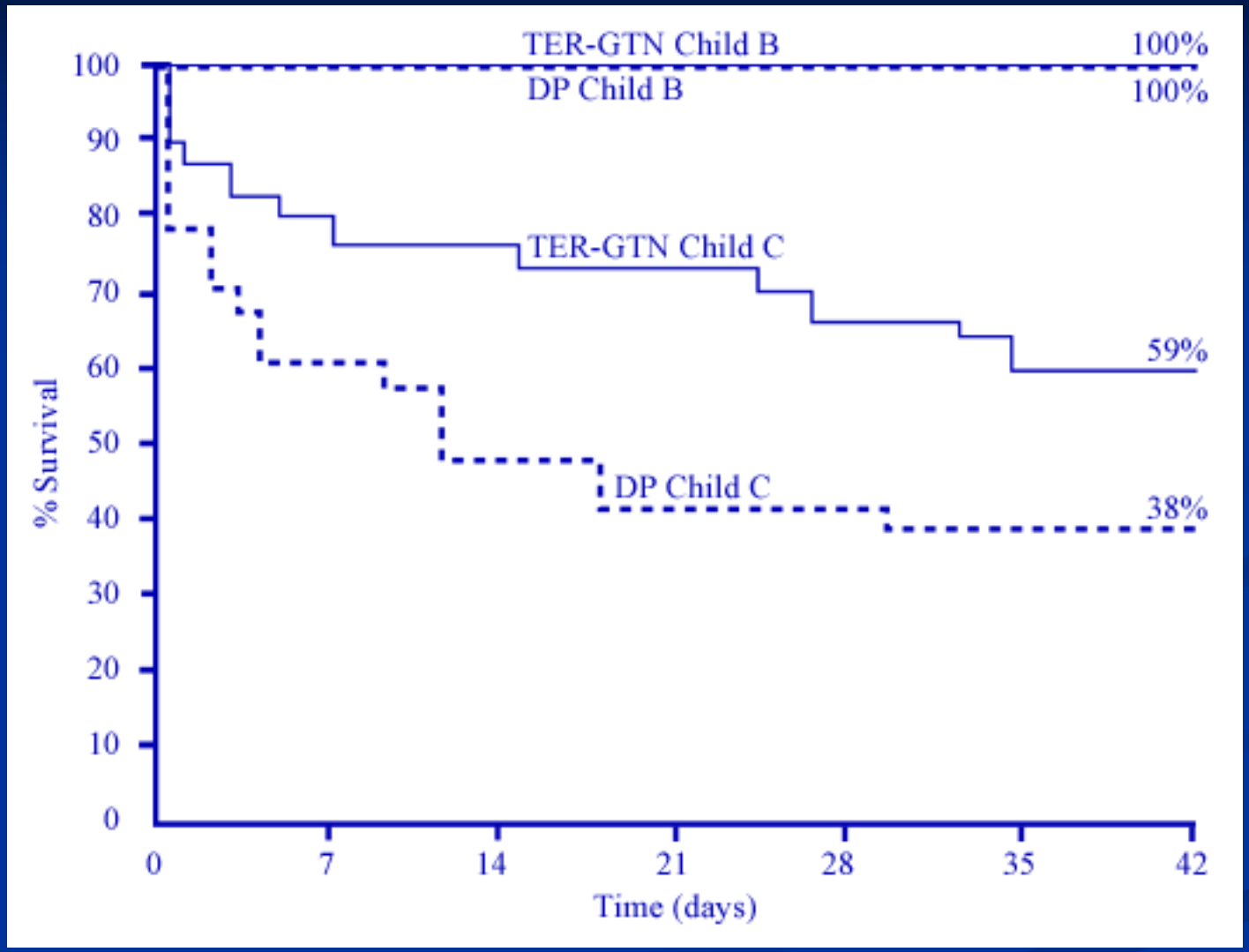
7 studies (n = 443) comparing terlipressin with placebo

Full publication: Walker 1986
Freeman 1989
Soderlund 1990
Pauwels 1994
Levacher 1995

Abstract: Brunati 1996
Patch 1999

Terlipressin associated with significant mortality benefit
RR 0.66, 95% CI 0.49 to 0.88

The Levacher graph



Case

- 51yo unemployed man
- Resident from homeless shelter
- Nil past medical/drug history or previous admissions
- But Heavy alcohol dependence, 60 units/week, many years
- Trying to cut down recently
- Jaundiced and confused

O/E

- Febrile, Tachycardia
- Chest clear, Heart sounds normal
- Tense abdominal distension + lateral dullness to percussion
- 2 cm hepatomegaly
- Tremulous + asterexis
- No focal neurological abnormalities

Ix

BR 220	Hb 10.8	Na 129
ALT 130	MCV 100	K 3.7
AST 250	Plat 90	Ur 12
Albumin 30	WCC 17.0	Creat 89
ALP 120		
GGT 400	INR 1.9	CRP 35

- ECG: sinus tachycardia
- Blood/Urine culture: Negative
- CXR: Loss of lung volume, nil focal
- USS - Liver increased in size, coarse edge
  - Diffusely increased echogenicity
  - Free fluid throughout abdomen

Chronic Liver Disease: Screening Investigations

- Chronic Alcohol Abuse (**History – collateral**)
- Hepatitis B (**Viral serology inc. HBcore**)
- Hepatitis C (**Viral serology**)
- Other Liver viruses: **Hep A, Hep E, CMV, EBV, HSV**
- Autoimmune Hepatitis/Primary Biliary Cirrhosis/Primary Sclerosing Cholangitis (**Liver Antibodies Anti-LKM, ANCA, ANA, ASMA, AMA**)
- Non-alcoholic Fatty Liver Disease (NASH) (**Fasting lipids, glucose**)
- Haemochromatosis (**Ferritin/Iron Studies, Transferrin satn**)
- Wilson's disease (younger patients) (**Serum copper/caeruloplasmin and 24hr urine Copper**))
- Alpha1-Antitrypsin Deficiency (**Alpha1-AT levels**)
- (Cystic fibrosis + other congenital diseases e.g. biliary artesia, glycogen storage disease)
- (Schistosomiasis)

Imaging
EEG?
Liver Biopsy?

Q for Discussion:

What immediate therapies should be instigated?

- IV fluids
- Pabrinex iv
- Vitamin K
- Vitamin B PO
- Thiamine PO
- Chlordiazepoxide PO: reducing dosage
- Address nutrition

Liver Biopsy (TJ) showed
Alcoholic Hepatitis on background of cirrhosis

A clinco-pathological syndrome of **Hepatitis** (inflammation of liver) due to excessive intake of **Alcohol**

- EtOH chronic liver disease
- Recently cut down/stopped
- AST > ALT (both usually < 500 IU/L)
- Higher level suggests viral, ischaemic or drug hepatitis (e.g. paracetamol [acetaminophen])

Fever, hepatomegaly (tender), jaundice, anorexia

Mathurin et al. Review. J Gastroenterol Hepatol. 2008

Alcoholic Hepatitis

- Steroids, Pentoxifylline – reduce mortality in selected cases
- Septic screen important

Discriminant function (Maddrey score):

- = **(4.6 x [prothrombin time - control PT]) + (serum bilirubin)**

- Score > 32 associated with a high short-term mortality

- used to decide treatment
  - **Prednisolone** 40mg/d for 28 days
  - or **Pentoxifylline** 400mg tid for 28 days

Alcoholic Hepatitis

- Steroids, Pentoxifylline – reduce mortality in selected cases
- Septic screen important

GLASGOW ALCOHOLIC HEPATITIS SCORE:

- Age, Bilirubin (d1 and d6 to 9), Urea, PT, WBC
- Benefit from corticosteroids only in patients with score ≥9

(Forest et al. Gut 2007)

- used to decide treatment
  - **Prednisolone** 40mg/d for 28 days
  - or **Pentoxifylline** 400mg tid for 28 days

- Prednisolone begun (Maddrey score 39)
- BR falls from 220 to 170 by day 7 of steroid

- **BUT:**
  - **Persisting fever**
  - **Still confused**
  - **Abdo discomfort + nausea**
  - **Worsening ascites**
  - **WCC 17 → 25**
  - **CRP 35 → 80**

Q for Discussion:

- What important bit of the septic screen don't we know yet?

  - Ascitic tap: 2500 WC, polymorphs
  - Patient is septic with **spontaneous bacterial peritonitis**

Causes of Ascites

- Cirrhosis 75%
- Malignancy 10%
- Heart Failure 3%
- Tuberculosis 2%
- Pancreatitis 1%
- Others 9%

Pathogenesis of ascites in liver disease – Appendix 1

Ascites: Basic Investigations

Serum Albumin – Ascitic Albumin Gradient

High > 11g/L

- Cirrhosis
- Heart Failure
- Massive Liver metastases
- Fulminant Liver Failure
- Vascular Occlusion
- Alcoholic Hepatitis
- Acute Fatty Liver of Pregnancy
- Myxoedema

Low < 11g/L

- Peritoneal carcinomatosis
- Peritoneal tuberculosis
- Pancreatitis
- Biliary leak
- Nephrotic syndrome
- Serositis
- Bowel infarction/perforation

Ascites: Basic Investigations – WCC

Spontaneous Bacterial Peritonitis (SBP)

- Ascitic neutrophil count >250 cells/mm^3
- 15% in-patients with ascites
- SBP develops in 25% patients within 1 year
- Subsequent prognosis < 40% at 1 year

Other Ix

Ascitic fluid Cytology and Amylase

Management of Ascites

Dietary Salt Restriction to 90mM/day (5.2g)

- Lower diuretic requirement
- Faster resolution of ascites
- Shorter hospital stay

Achievable by:

- no-added salt
- avoid pre-prepared food

Management of Ascites: Diuretics

Diuretics and Regular Weights

- Spironolactone
  - Initially; aldosterone antagonist; distal tubules
  - 100-400mg/d; 3-5 day lag before natriuresis (urine Na > K)
- Then add loop diuretic (Frusemide 40 – 160mg/d)

Management of Ascites: Hyponatraemia

Hyponatraemia - Poor prognostic indicator

Na > 126mmol/l

- no need for H2O restriction
- continue diuretics if renal function stable

Na < 125mmol/l

- little data
- consider stopping diuretics esp if Na < 121mmol/l
- if creatinine rising (>150µmol/l), volume expansion
- maintaining renal function crucial

INTENSIVE CARE AND THE LIVER

Mark Hudson
Consultant Hepatologist, Liver Unit
Freeman Hospital

FACTORS INVOLVED IN ASCITES PATHOGENESIS IN ACUTE LIVER DISEASE

- Portal hypertension – required
  - Budd-Chiari, veno-occlusive disease, acute hepatitis
  - so not seen in PVT

And subsequent…..

- Trans-sinusoidal fluid exchange
  - backed up by experiments in cats

ASCITES - STAGES

1. Hyper dynamic circulation – no ascites
2. Mild/moderate sodium retention – diuretic responsive ascites
3. Severe sodium retention – diuretic resistant ascites

TREATMENT FOR ASCITES

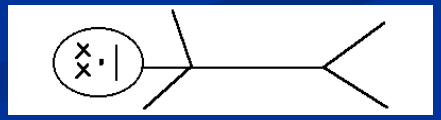
- Bed rest
- No added salt
- Diuretics
  - Spironolactone
  - Spironolactone and frusemide
- Paracentesis
- TIPSS
- Transplantation

A

A

B

C



Background

- 4000 patients died in UK from complications of cirrhosis in the year 2000
  - Incidence of cirrhosis is rising dramatically
  - Increasing numbers of patients will present with cirrhosis and organ dysfunction
- Patients are frequently denied access to ITU on basis of presumed futility
  - "Prognostic pessimism"

Aims

- Report our experience of cirrhotic patients admitted to ITU
- Identify clinical variables associated with mortality
- Estimate the costs incurred in managing these patients

Methods

- Kings College Hospital Liver Intensive Therapy Unit (LITU)
  - 15 bed, tertiary referral, dedicated unit
  - Aggressive, early ITU intervention
- Prospective data collected from 2000-2007
- Cirrhosis confirmed by combination of at least 2 modalities: histology, radiology, clinical, biochemical
- Physiological & laboratory data collected on Day 1 and Day 3 via dedicated ITU database

Methods

- Critical Illness scoring systems:
  - SOFA, APACHE II
- Liver specific scores:
  - MELD, Child-Pugh
- Use of vasopressors, invasive ventilation and renal replacement therapy (RRT) recorded
- Therapeutic Intervention Scoring System (TISS) points calculated for each admission
  - 1 TISS point = £48

Scores in Variceal Bleeders Vs Non Bleeders

	Variceal Bleed	Non Variceal	p value
Child Pugh	11	12	<0.0001
MELD	14	29	<0.0001
APACHE II	17	24	<0.0001
SOFA	8	11	<0.0001

RESUSCITATION

- Judicious volume replacement with plasma expanders/blood.
- Keep systolic around 100 mm Hg.
- X-match 4-6 units of blood.
- Keep Hb around 7-8 except in IHD/rapid ongoing bleeding.
- Ensure airway protection in encephalopathic patients.
- Urinary catheter.
- Consider HDU/ITU for invasive monitoring/airway management discuss earlier rather than later.

Initial management

- Resuscitation.
- Prospective one centre study.
- Group observed and group more intensly resuscitated.
- Mortality was better in the intervention group.
- Longer period in ICU in the intervention group.

American Journal of Gastroenterology April 2004
Robin Baradarian et al

INITIAL MANAGEMENT

- Correct clotting (FFP/PLT)
- VIT K 10 mg stat IV (continue this daily for 3 days).
- Glypressin: 1-2 mg IV every 4-6 hours.
- Antibiotics: reduce risk of re-bleeding and mortality. Local practice: Cefuroxime
- PPI.

ENDOSCOPY

- Should ideally be performed within 12 hours.
- Banding is the method of choice, but sclerotherapy may be used.
- EBL is better than sclerotherapy and associated with less side effects.
- Remember the need of intubation in encephalopathic patients.

Rescue Therapies

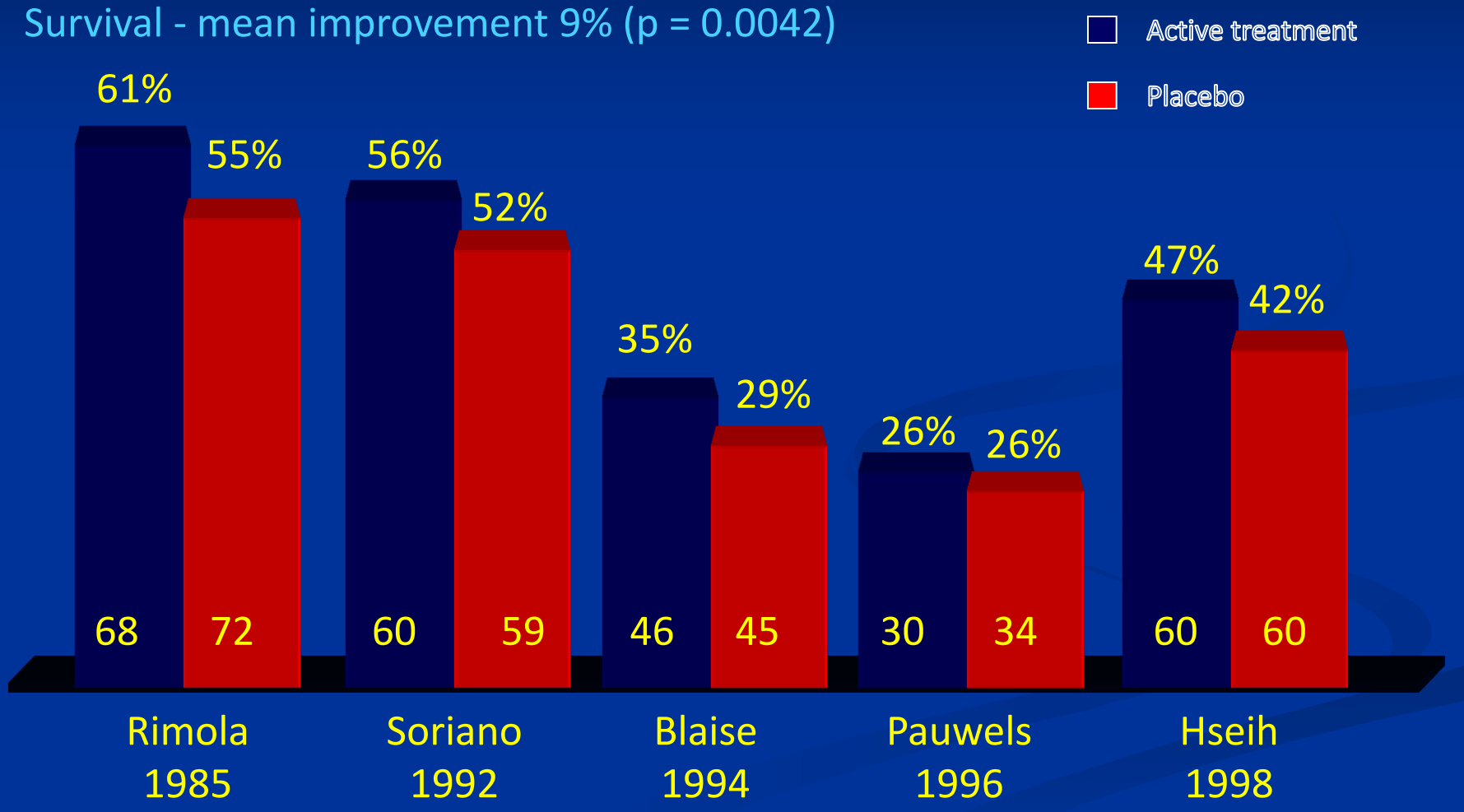
- Balloon tamponade. Should only be performed by competent clinician and after OGD.
- TIPS.

Cost Comparison

Category	Median Cost in thousands £ (Interquartile range)	p value
Survivor	£ 8 k (4-20k)	<0.001
Non Survivor	£ 21 k (8-37k)	
Variceal Bleed	£ 10 k (4-27k)	<0.05
No variceal bleed	£ 17 k (6-34k)	
RRT	£ 25 k (13-43k)	<0.001
No RRT	£ 6 k (3-18k)	
Cost per ITU Survivor	£ 41k	

Randomised controlled trials of prophylactic antibiotics in GI bleeding in cirrhotics

(Bernard et al., 1999)



* The studies used a range of drugs, ranging from gut steralisation (Rimola - Gent, Nystatin, Vancomycin) to oral antibiotics (Sofiano, Norfloxacin 800mg/d for 7 days) to a combination (Pauwels, oral ciprofloxacin plus amoxycillin and clavulanic acid IV).

GLASGOW ALCOHOLIC HEPATITIS SCORE (GAHS)

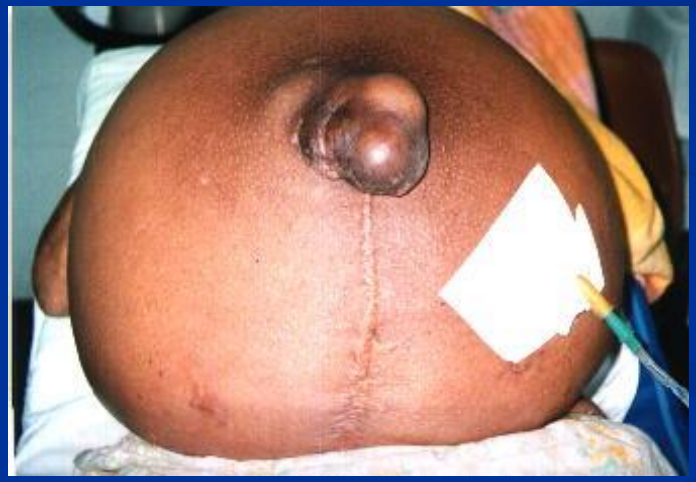
Score Value	1	2	3
Age	<50	≥50	-
WCC (10^9/l)	<15	≥15	-
Urea (mmol/l)	<5	≥5	-
Bilirubin (µmol/l)	<125	125 - 250	>250
PT (ratio)	<1.5	1.5 - 2.0	>2.0

Score	28d mortality	84d mortality
< 9	13%	21%
≥ 9	54%	60%

- Score 5-12
- Derived from 241 patients with ASH
- Verified in 195 patients
- GAHS correctly predicted 28 day outcome in 81%

Forrest Gut 2005

ASCITES



FACTORS INVOLVED IN ASCITES PATHOGENESIS IN CIRRHOTIC LIVER DISEASE

- Portal hypertension
- Trans-sinusoidal fluid exchange
- Splanchnic fluid exchange
  - sinusoids become capillarized
  - there is increased splanchnic permeability
  - massive increase in lymph production (8-9l/day)
  - BUT ALSO

PRINCIPLES OF MANAGEMENT?

- Isolate the problem
  - Bleeding
  - Sepsis
  - Decompensated cirrhosis
  - Acute alcoholic hepatitis