Refractory ascites

Hepatology Day
Beirut, May 28, 2011
Alexandre Pariente, Pau, France

Thanks to Christophe Bureau, Toulouse
Plan

- Definition
- Incidence and Prognosis
- General Measures
- Specific measures
  - Liver Transplantation
  - Large Volume Paracentesis (LVP)
  - Transjugular Intra Hepatic Shunt (TIPS)
- Recommendations
- 2 news about βblockers and clonidine
Definition

“Ascites that cannot be mobilized or the early recurrence of which cannot be prevented by medical therapy”

1 Diuretic-resistant ascites: lack of response to dietary sodium and intensive diuretic treatment (400 mg of spironolactone and 160 mg of furosemide)

2 Diuretic-intractable ascites: diuretics can not be used because of the development of complications (encephalopathy, renal impairment, hyponatremia, hyperkaliemia or hypokalemia…) that preclude the use of an effective diuretic dosage

Moore KP et al. Hepatology 2003;38:258-66
Definition

**Treatment duration**: at least 1 week

**Lack of response**: mean weight loss < 0.8 kg over 4 days and urinary sodium output less than the sodium intake

**Early ascites recurrence**: recurrence of grade 2 or 3 ascites within 4 weeks after initial mobilization

**Diuretic-induced complications**:
- **encephalopathy** in the absence of any other precipitating factors
- ↑ **serum creatinine** by >100 % to a value >2 mg/dl (177 uM)
- ↓ **serum sodium** by >10 mmol to a serum sodium <125 mmol/l
- **serum potassium** < 3 mmol/l or > 6 mmol/l

Moore KP et al. Hepatology 2003;38:258-66
RA is rare and severe

263 patients were followed after their first significant ascites (3yrs)

30

Refractory ascites (11%)

28

Intractable ascites (90%)

2

Resistant ascites (10%)

1-year survival was 32 %

...and in France

- 93% intractable-ascites
- 7% resistant-ascites
- 1 yr survival: 52%
- Survival predictive factors
  - Age, HCC, diabetes, persistence of alcohol

Moreau R et al. Liver Int 2004;24:467

*Fig. 2. Probability of survival in patients with cirrhosis and refractory ascites.*
Don’t forget…

- To eliminate other causes of « refractory » ascites (cardiac ascites, pancreatitis, tuberculosis, malignant ascites and hypothyroidism…)
- To evaluate the heart
- To look for PVT and HCC
- To measure natriuresis
So, Refractory Ascites is

- diuretic-intractable ascites in most cases
- a severe complication occurring in 10% of patients
- resulting in poor quality of life, high risk of spontaneous bacterial peritonitis and hepatorenal syndrome
- a sign of end stage liver disease associated with poor survival
Plan

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• 2 news about β-blockers and clonidine
General measures

- Ascitic fluid should be examined to rule out SBP
- The cause of cirrhosis must be treated (alcohol withdrawal, antiviral therapy etc...)
- A precipitating factor must be looked for (PVT, HCC)
- Patients should be maintained on a low sodium diet (90 mmol/d)
- Diuretics can be discontinued (sodium urinary excretion <30 mmol/d)

SBP and HRS must be prevented (nephrotoxic antibiotics, NSAID’s, hypotensive agents, iodine contrast media)
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Liver Transplantation

![Graph showing survival rates after liver transplant (LT) and with RA]

- Survival of patients after LT: 75%
- Survival of patients with RA: 30%
MELD underestimates early mortality in patients with Refractory Ascites

- 507 cirrhotics on TList
- 61/296 (21%) death < J180
  - Mean MELD 21

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  – Vasoconstrictors
  – Beta-blockers
LVP and post-paracentesis induced circulatory dysfunction

Any complications

Relapse of ascites

A : Patients with circulatory dysfunction
B : Patients without circulatory dysfunction

Ginès P et al Gastroenterology 1996;111:1002
Survival
Any complications
Relapse of ascites

LVP and post-paracentesis induced circulatory dysfunction

% of patients with PPCD

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</table>

Ginès P et al Gastroenterology 1996;111:1002

A : Patients with circulatory dysfunction
B : Patients without circulatory dysfunction
Diuretics

• Inefficacy in > 90% of patients
  – Stop definitely if complications
  – Pursue if natriuresis is > 30 mM/d

AASLD. J Hepatol 2010;53:397-417
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TIPS effects

Rössle M, Gerbes AL. Gut 2010;59:988-1000
TIPS effects

Rössle M, Gerbes AL. Gut 2010;59:988-1000
TIPS effects

Rössle M, Gerbes AL. Gut 2010;59:988-1000
Paracentesis or TIPS?
TIPS vs PA
5 trials, 4 metaanalyses

42 % vs 80 %

TIPS vs PA
5 trials, 4 metaanalyses

Recurrence of ascites
- Lebrec, 1996
- Rössle, 2000
- Ginés, 2002
- Sanyal, 2003
- Salerno, 2004
- Pooled RR fixed effects
- Pooled RR random effects

Encephalopathy
- Lower with TIPS
- Lower with paracentesis

54 % vs 36 %

TIPS vs PA
5 trials, 4 metaanalyses

Recurrence of ascites
Lebrec, 1996
Rössle, 2000
Ginés, 2002
Sanyal, 2003
Salerno, 2004
Pooled RR fixed effects
Pooled RR random effects

Encephalopathy

Mortality

Lower with TIPS
Lower with paracentesis

Lower with TIPS
Lower with paracentesis

Lower with TIPS
Lower with paracentesis

Lower with TIPS
Lower with paracentesis

Cumulative probability of transplant-free survival according to treatment allocation

Salerno F et al. Gastroenterology 2007;133:825
Meta-analysis according to individual data

Cumulative probability of transplant-free survival according to treatment allocation

Salerno F et al. Gastroenterology 2007;133:825
Cumulative probability of transplant-free survival according to treatment allocation

Salerno F et al. Gastroenterology 2007;133:825
1-year survival in 105 patients treated by TIPS for RA

![Graph showing survival rate over months with actuarial rates of survival at 0.2, 0.4, 0.6, 0.8, 1.0.]

- Serum bilirubin < 3 mg/dl (50 uM) and platelets count > 75 000
- Serum bilirubin > 3 mg/dl (50 uM) or platelets count < 75 000

**Actuarial rate of survival**

Month

- 73 %
- p < 0.05
- 31 %

Bureau C et al. J Hepatol 2011
Prospective validation

Platelet count > 75,10^9/l and serum bilirubin concentration < 50 µmol/l

Platelets count < 75,10^9/l or Serum bilirubin concentration > 50 µmol/l

p=0.02

AUROC - Bilirubine 0.668
- Plaquettes 0.823

< 50 µmol/l bilirubine : sensibilité 95 % - spéficité de 31 %
Plaquettes > 75 000 : sensibilité 95 %, spécificité 32 %
External validation (Barcelone)

Figure 4: Actuarial rates of survival in the 40 patients with cirrhosis and refractory ascites treated with TIPS according to serum bilirubin concentration and platelet count

Platelet count > 75 $10^9$/l and serum bilirubin concentration < 50 $\mu$mol/l

Platelet count < 75 $10^9$/l or Serum bilirubin concentration > 50 $\mu$mol/l

p < 0.001

AUROC
- Bilirubine 0.803
- Plaquettes 0.750

< 50 $\mu$mol/l bilirubine : sensibilité 89 % - spécificité of 46 %

Plaquettes > 75 000 : sensibilité 77 %, spécificité 68 %
Fig. 1. Probability of remaining free of shunt dysfunction after the transjugular intrahepatic portosystemic shunts (TIPS).
Fig. 2. Probability of remaining free of encephalopathy after the transjugular intrahepatic portosystemic shunts (TIPS)
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• Repeated LVP with albumin infusion (8 g/L of ascites removed) is the first line of treatment for refractory ascites (A1). Diuretics should be discontinued in patients with RA who do not excrete > 30 mM of sodium under treatment.
Recommendations 2

• TIPS is effective in the management of RA but is associated with a high risk of encephalopathy and studies have not been shown to convincingly improve survival compared with LVP (A1).

• TIPS could be considered in patients with very frequent requirement of LVP, or in those in whom paracentesis is ineffective (e.g. due to the presence of loculated ascites (B1)

AASLD. J Hepatol 2010;53:397-417
Recommendations 3

- Resolution of ascites after TIPS is slow and most patients require continued administration of diuretics and salt restriction (B1)
- TIPS cannot be recommended in patients with severe liver failure (serum bilirubin > 5 mg/dL, INR >2 or Child-Pugh score > 11, current encephalopathy >1 or chronic hepatic encephalopathy), concomitant active infection, progressive renal failure, or severe cardiopulmonary disease (B1)
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Deleterious effect of propranolol in patients with RA?

- Observational single-center study
- 151 patients with refractory ascites
- LVP with albumin
- 77 took beta blockers for the prevention of GI bleeding
- Median follow-up 8 months
- 1-year survival 41%
  - Propranolol 19% (IC 95%: 8-29%)
  - Non Propranolol 64% (IC 95%: 52-76%)

Deleterious effect of propranolol in patients with RA?

- Independent factors of mortality
Propranolol and Post-Paracentesis Circulatory Dysfunction

- 10 patients with RA treated with propranolol
- Self control cross over study
- Before, D0 and D7
- Then eradication of VO by banding, and new identical study without propranolol
- PPCD
  - 80% on propranolol
  - 20% off propranolol

Sersté T et al. J Hepatol 2011, in press
Clonidin in Refractory Ascites

- RCT, 270 patients with RA
- β blockers 35 vs 37%
- Spironolactone and furosemide on individual basis
- Clonidine 0.075 mg x 2 /d/3 months vs nothing
- Response: 20% decrease in body weight and 20% increase in \( U_{NaV} \) at 1 and 3 months

Clonidine in Refractory Ascites

- ↓ Aldosterone, PRA, Norepi
- ↑ UNaV, GFR
- Response:
  - 1 month 55%
  - 3 months 60%
- Responders:
  - ↓ Paracentesis
  (9 vs 13/3m)

Thank you for your attention