Leids Universitair
Medisch Centrum

Ascites and AKI-HRS

DLW 2019

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No disclosures

Learning objectives

Pathogenesis of decompensated cirrhosis

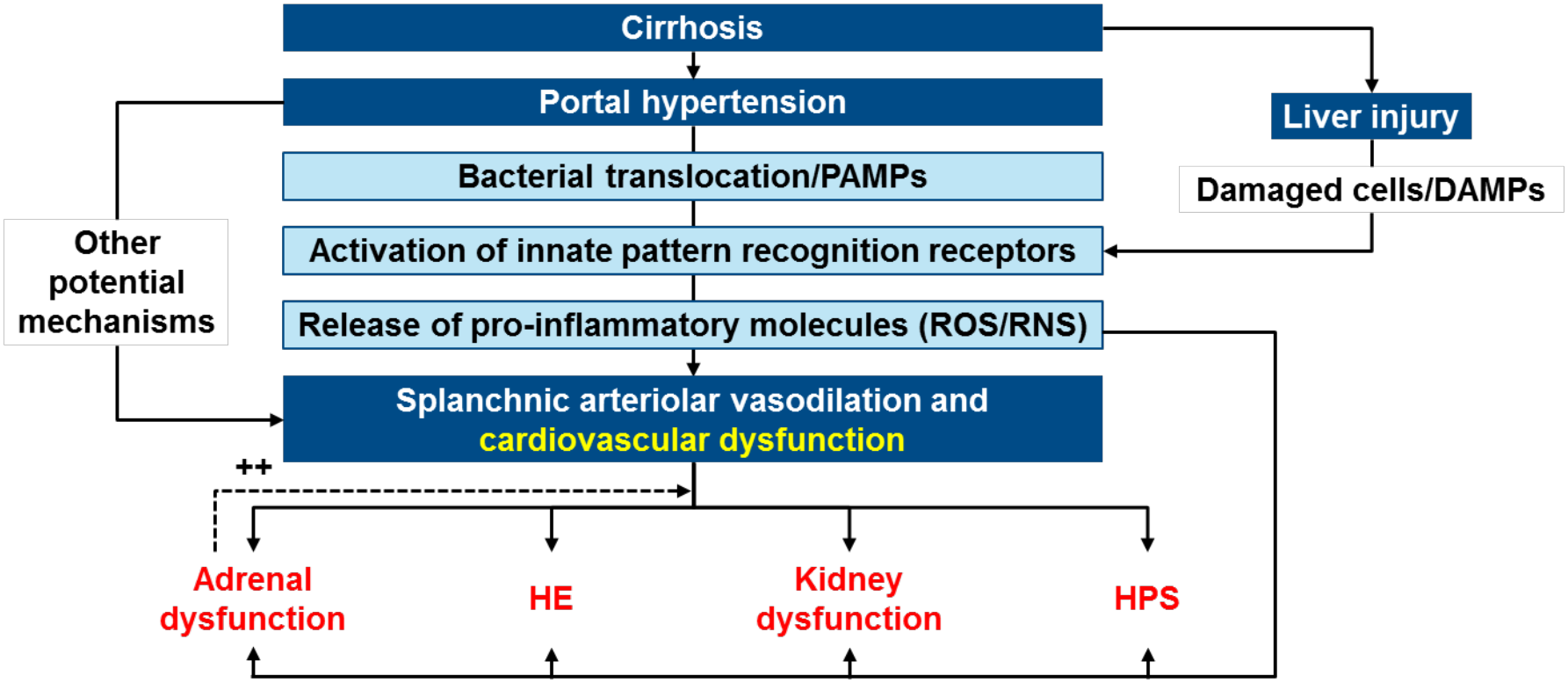
Principles of therapeutic approaches of ascites/ AKI-HRS

Recognise and treat refractory ascites

Knowledge of revised definitions of renal failure in cirrhosis

Therapy of AKI-HRS

Pathophysiology of decompensated cirrhosis



Bernardi M, et al. J. Hepatol 2015;63:1272–84 EASL CPG decompensated cirrhosis.

Mechanisms of portal hypertension

Increase in intrahepatic vascular resistance

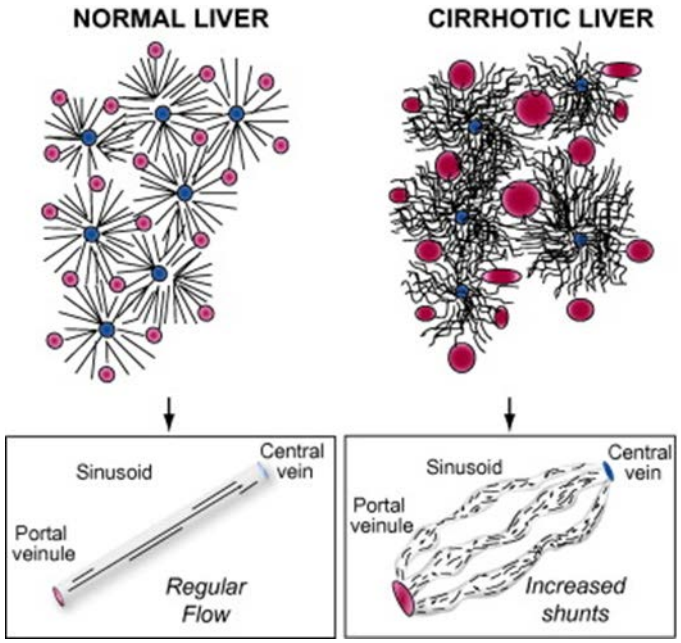
- Mechanic (fibrosis deposition)
- Dynamic (endothelial dysfunction by NO/ imbalance)
- Angiogenesis and sinusoidal remodelling

Splanchnic vasodilatation

Decreased effective circulating volume

Increased portal inflow

↑RAAS/ AVP/ sympathetic nervous activity



Management of decompensated cirrhosis

1. Prevent cirrhosis progression: remove aetiological factor

2. Prevent or improve each complication

- Renal sodium retention in ascites
- Ammonia production in hepatic encephalopathy
- Circulatory dysfunction in post-paracentesis circ. dysfunction/ AKI-HRS/ SBP
- Intestinal dysbiosis/ bacterial overgrowth in high risk of infections

3. Mechanistic approaches

- target microbiome
- improve circulatory dysfunction
- target inflammatory state
- target portal hypertension

Casus
Vrouw 54 jaar

VG/ Doorgemaakte hepatitis B, DM, obesitas, hypertensie

4-2016 cirrose vastgesteld, splenomegalie, grote oesofagusvarices,

8-2016 toenemende buikomvang, 5 kg gewichtstoename, dikke enkels

L.O.: helder bewustzijn, niet icterisch,

Graad 2 ascites

Enkeloedeem

Lab: bilirubine 22 µmol/l, albumin 40 g/l, INR 1.7, kreatinine 61 µmol/l, Na 138

Child Pugh B (7 punten), MELD score 13 punten, MELD-Na 15 punten

Conclusie?

Beleid tav diagnostiek? Therapie?

Ascites work-up

Diagnostic paracentesis (PMN/total protein/SAAG/cytology) indicated in:

- All patients with new-onset grade 2 or 3 ascites
- Patients hospitalized for worsening ascites or any complication of cirrhosis

Grading of ascites*	
Grade 1	Mild ascites: only detectable by ultrasound examination
Grade 2	Moderate ascites: manifest by moderate symmetrical distension of abdomen
Grade 3	Large or gross ascites: provokes marked abdominal distension

Vervolg casus

Diagnostiek:

Echo bovenbuik: cirrotische lever, geen focale laesies, vaten open, splenomegalie 15 cm, ascites++

Ascitespunctie: PMN 75/µl, ascites albumine 20 g/l, SAAG 14 g/l

Beleid:

Zoutbeperkt dieet

Start spironolacton 100 mg

Verwijzing naar transplantatiecentrum

Timing van verwijzing naar transplantatiecentrum

A. Zou ik ook nu hebben gedaan

B. Ik zou patient nu niet hebben verwezen

Ascites treatment

Treat underlying disorder

Sodium restriction (4.6-6.9 g/day) and antimineralocorticoid / loop diuretics

Fluid restriction only if Na concentration < 125 mmol/l

Development of ascites in patients with cirrhosis is associated with a poor prognosis

- 1-year mortality: 40%
- 2-year mortality: 50%

Patients with ascites should be considered for referral for LT

However; prioritization may not be adequate (MELD: bilirubin,INR,creatinin)

Vervolg casus

10-2017 Acute oesofagusvaricesbloeding; EVL, propranolol

4-2018 sterk toegenomen buikomvang, opname voor ontlastende drainage
In 4 dagen +9 kg gewichtstoename
Ernstige mechanische bezwaren, kortademig

Relevante medicatie: furosemide 2x 40 mg, spironolacton 200 mg, propranolol 2x30 mg

L.O.: Graad 3 ascites, caput medusae

Lab: Na 132 mmol/l, creatinine 87 µmol/l, Bilirubine 19 µmol/l, Albumine 25 g/l
INR 1.3
Child Pugh B (9 punten), MELD 10 punten, MELD-Na 16 punten

Refractory ascites

Diuretic-resistant ascites

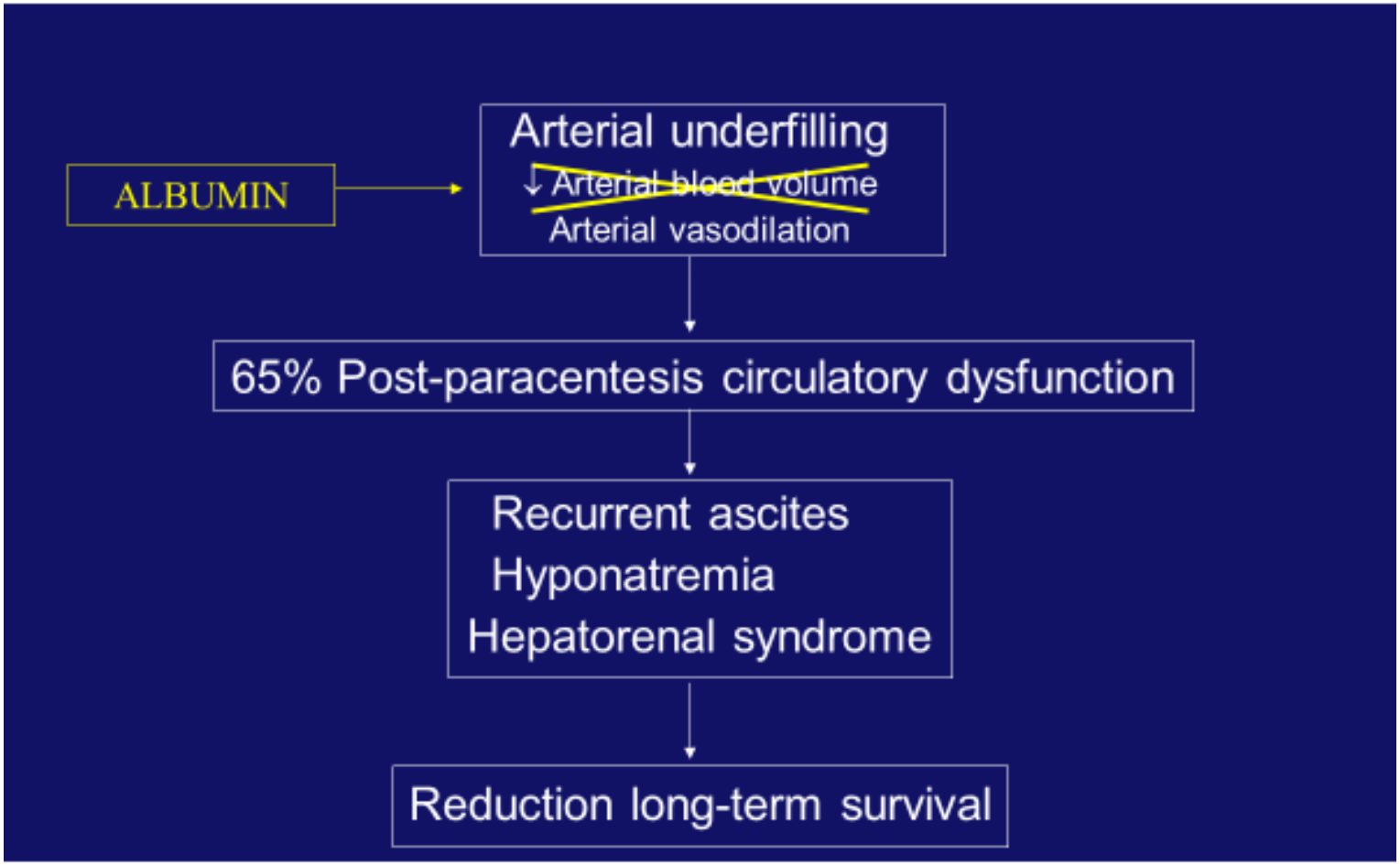
Lack of response to sodium restriction and diuretics

Diuretic-intractable ascites

Diuretic-induced complications preclude effective dosage

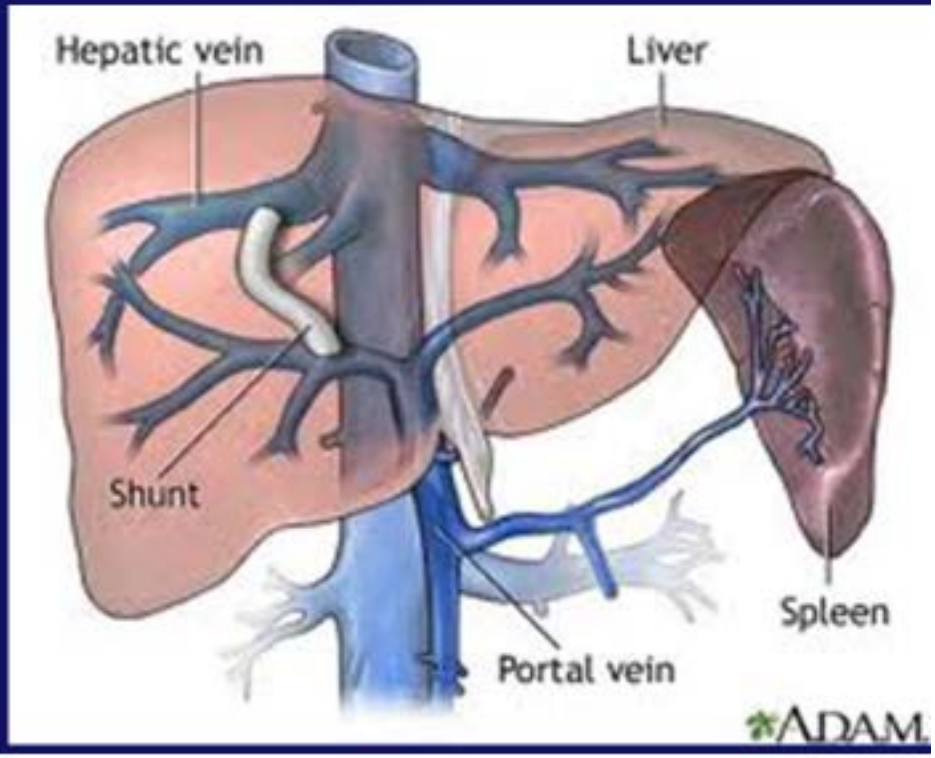
- **Hepatic encephalopathy**
- **Renal impairment**: increase of serum creatinine by >100% to >177 µmol/L
  Hyponatraemia: serum sodium of <125 mmol/L
- **Hypo-** or **hyperkalaemia**: <3 mmol/L or >6 mmol/L despite measures
- **Incapacitating muscle cramps**

Large volume paracentesis



Transjugular intrahepatic portosystemic shunt

TIPS: ↓ pressure intrahepatic portal system and splanchnic veins



TIPS versus paracentesis in refractory ascites

TIPS:

Improved control of ascites

Increased number of hepatic encephalopathy episodes

Improved survival?

Cautious selection of patients for TIPS treatment

Exclusion: bilirubin > 85 µmol/l

INR>2

Child Pugh C (>11)

Encephalopathy

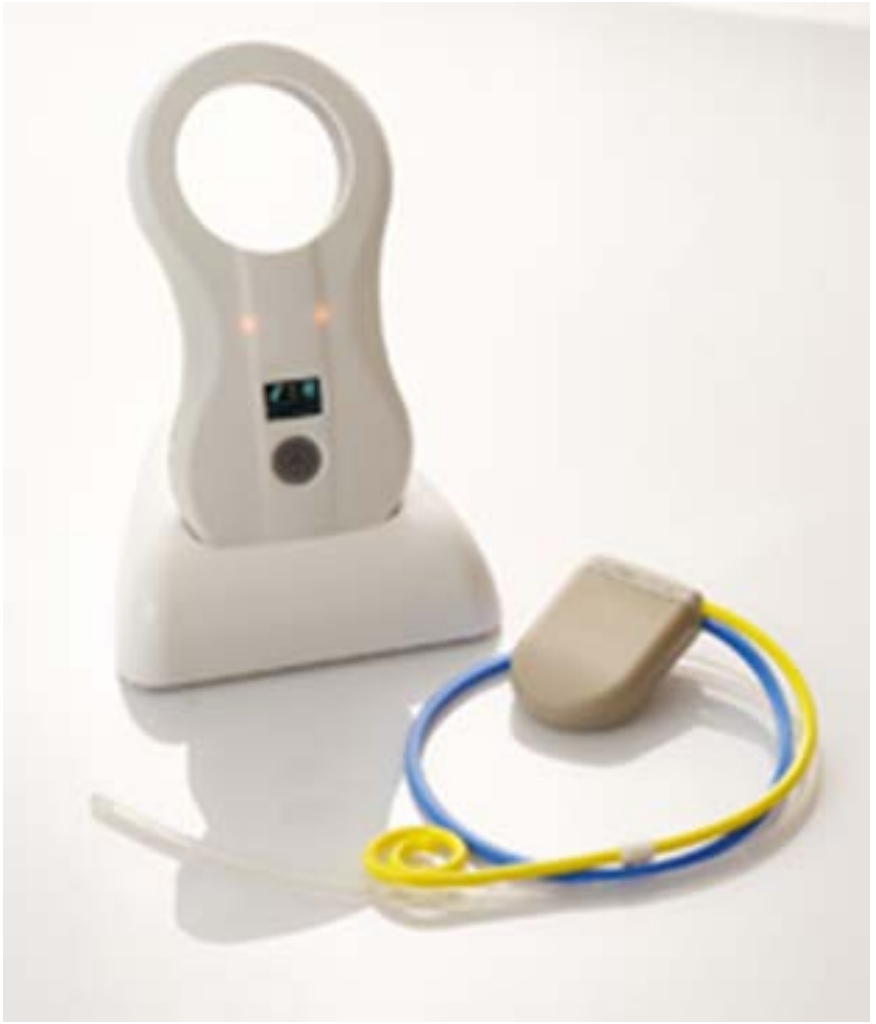
ALFA pump
Automatic low-flow ascites pump

85% Reduction in number of paracenteses

Improved quality of life

Improved nutritional parameters

85% vs 45% SAEs (AKI, GFR decline)



Bureau et al., J Hep 2017: 67: 940

Vervolg casus

Ascites diagnostiek:

SAAG 18 g/l

Ascites PMN 0.35 x 109/l: Spontane bacteriële peritonitis

Ontlastende paracentese: 6 liter, waarna afname dyspneu

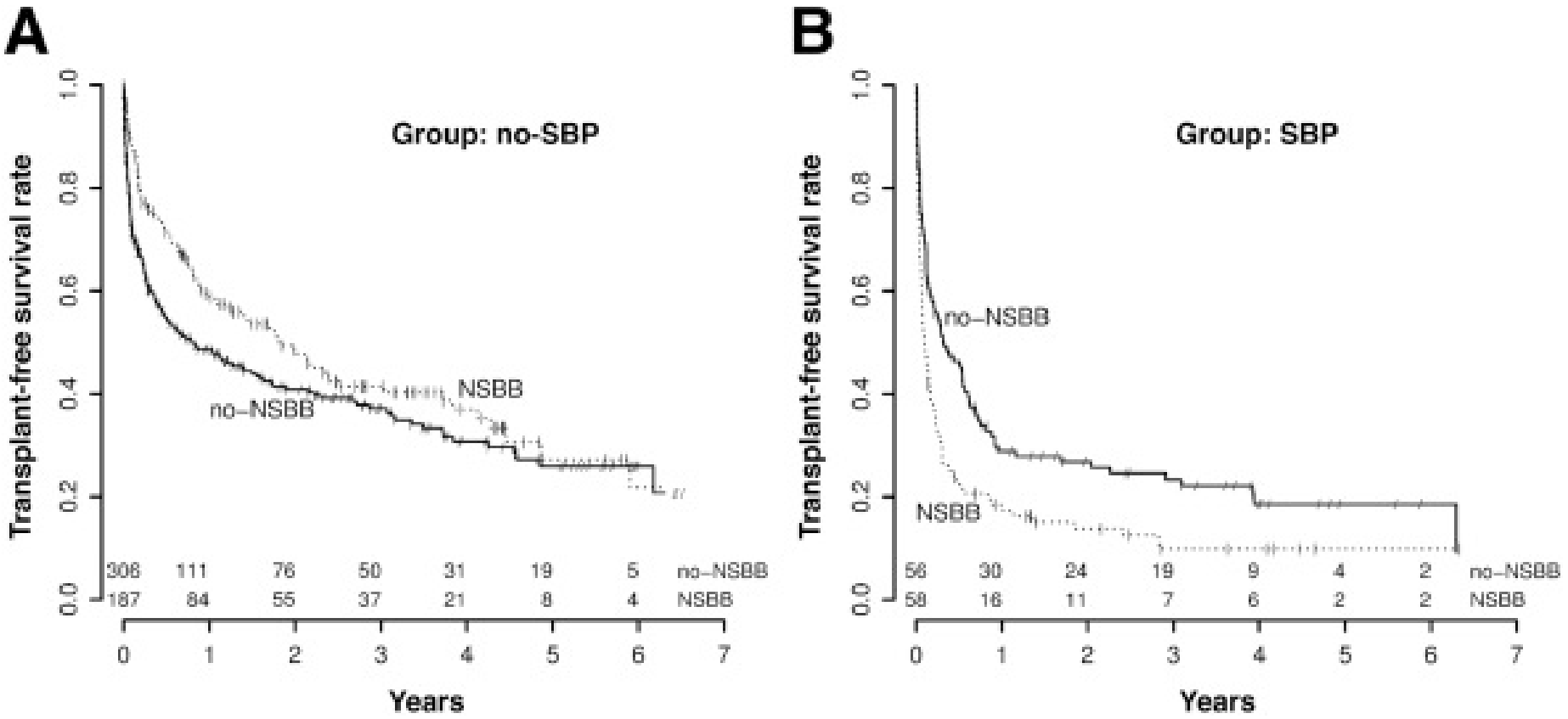
Albumine 8 g per liter infusie

Na paracentese RR 95/49 mmHg (was 115/63 mmHg)

Vraag: propranolol staken?

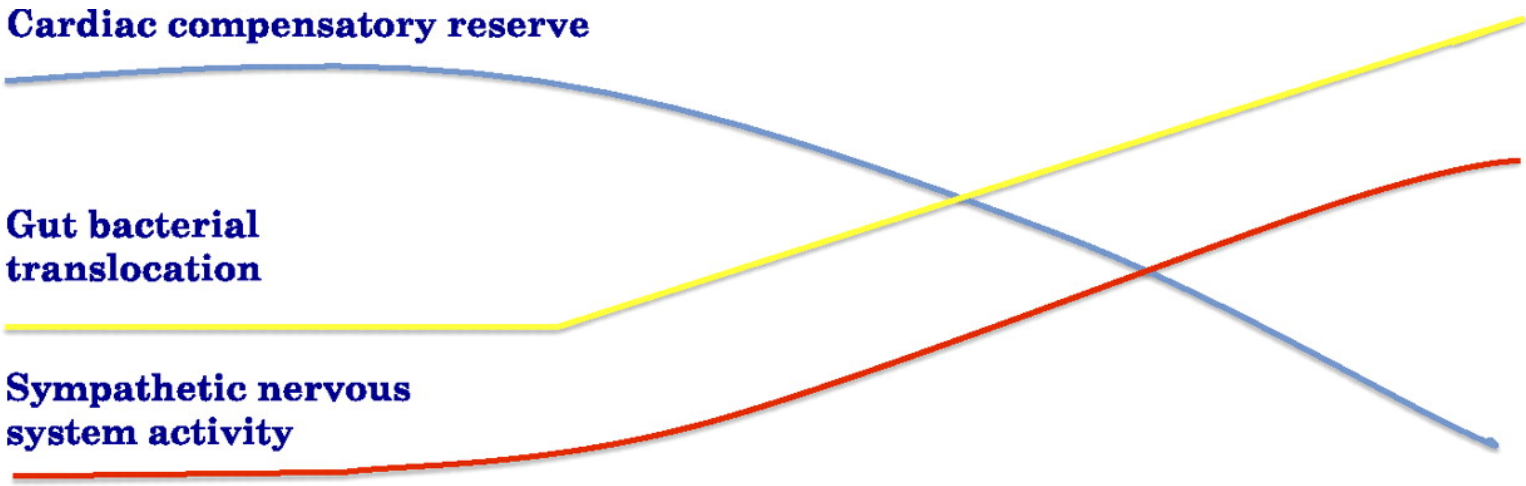
- Ja
- Nee
- Weet niet

Impact of NSBB treatment on transplant-free survival according to SBP status



Mandorfer et al., Gastroenterology 2014

Hypothesis of the therapeutic window for non-selective β-blockers (BB) in cirrhosis



BB have **no effect on survival**

Early cirrhosis

I. No risk of bacterial translocation
II. No increase in sympathetic nervous system activity
III. Cardiac compensatory reserve intact

Window opens

BB **improve survival** by reducing the risk of variceal bleeding and bacterial translocation

Compensated and decompensated cirrhosis
(Medium-large varices)

I. Increased risk of bacterial translocation
II. Increased sympathetic nervous system activity
III. Cardiac compensatory reserve intact and blood pressure and organ perfusion protected

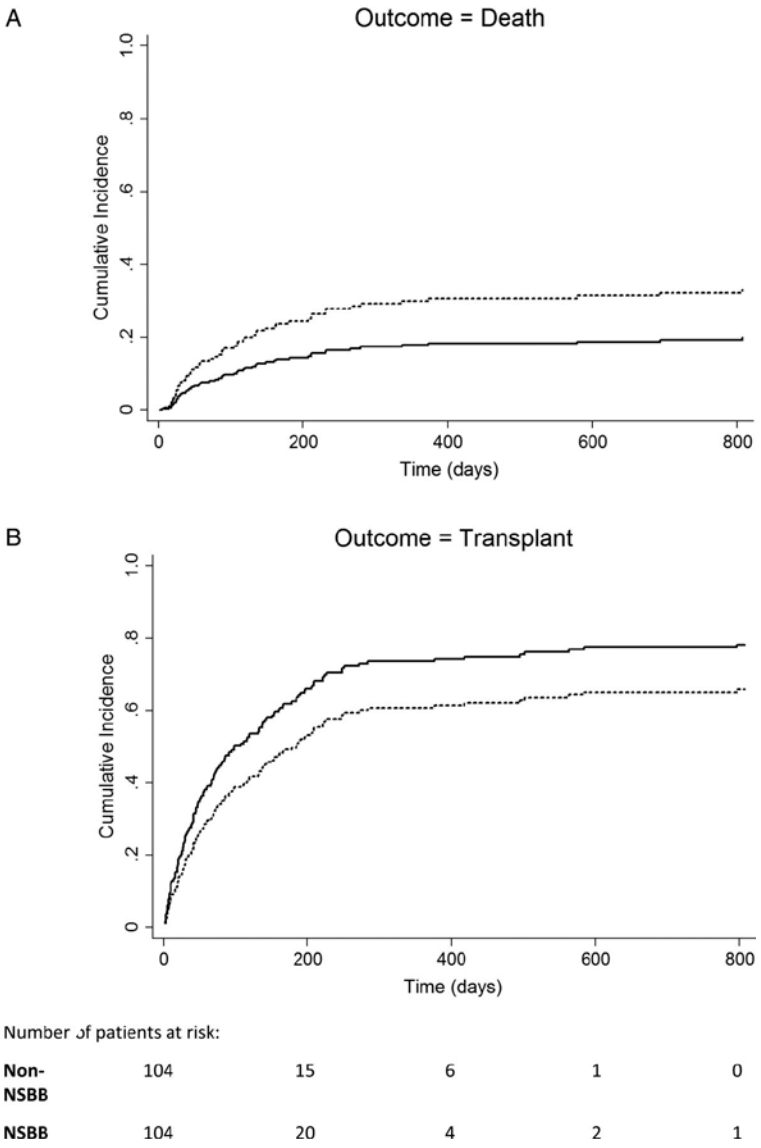
Window closes

BB **reduce survival** due to a negative impact on the cardiac compensatory reserve. The inability to increase the cardiac output during stress compromises organ perfusion.

End-stage cirrhosis
(Refractory ascites)

I. Increased risk of bacterial translocation
II. Maximum sympathetic nervous system stimulation
III. Cardiac compensatory reserve impaired

Cumulative incidence of (A) death and (B) transplantation in propensity risk score-matched patients with ascites listed for liver transplantation

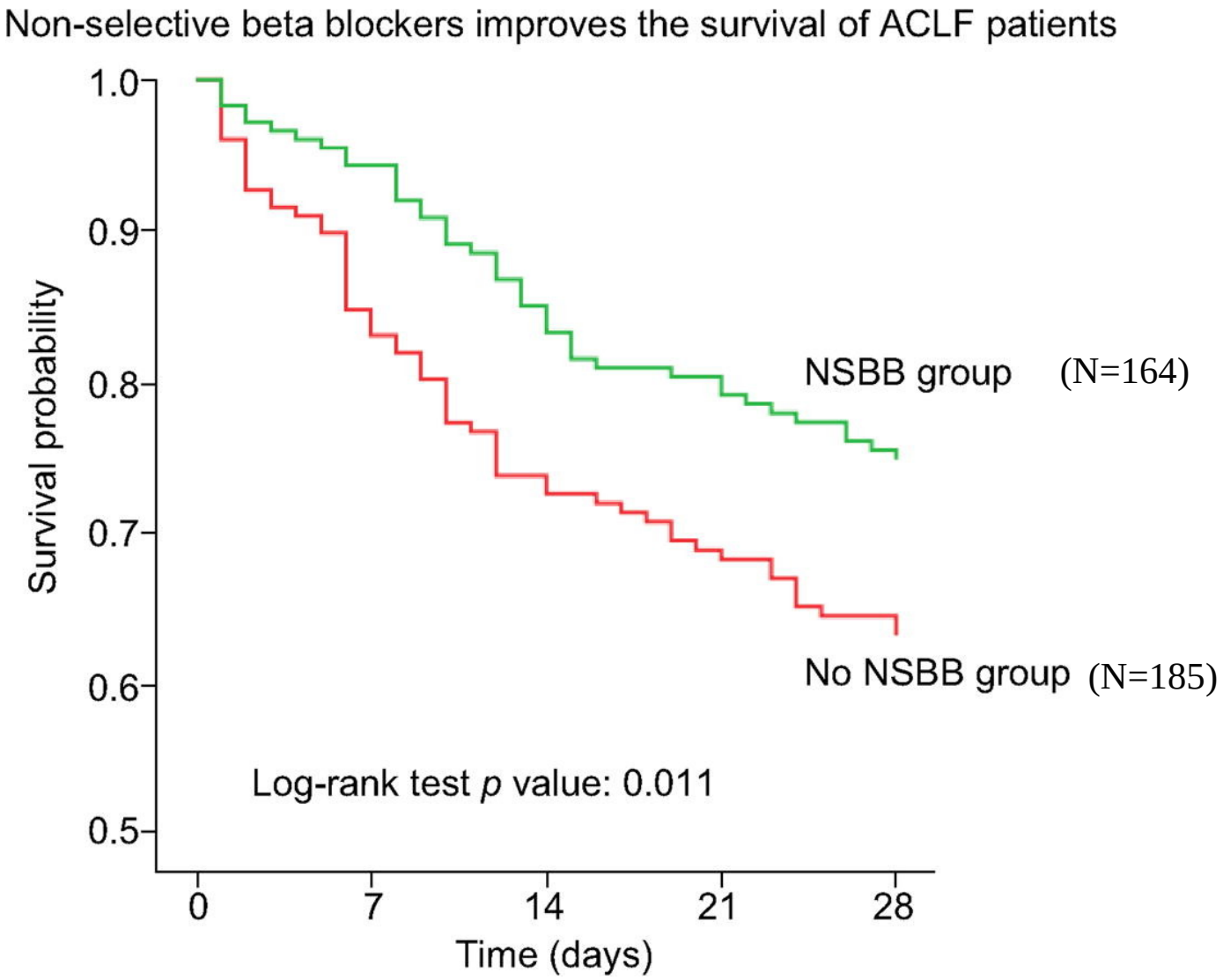


Single center retrospective study
Birmingham
35% refractory ascites

NSBB (solid line)

absence of NSBB (dashed line)

Survival curves at 28 days after diagnosis ACLF in relation to NSBB use



Recommendation		
Repeated LVP plus albumin (8 g/L of ascites removed) are recommended as first-line treatment for **refractory ascites**	I	1
Diuretics should be discontinued in patients with refractory ascites who do not excrete >30 mmol/day of sodium under diuretic treatment	III	1
Although controversial data exist on the use of NSBBs in refractory ascites, caution should be exercised in severe cases*		
• High doses of NSBB should be avoided (i.e. propranolol >80 mg/day)	II-2	1
• Carvedilol can not be recommended at present	I	2

EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024

Other potential beneficial effects of NSBB

- Gut motility
- Gut permeability
- Bacterial translocation
- Systemic inflammation
- Inhibition of angiogenesis

Spontaneous Bacterial Peritonitis

Prevalence: 10-30% hospitalized, 3.5% outpatients

Presentation

- peritoneal infection, encephalopathy, renal failure
- asymptomatic

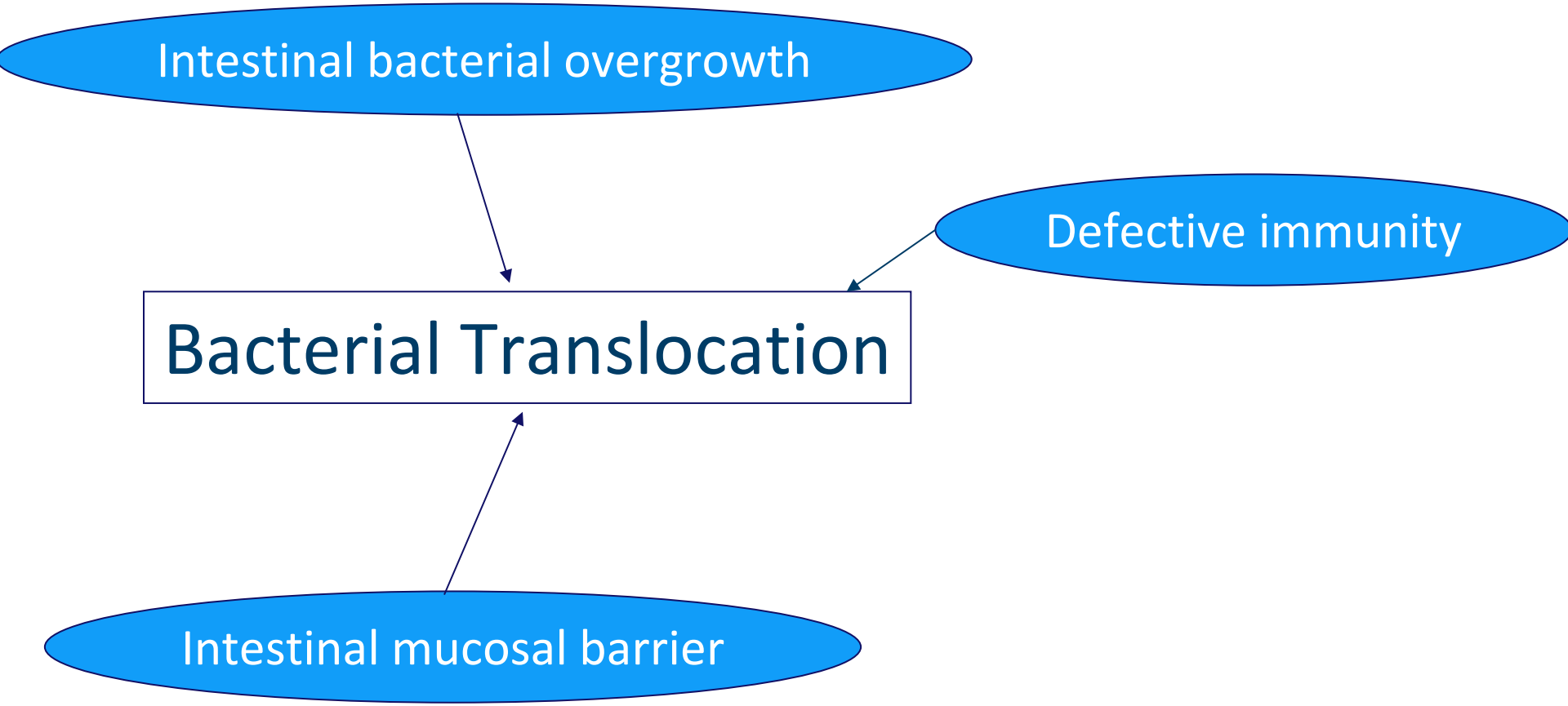
Ascites polymorphonuclear count $\geq 250/mm^3$ ($0.25x10^9/l$)

40% Ascites culture negative (bedside inoculation)

SBP pathogenesis

Intestinal-type flora:

70% gram negative, 25% gram positive, 5% anaerobic



SBP treatment

Consensus International Ascites Club 2000, EASL guideline 2018:

Third generation cefalosporin

Follow-up paracentesis after 2 days of antibiotic therapy

Treatment failure if reduction in PMN count< 25%

Outcome SBP:

SBP resolution 80-95%

In-hospital mortality: 30-50%

Hepatorenal syndrome: 33%

EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024

Casus vervolg

Ondanks antibiotische behandeling en albumine dag 1 en dag 3: acute nierinsufficientie

Kreatinine op dag 5 SBP opgelopen van 87 µmol/l naar 213 µmol/l

Meest waarschijnlijke diagnose?

1. AKI-HRS
2. Tubulointerstitiele nefritis door cefalosporines
3. Acute tubulus necrose
4. Postparacentese circulatoire dysfunctie na ontlastende paracenteses
5. Dehydratie

Differential diagnosis of renal insufficiency

Etiologies of renal impairment

	n **(%)**
Hepatorenal syndrome type 1	15 (17)
Hepatorenal syndrome type 2	20 (23)
Prerenal failure (e.g. bleeding)	13 (15)
Diuretics/nephrotoxic drugs	17 (19)
Renal parenchymal disease	20 (23)
Other/unclear	3 (3)

n=88 (12 Child A/ 19 B/ 57 C), creatinine> 120 µmol/l)

Hepatorenal syndrome survival

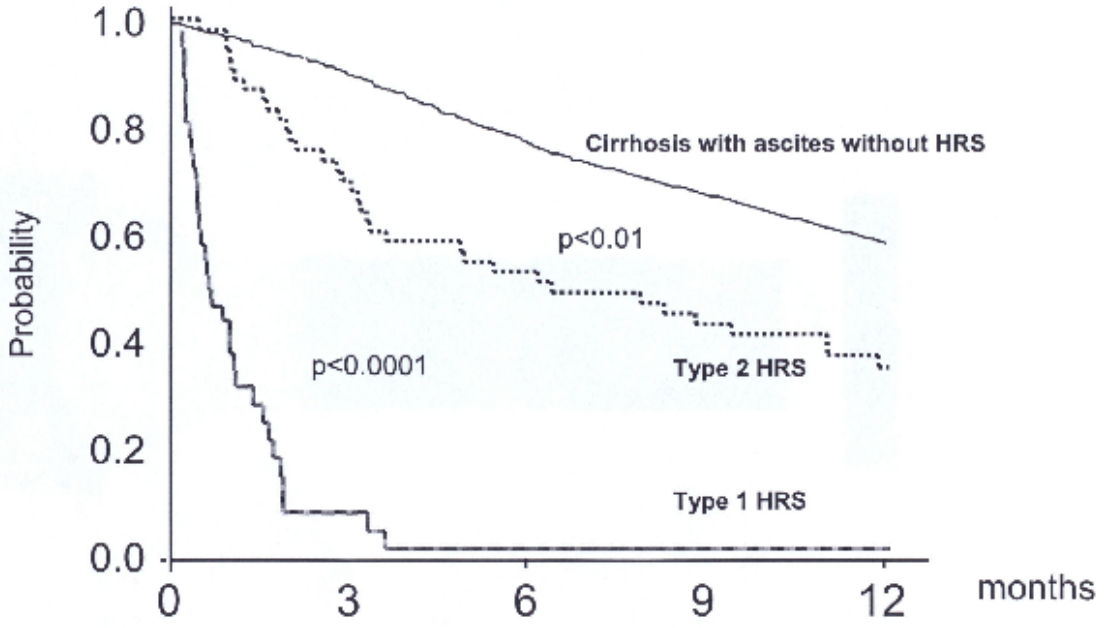
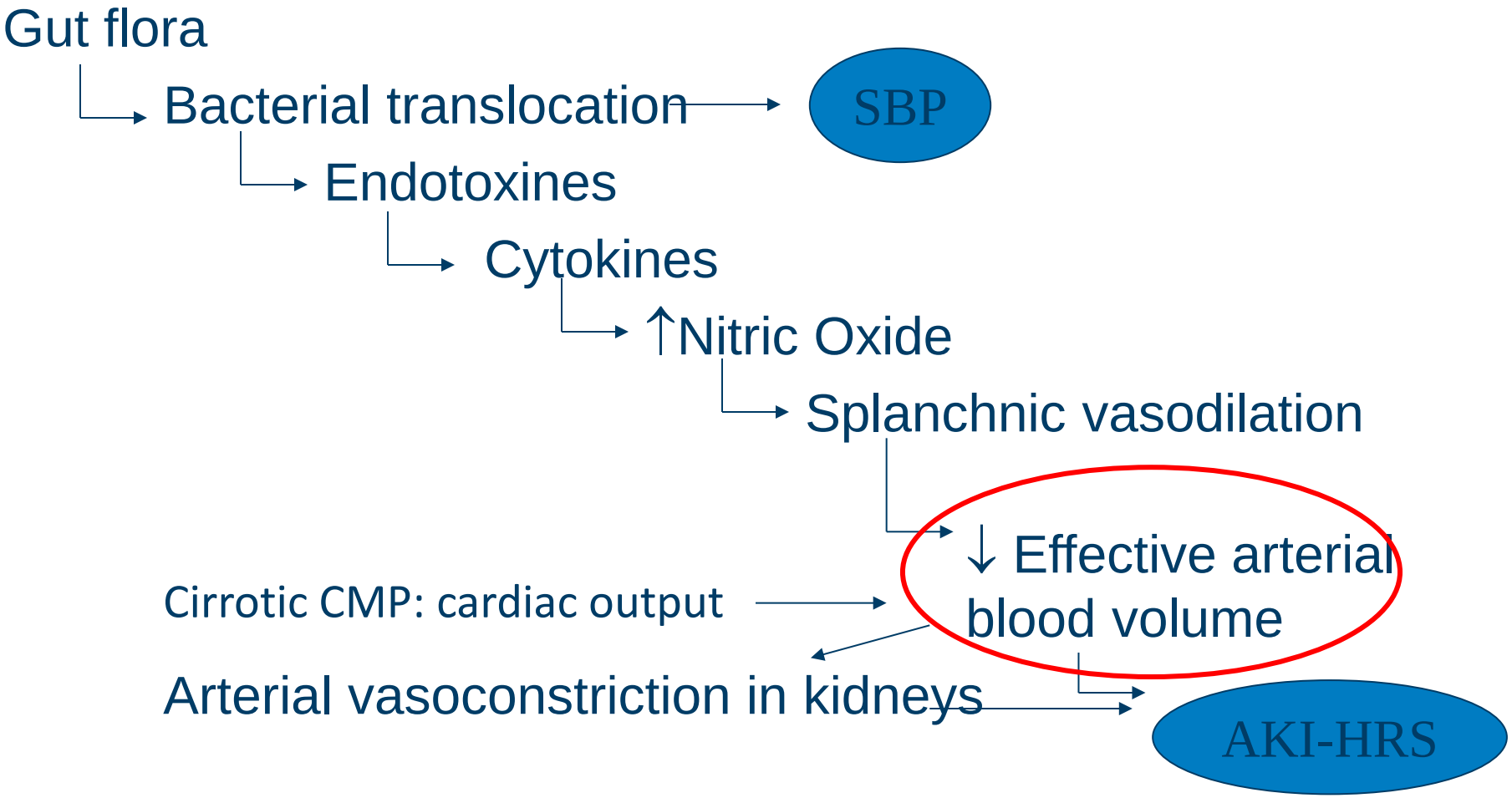


Figure 2

Pathogenesis SBP – renal impairment

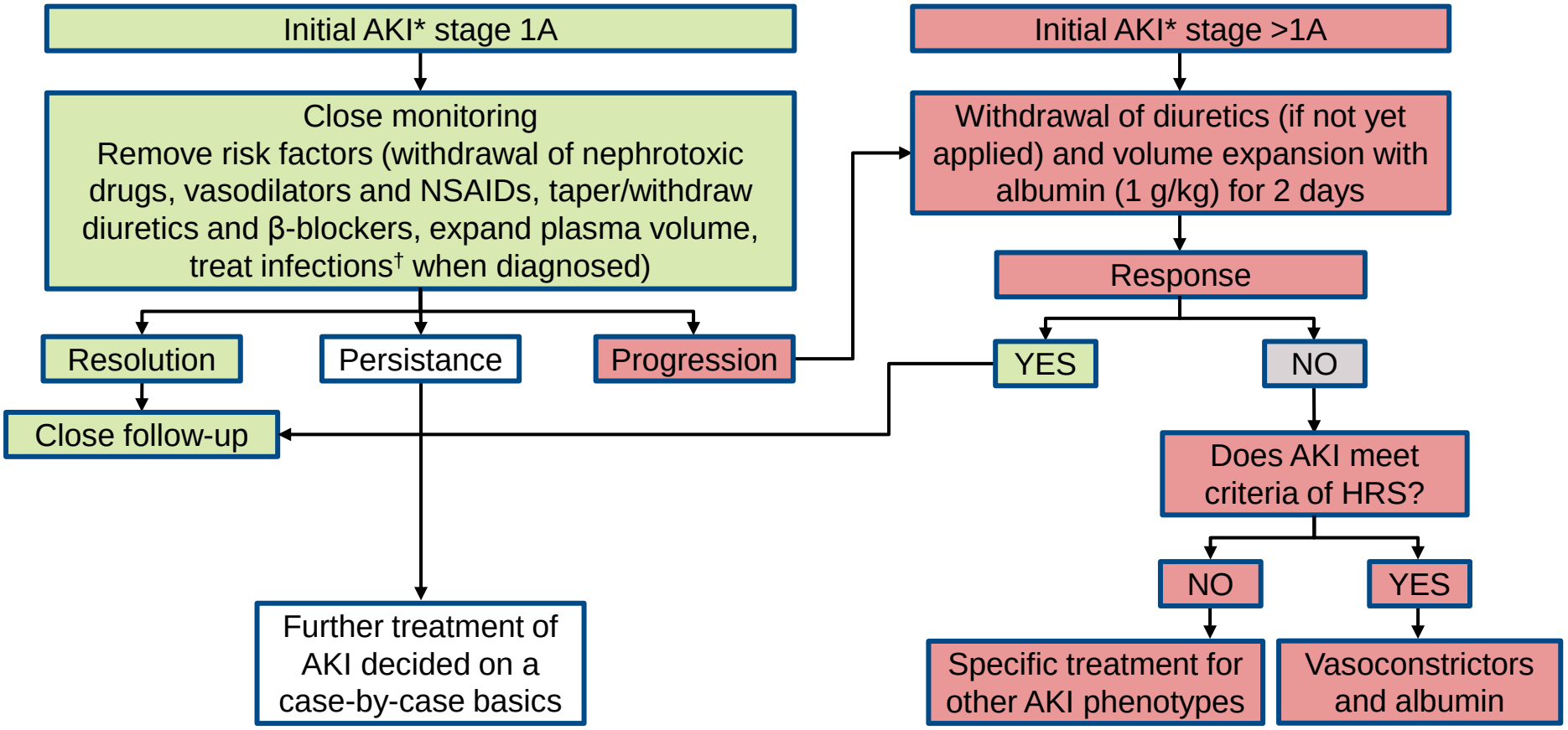


Diagnostic criteria AKI-HRS

- Cirrhosis and ascites
- Diagnosis of AKI (>50% creat/7 days or > 26 µmol/l/ 2days) according to ICA-AKI criteria
- No response after 2 days of diuretic withdrawal and albumin 1 g/ kg
- Absence of shock
- No current or recent use of nephrotoxic drugs
- No macroscopic signs of structural kidney injury

ICA management algorithm for AKI in cirrhosis

- Investigation and management should begin immediately



*Initial AKI stage is defined as AKI stage at the time of first fulfilment of the AKI criteria;
†Treatment of spontaneous bacterial peritonitis should include albumin infusion according to current guidelines
Adapted from Angeli P, et al. J Hepatol 2015;62:968–74;
EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024

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Therapy AKI-HRS

Terlipressin: V_1 receptor agonist: splanchnic constriction

Albumin: ↑ cardial preload

Aliment Pharmacol Ther 2006

Reversal of renal function 65%

Recurrence of HRS 20%

Side effects 25%, severe 5-10%

Mortality: odds ratio 5.7 for nonresponders

Alternative in outpatient setting:

Midodrine: α adrenerge agonist (vasoconstrictor)

Octreotide: inhibits release of vasodilator glucagon

Albumin

Take home messages

Pathogenesis of decompensated cirrhosis:

portal hypertension- bacterial translocation- systemic inflammation- circulatory dysfunction

Principles of therapeutic approaches of ascites/ AKI-HRS:

Prevent or improve mechanisms of all complications

Recognize and treat refractory ascites: LVP/ TIPS in selected cases

Knowledge of revised definitions of renal failure in cirrhosis:

AKI stage 1-3, AKI-HRS

Therapy of AKI-HRS: terlipressin and albumin

Timely contact a transplant center

Management of HRS-AKI: treatment

- First-line therapy is terlipressin plus albumin*

Recommendation	Grade of evidence	Grade of recommendation
All patients meeting the current definition of **HRS-AKI stage >1A** should be expeditiously treated with **vasoconstrictors and albumin**	III	1
Terlipressin can be administered by IV boluses (1 mg every 4–6 hours) or by continuous IV infusion (2 mg/day)† • In case of **non-response** (decrease in SCr <25% from the peak value) after 2 days, the dose of **terlipressin should be increased** in a stepwise manner to a **maximum of 12 mg/day**	I	1
Albumin solution (20%) should be used at 20–40 g/day • Serial measures assessing central blood volume can help to titrate the dose of albumin to prevent circulatory overload	II-2	1
Noradrenaline can be an alternative to terlipressin‡ • Requires a central venous line often in an ICU Midodrine + octreotide can be an option when terlipressin or noradrenaline are unavailable (but efficacy is much lower)	I I I	2 1 1

*Grade of evidence I, grade of recommendation 1;
†Continuous IV infusion allows for dose reduction to reduced adverse effects; ‡ Limited data are available
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Refractory ascites: diagnostic criteria

Diagnostic criteria	
Treatment duration	Patients must be on intensive diuretic therapy* for at least 1 week and on a salt-restricted diet of less than 90 mmol/day
Lack of response	Mean weight loss of <0.8 kg over 4 days and urinary sodium output less than the sodium intake
Early ascites recurrence	Reappearance of grade 2 or 3 ascites within 4 weeks of initial mobilization
Diuretic-induced complications	• **HE**: development of encephalopathy in the absence of any other precipitating factor • **Renal impairment**: increase of serum creatinine by >100% to a value >2 mg/dl (177 µmol/L) in patients with ascites responding to treatment • **Hyponatraemia**: a decrease of serum sodium by >10 mmol/L to a serum sodium of <125 mmol/L • **Hypo-** or **hyperkalaemia**: a change in serum potassium to <3 mmol/L or >6 mmol/L despite appropriate measures • **Incapacitating muscle cramps**

*Spironolactone 400 mg/day and furosemide 160 mg/day

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