


Optimal management of ascites

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Clinical Case

- Female, 59 years old
- HBV-related cirrhosis (2013)
- In January 2015 first episode of decompensation (ascites)
- Esophageal varices: F2
- Medication:
  - Spironolactone 200 mg daily
  - Propranolol 30 mg b.i.d.

- In May 2016 she presented an increase of the volume of ascites (moderate non tense ascites) during a one day check up.

Laboratory Tests

WBC (n.v 4.40-11.0)	3.56 x 109/l
Hb (n.v 14.0-17.5)	11.5 g/l
PLTs (n.v 150-450)	89 x 109/l

Creatinine (n.v 59-104)	82 µmol/L
Sodium (n.v 136-145)	135 mmol/L
Potassium (n.v 3.4-4.5)	4.5 mmol/L
CRP (n.v 0-6)	12 mg/L

AST (n.v 10-45)	20 U/L
ALT (n.v 10-50)	39 U/L
GGT (n.v 3-65)	35 U/L
ALP (n.v 53-151)	100 U/L
Bilirubin (n.v 1.7-17.7)	35.6 µmol/L
INR (n.v 0.9-1.20)	1.40
Albumin (n.v 38-44)	32 g/L

What is the treatment for ascites?

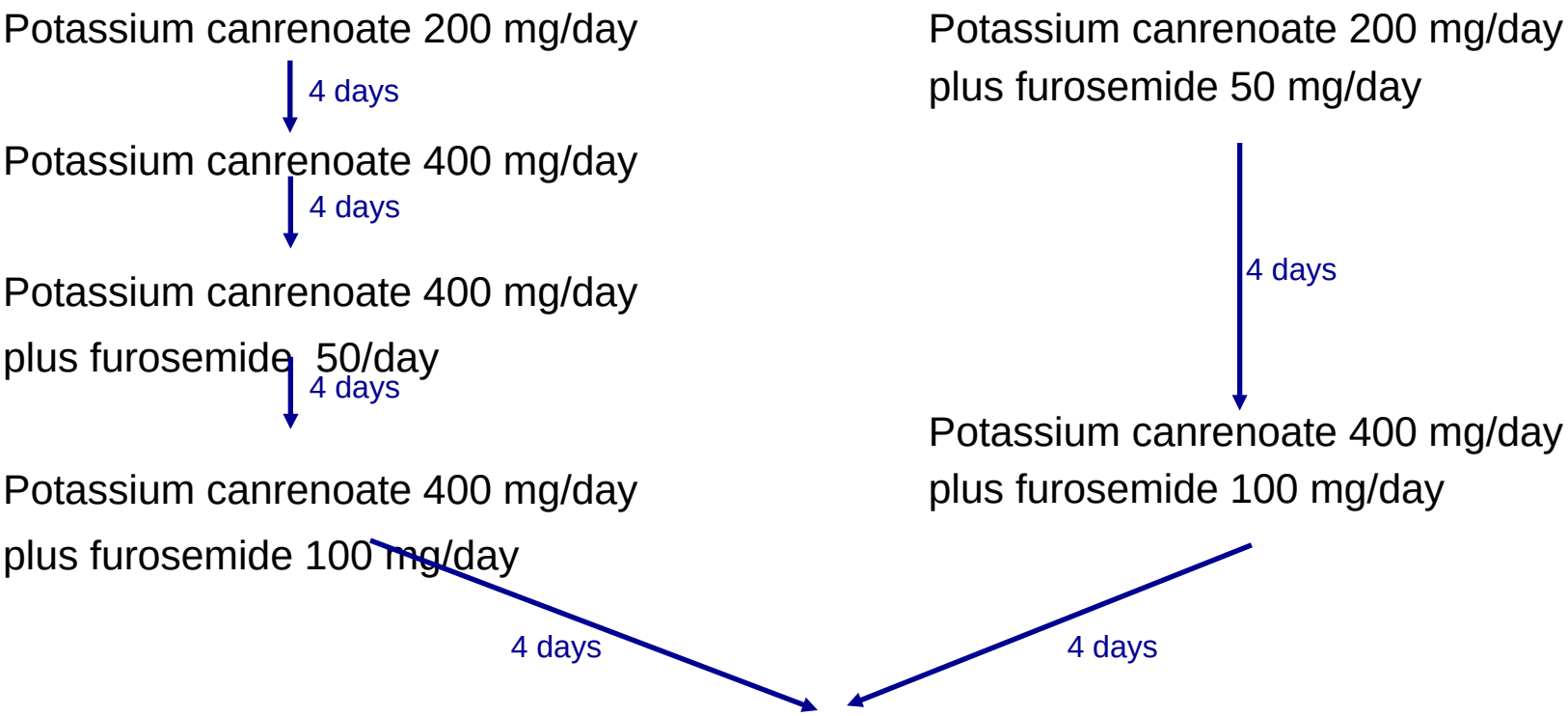
- Spironolactone 400 g
- Spironolactone 200 mg + furosemide 25 mg b.i.d.
- Therapeutic paracentesis

Treatment of uncomplicated ascites

Grade of ascites	Type of tretament
• Grade 1 or minimal ascites	• No treatment
• Grade 2 or moderate ascites	• Sodium restriction an diuretics
• Grade 3 or massive ascites	• Therapeutic paracentesis

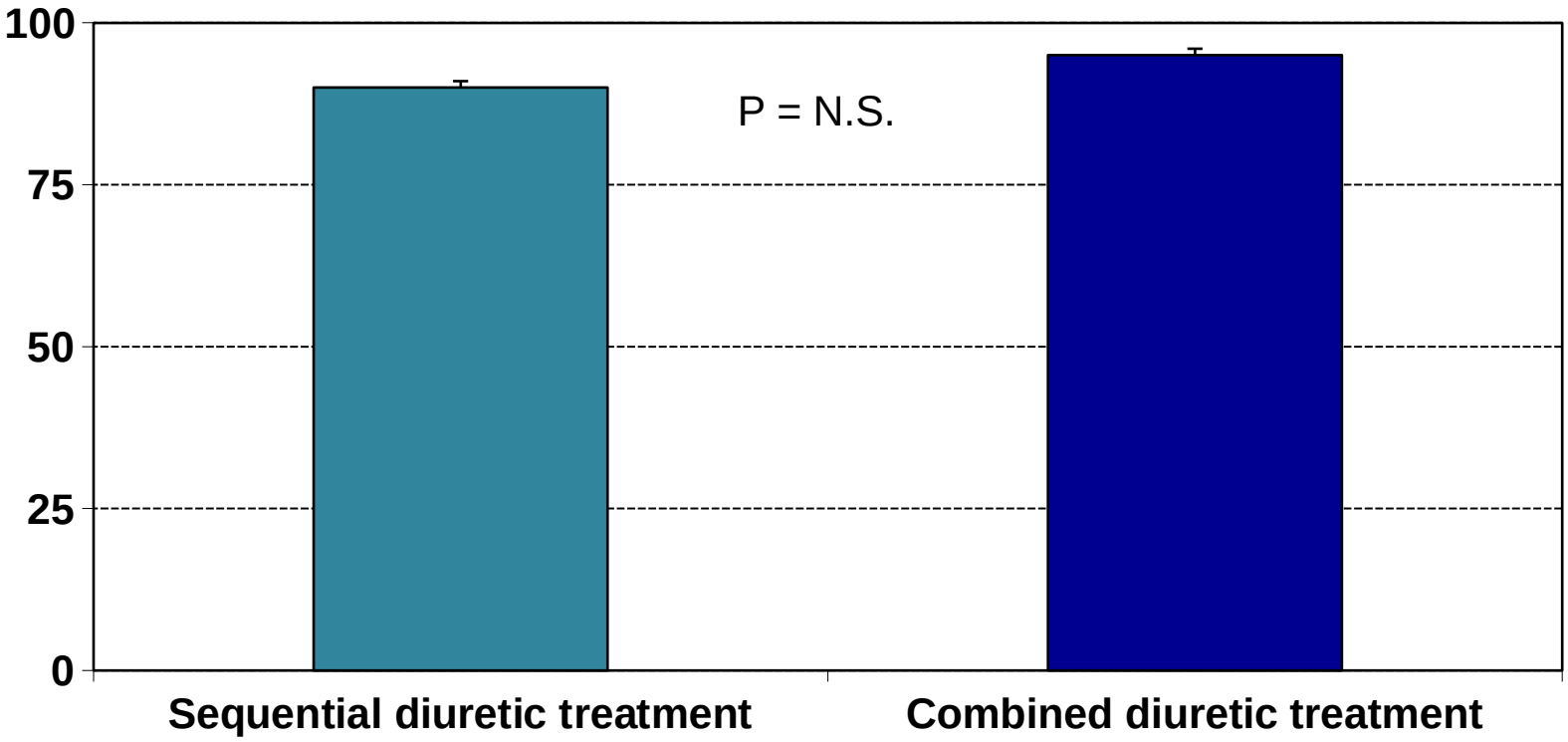
K. Moore et al. Hepatology 2003 ; 38 : 258-266.

Comparison between sequential versus combined diuretic treatment



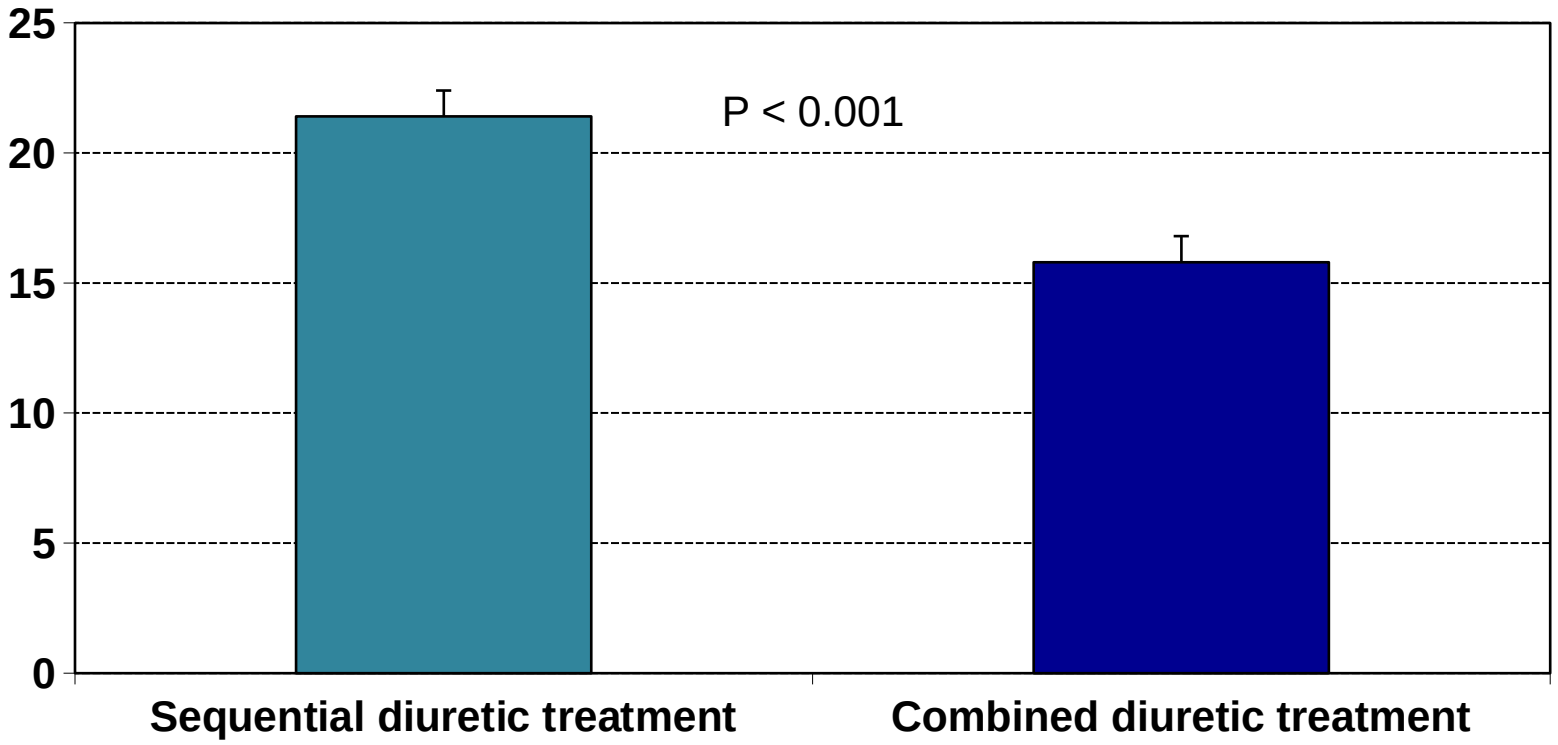
P. Angeli et al Gut 2010 ; 59 : 98-104.

Comparison between sequential versus combined diuretic treatment: responders (%)



P. Angeli et al Gut 2010 ; 59 : 98-104.

Comparison between sequential versus combined diuretic treatment: time to mobilize ascites (days)



P. Angeli et al Gut 2010 ; 59 : 98-104.

Comparison between sequential versus combined diuretic treatment: adverse effects

	Sequential diuretic treatment (n = 50)	Combined diuretic treatment (n = 50)	P
Pts with adverse effects	19 (38%)	10 (20%)	< 0.05
Pts with hyperkalemia	9 (18%)	2 (4%)	< 0.05
Pts with hypokalemia	1 (2%)	--	N.S.
Pts with hyponatremia	4 (8%)	4 (8%)	N.S.
Pts with renal failure	8 (16%)	6 (12%)	N.S.
Pts with encephalophaty	4 (8%)	1 (2%)	N.S.

P. Angeli et al Gut 2010 ; 59 : 98-104.

Follow up

- Spironolactone 200 mg + furosemide 25 mg b.i.d were prescribed with success.
- Nevertheless, in July 2016 she was admitted to our one day hospital for tense ascites and a large volume paracentesis (8 l) was performed.
- In August 2016 she was admitted into hospital for a first episode of hepatic encephalopathy (grade 2), ascites and abdominal pain

Laboratory Tests

WBC	13.26 x 109/l
Hb	10.2 g/l
PLTs	66 x 109/l

Creatinine	188 µmol/L
Sodium	129 mmol/L
Potassium	5.0 mmol/L

CRP	61 mg/L

Bilirubin	78.6 µmol/L
INR	1.8
Albumin	29 g/L
Ammonia	88 µmol/L

MELD	26

What is the initial diagnostic approach ?

- Complete Work-up for infections
- Diagnostic paracentesis
- Xray of abdomen

Laboratory Tests

WBC (n.v 4.40-11.0)	13.26 x 109/l
Hb (n.v 14.0-17.5)	10.2 g/l
PLTs (n.v 150-450)	66 x 109/l

Creatinine (n.v 59-104)	188 µmol/L
Sodium (n.v 136-145)	129 mmol/L
Potassium (n.v 3.4-4.5)	4.5 mmol/L

CRP (n.v 0-6)	61 mg/L

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Ammonia (n.v 11-35)	88 µmol/L

MELD	26

PMN on ascitic fluid	1,258 cells/µL

EASL-CLIF consortium definition of organ failure

Organ/system	0	1	2	3	4
Liver (Bilirubin, mg/dL)	<1.2	≥1.2 - ≤2.0	≥2.0 - <6.0	≥6.0 - <12.0	≥12.0[a]
Kidney (Creatinine, mg/dL)	<1.2	≥1.2 - <2.0	≥2.0 - <3.5[b]	≥3.5 - <5.0 or use of renal-replacement therapy	≥5.0
Cerebral (HE grade)	No HE	I	II	III[c]	IV
Coagulation (INR)	<1.1	≥1.1 – <1.25	≥1.25 - <1.5	≥1.5 – <2.5	≥2.5 or Platelets≤20x10^9/L[d]
Circulation (MAP mm Hg)	≥70	<70	Dopamine ≤5 or Dobutamine or Terlipressin[e]	Dopamine >5 or E ≤ 0.1 or NE ≤ 0.1	Dopamine >15 or E > 0.1 or NE > 0.1
Lungs PaO/FiO2:	>400	>300 - ≤400	>200 - ≤300	>100 - ≤200	≤100
or SpO2/FiO2	>512	>357 - ≤512	>214 - ≤357	>8 - ≤214[f]	≤89

Organ failure

Moreau et al., Gastroenterology 2013;144:1426-1437

What is the diagnosis ?

- Acute decompensation of cirrhosis
- SBP related related Acute on Chronic Liver Failure (ACLF) grade 2
- SBP related Acute on Chronic Liver Failure (ACLF) grade 1 type a

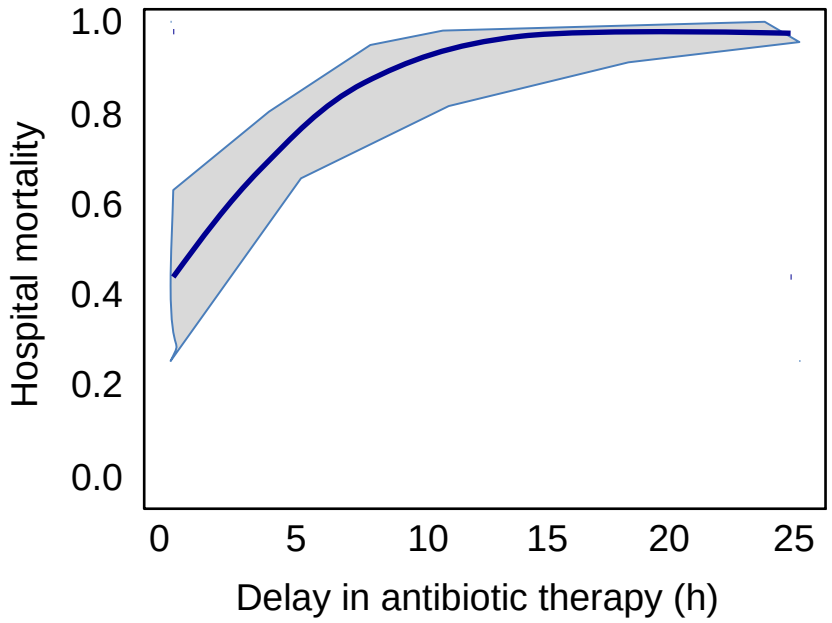
Acute on chronic liver failure (ACLF)

Grade of ACLF	28 day mortality	90 day Mortality
Grade 1-Type a : patients with single kidney failure **Grade 1-Type b: patients with one "non-kidney" organ failure but with serum creatinine ranging from 1.5 to 1.9 mg/dL and/or mild-to moderate-hepatic encephalopathy**	22.1 %	40.7 %
Grade 2: patients with two organ failures	32.0 %	52.3 %
Grade 3: patients with three or more organ failures	76.7 %	79.1 %

R. Moreau et al. Gastroenterology 2013 ; 144 : 1426-1437

SBP-precipitated ACLF Grade 1 (type A)

Effect of the delay in antimicrobial therapy on inhospital mortality in patients with SBP related septic shock



C. J. Karvellas et al. APT ; 2015 ; 41 : 747-757.

Treatment: which antibiotic treatment for SBP?

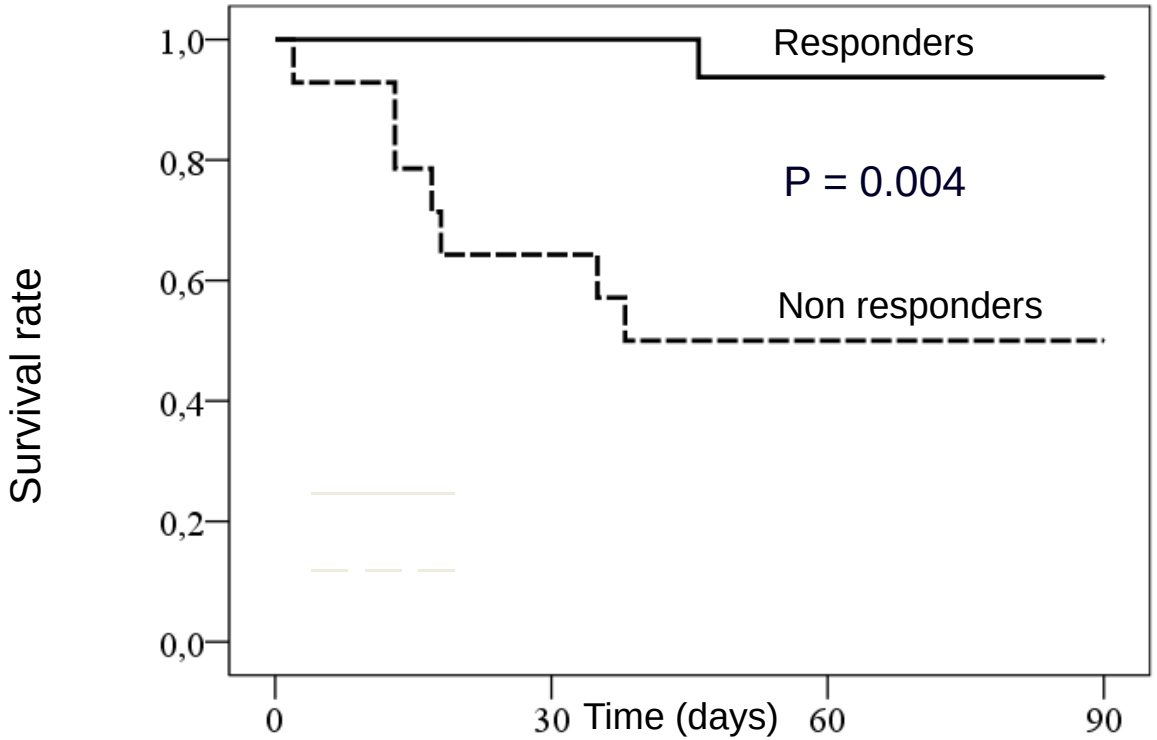
- Third generation cephalosporin
- A broader spectrum antibiotic treatment

Independent predictors of 90-day survival in patients with SBP

Variables	Hazard Ratio	95% CI	P value
Mean arterial pressure (mmHg)	0.92	0.84-0.99	0.04
Development of AKI (Yes vs No)	23.24	2.13-253.14	0.01
Response to first line treatment (No vs Yes)	20.63	2.10-202.89	0.009

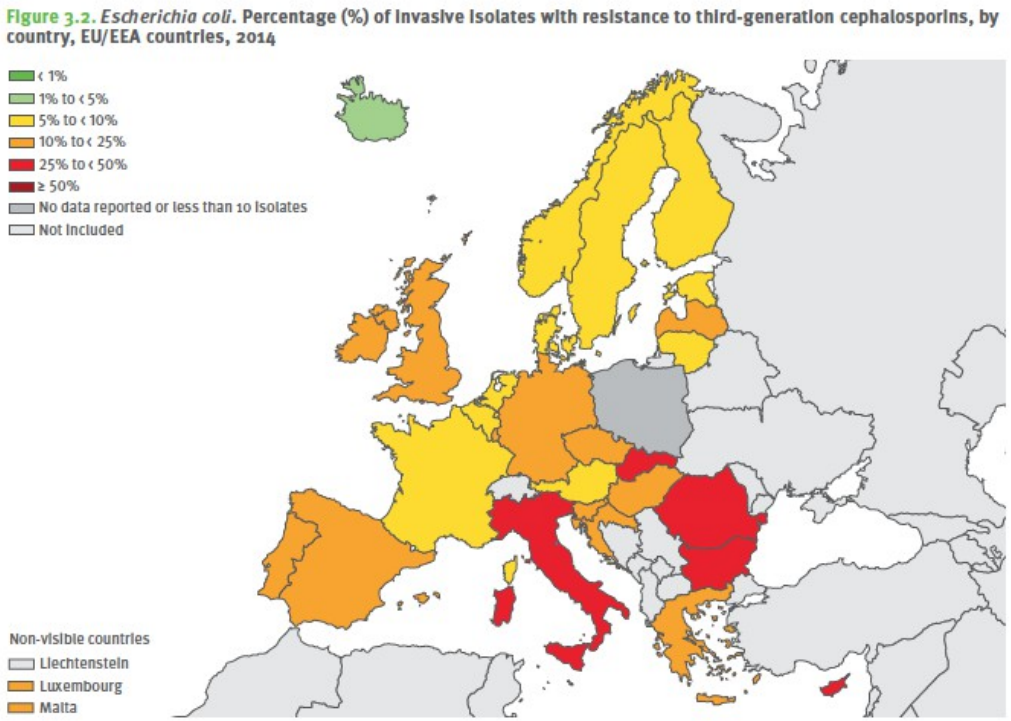
S. Piano et al. Hepatology 2016 ; 63 : 1299-309.

Probability of 90-day survival according to the efficacy of first line treatment



S. Piano et al. Hepatology 2016 ; 63 : 1299-309.

Escherichia coli: percentage (%) of invasive isolates with resistance to third-generation cephalosporins by country



European Centre for Disease Prevention and Control, Report , 2014

Comparison between standard antibiotic tretament and broad spectrum antibiotic tretament in patients with cirrhosis with health care associated infections

Type of infection	Standarda antibiotic tretament	Broad spectrum antibiotic tretament
SBP, chlangites, spontaneous bacteremia	Cefotaxime 2g *tid* e.v	Imipemen/Ciilastatin 500 mg *qid* e.v. plus vancomycin 1 gr bis e.v.
UTI	Amoxicillin/Clavulanic acid 2.2 g *tid* e.v.) or ciprofloxacin 500 mg bis orally (in no quinolone prophylaxis)	Imipemen/Cilastatin (500 mg *qid* e.v.
Pneumoniae	Amoxicillin/Clavulanic acid 2.2 g *tid* e.v. plus azitromycic (500 mg/24 hr orally)	Imipemen/Ciilastatin 500 mg qid e.v. plus vancomycin 1 gr *bid* e.v. . plus azitromycic (500 mg/24 hr orally)
Soft tissue infections	Amoxicillin/Clavulanic acid 2.2 g *tid* e.v.	Imipemen/Ciilastatin 500 mg *qid* e.v. or tigecyclllin 50 mg *bis* e.v. after a load of 100 mg e.v.

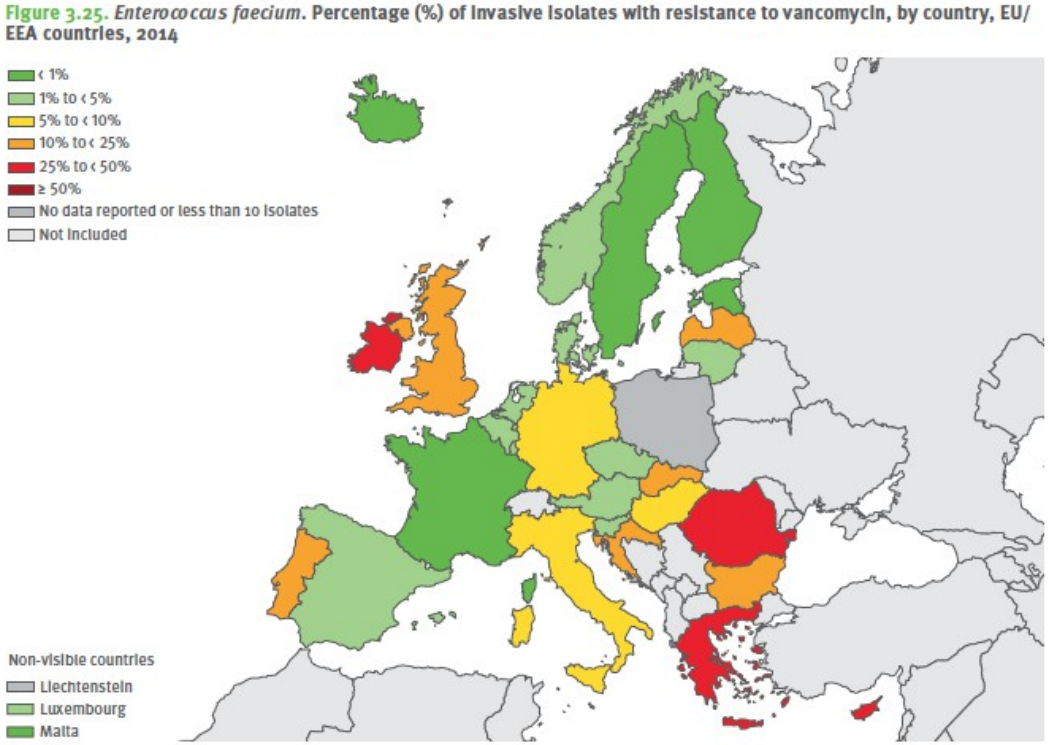
M. Merli et al. Hepatology 2016 ; 63 : 1632-1639

Comparison between standard antibiotic tretament and broad spectrum antibiotic tretament in patients with cirrhosis with health care associated infections

Outcome	Standard antibiotic treatment	Broad spectrum antibiotic treatment	P
In hospital mortality	25%	6%	< 0.01
Resolution of infection			
- SBP	25%	50%	< 0.001
- UTI	25%	50%	< 0.001
- Pneumoniae	20%	40%	< 0.001
Lenght of hospital stay	18±15	12.3±7	<0.05

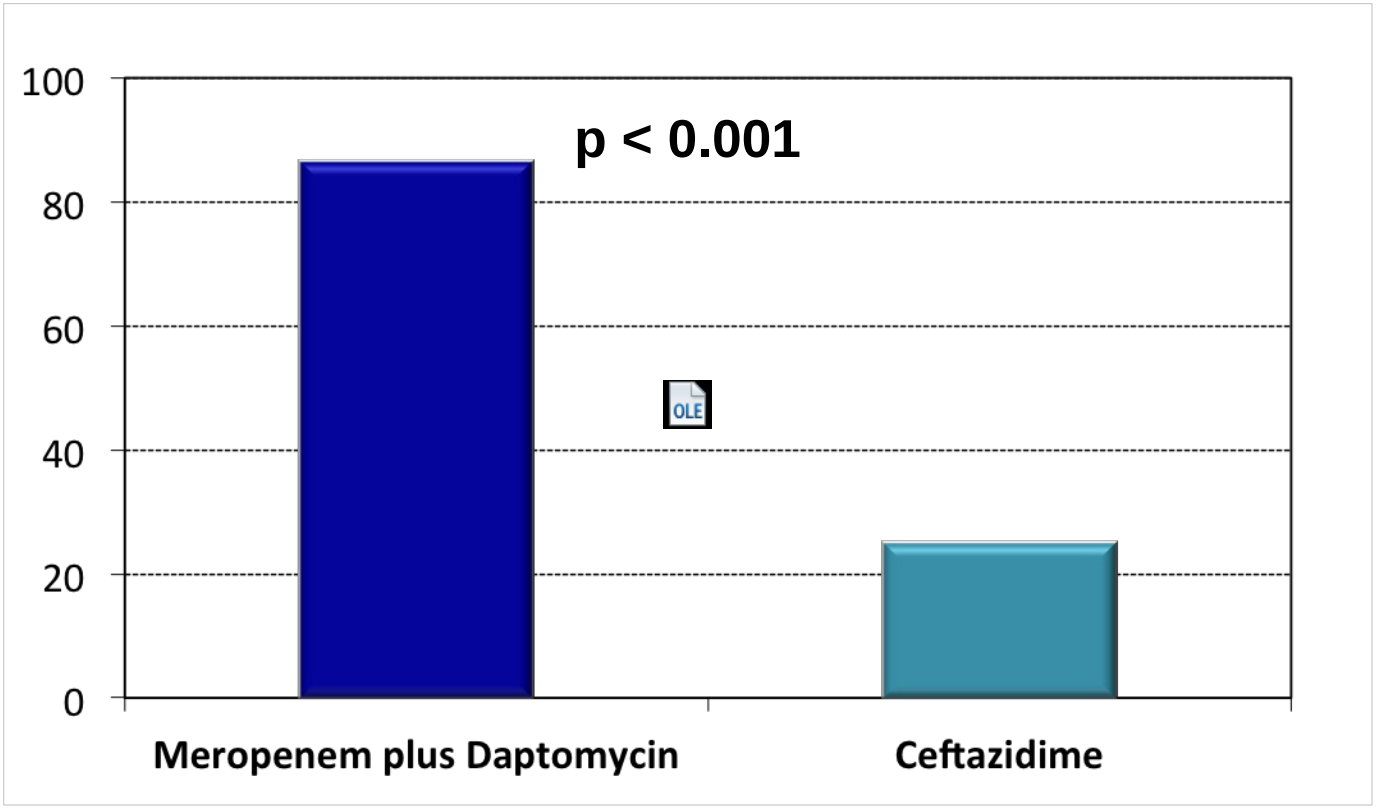
M. Merli et al. Hepatology 2016 ; 63 : 1632-1639

Enterococcus faecium: percentage (%) of invasive isolates with resistance to vancomycin by country



European Centre for Disease Prevention and Control, Report , 2014

Response to first line antibiotic treatment according to the assigned group



S. Piano et al. Hepatology 2016 ; 63 : 1299-309.

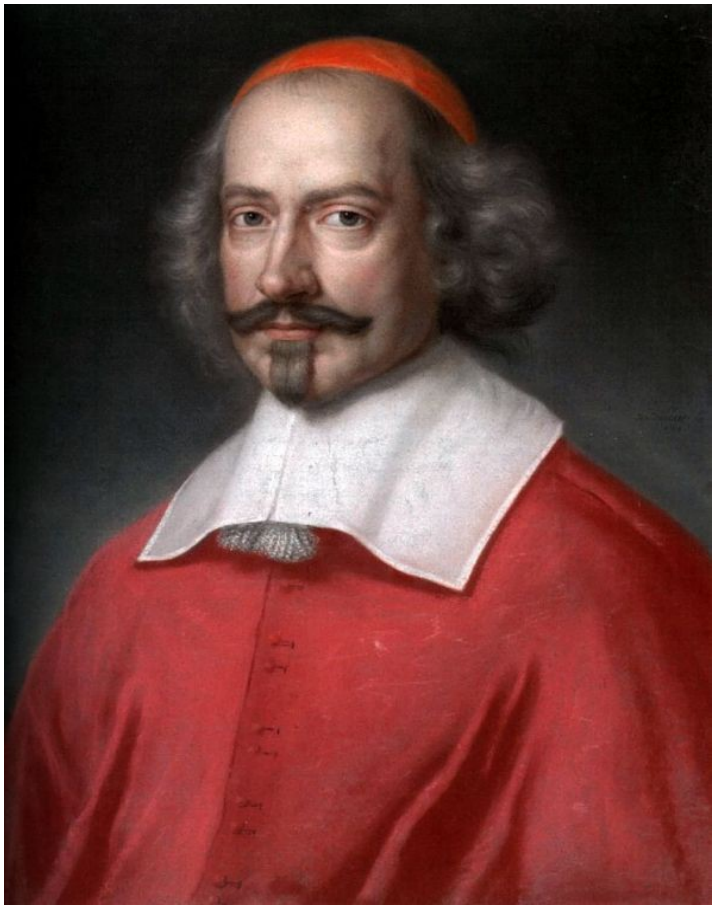
Follow up

The patient was treated as follows:

- Meropenem (1 g b.i.d.)
- Daptomycin (450 mg/48 hours)

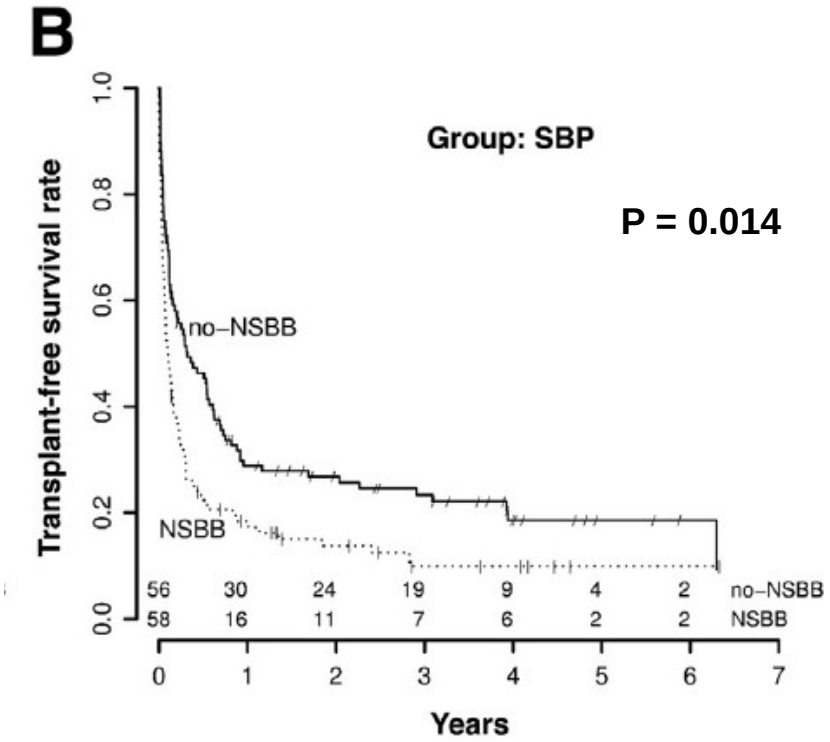
Treatment: what about propanolol?

- To be continued
- To be stopped



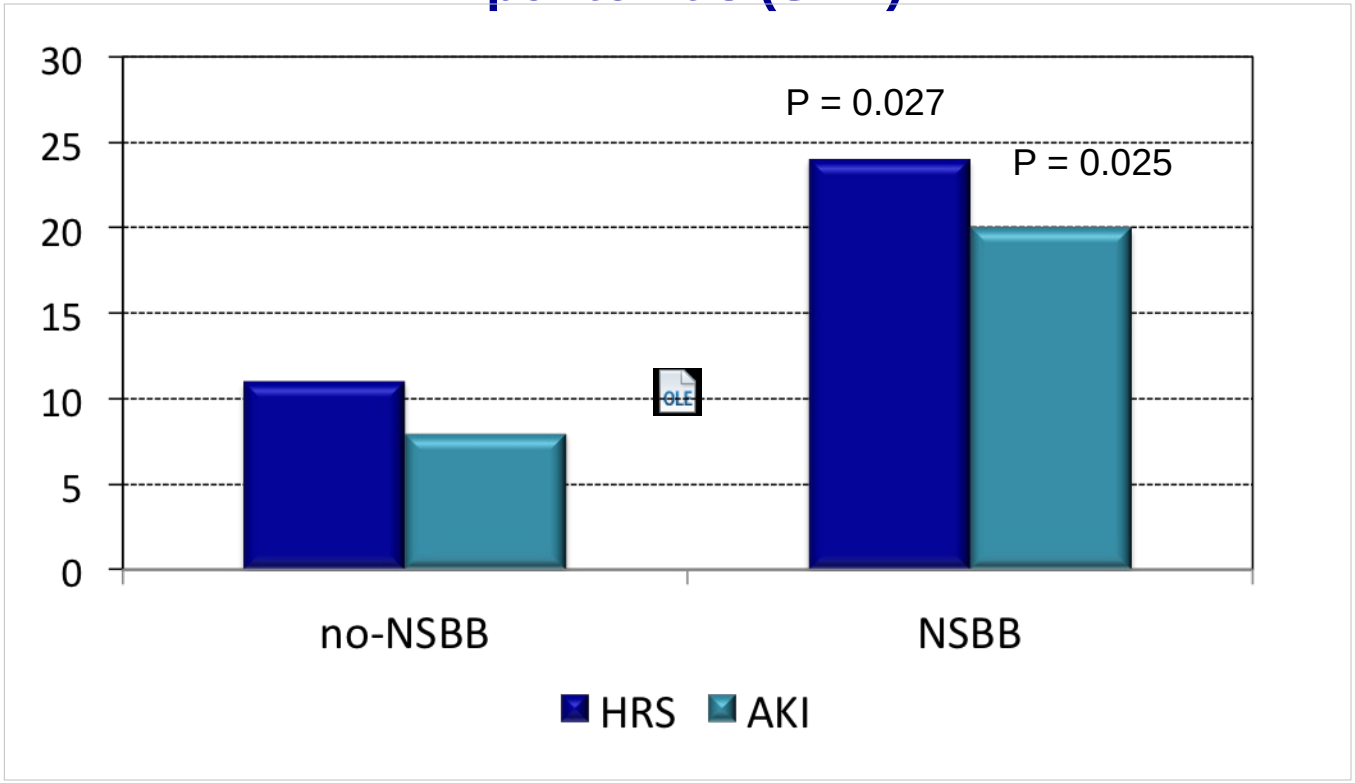
Cardinal Mazzarino
(Pescina, 14 luglio 1602 – Vincennes, 9 marzo 1661)

Effect of nonselective β-blockers (NSBB) on transplant free survival in patients with spontaneous bacterial peritonitis (SBP)



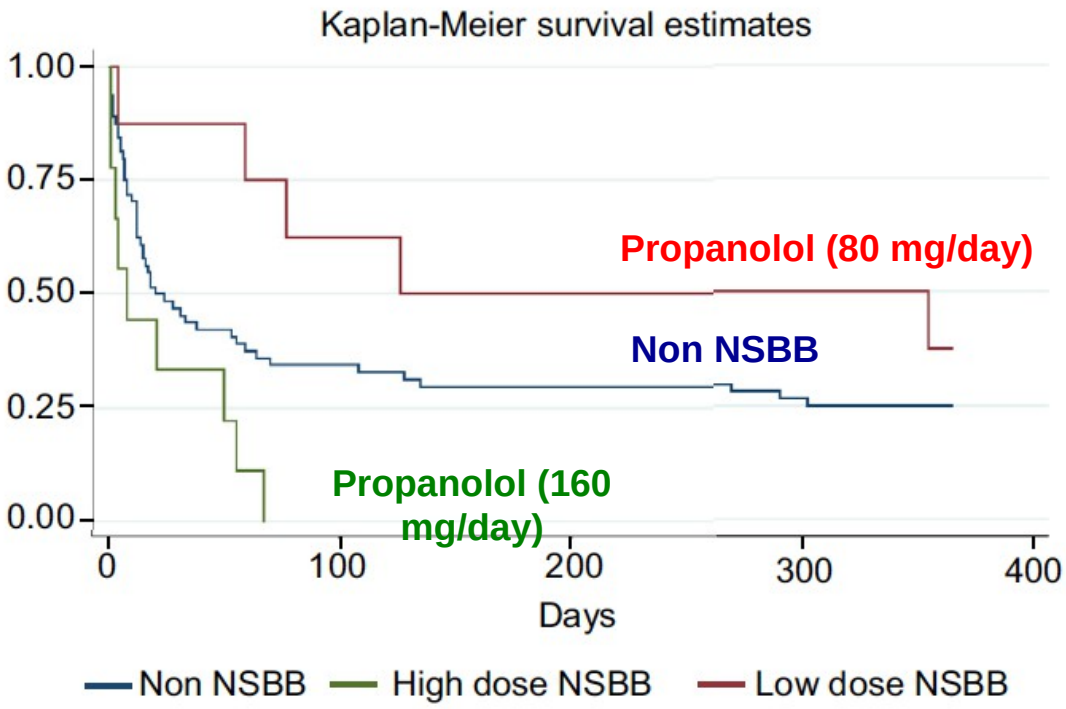
M. Mandofer et al. Gastroenterology 2014 ; 146: 1680-1690

Effect of nonselective β-blockers (NSBB) on the development of grade C AKI and HRS within 90 days after spontaneous bacterial peritonitis (SBP)



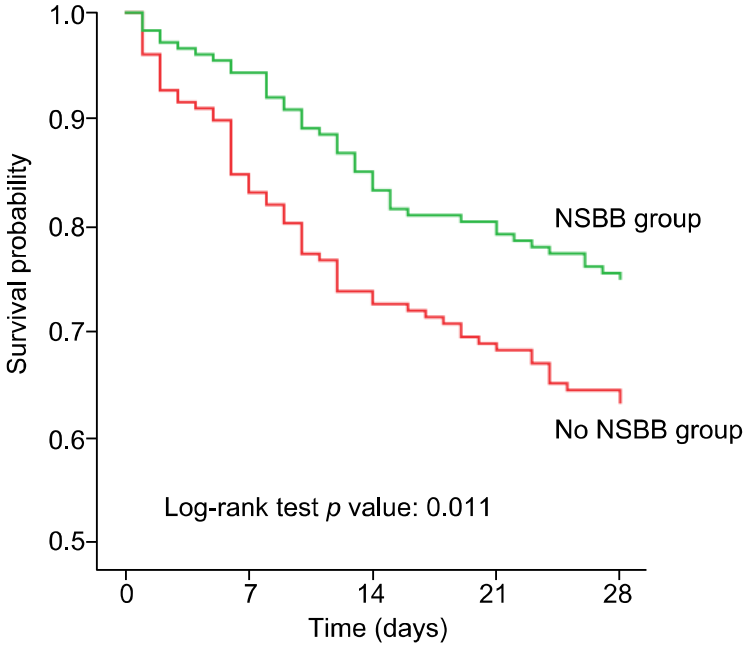
M. Mandofer et al. Gastroenterology 2014 ; 146: 1680-1690

Survival after first episode of sponatenous bacterial peritonitis by the dose of NSBBs



BS. Madsen et al. J. Hepatol 2016 ; 64 : 1455-1456

Effect of β-blockers on survival in patients with acute on chronic liver failure



R.P. Mookerjee et al. J Hepatol. 2016 ; 64 : 574-582

Evolution of ACLF grade up to one week after its first onset

ACLF grade at the 1st onset	ACLF grade after 3-7 days from the onset			
	No NSBBs (n = 171)			
	NO ACLF	ACLF-1	ACLF-2	ACLF-3
ACLF-1 (n = 76)	36 (47.4%)	19 (25.0%)	12 (15.8%)	9 (11.8%)
ACLF-2 (n = 68)	24 (35.3%)	7 (10.3%)	18 (26.5%)	19 (27.9%)
ACLF-3 (n = 27)	4 (14.8%)	2 (7.4%)	4 (14.8%)	17 (63.0%)
Evolution of the initial ACLF grade				
Resolution of the ACLF	64/171 (37.4%)			
Worsening of the ACLF	40/171 (23.4%)			

ACLF grade at the 1st onset	ACLF grade after 3-7 days from the onset			
	Use of NSBBs (n = 148)			
	NO ACLF	ACLF-1	ACLF-2	ACLF-3
ACLF-1 (n = 83)	53 (63.9%)	19 (22.9%)	5 (6.0%)	6 (7.2%)
ACLF-2 (n = 52)	15 (28.9%)	9 (17.3%)	18 (34.6%)	10 (19.2%)
ACLF-3 (n = 13)	1 (7.7%)	0	2 (15.4%)	10 (76.9%)
Resolution of the ACLF	69/148 (46.6%)			$p = 0.0967$
Worsening of the ACLF	21/148 (14.2%)			$p = 0.0371$

NSBBs, non-selective beta blockers.

- The prevalence of ACLF-1 was higher in patients receiving NSBBs. In contrast, the prevalence of ACLF-2 and ACLF-3 was higher in patients not receiving NSBBs.
- Only 77 out of 148 patients continued NSBBs after the diagnosis of ACLF and the rate od ACLF development after the inclusion was similar in both groups (13% in pts discontinuing NSBB vs 17% in pts continuing NSBB)

R.P. Mookerjee et al. J Hepatol. 2016 ; 64 : 574-582

Use of Non Selective Beta-Blockers (NSBB) in patients with end-stage liver disease

- In patients with cirrhosis and refractory ascites NSBB should be used cautiously with close monitoring of blood pressure, serum sodium and serum creatinine.
- Until randomized trials are available NSBB should be reduced/discontinued if a patient with refractory ascites develops any of the following events:
  - Systolic blood pressure < 90 mmHg
  - Severe hyponatremia (< 125 mEq/L)
  - Acute kidney injury
  - When ever terlipressin is used

Adapted from R. De Franchis et al. J. Hepatol. 2015 ; 63 : 743-752

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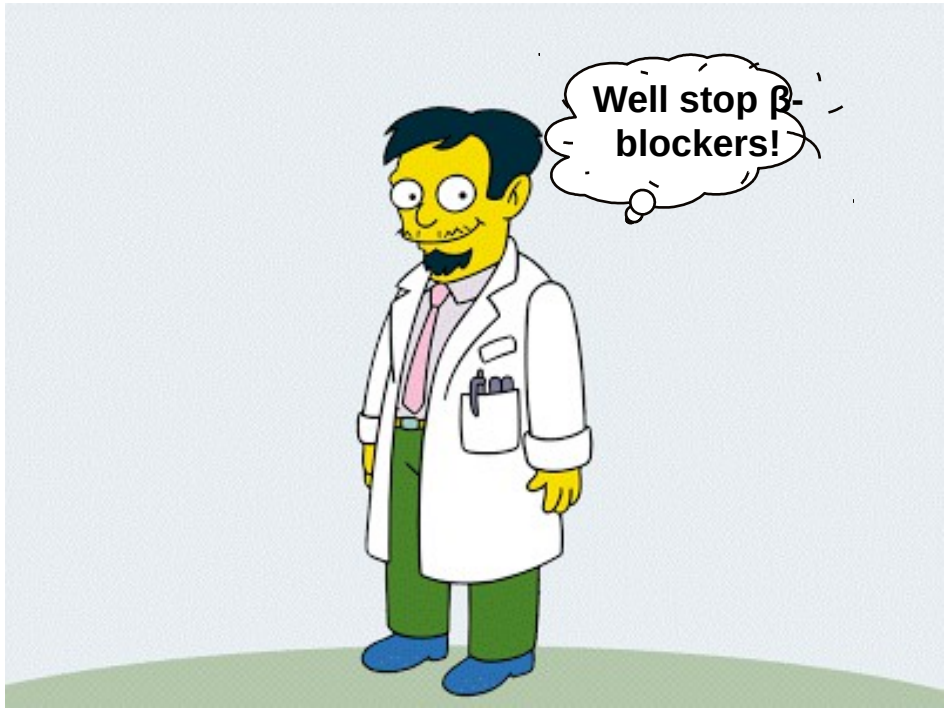

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  - Systolic blood pressure < 90 mmHg
  - Severe Hyponatremia (< 125 mEq/L)
  - Acute kidney injury
  - When ever terlipressin is used
- If NSBB are stopped endoscopic band ligation should be performed.

Adapted from R. De Franchis et al. J. Hepatol. 2015 ; 63 : 743-752

Follow up

- Propanolol was stopped and the patient uderwent endoscopic band ligation of varices.

Treatment: How to use albumin in this patient?

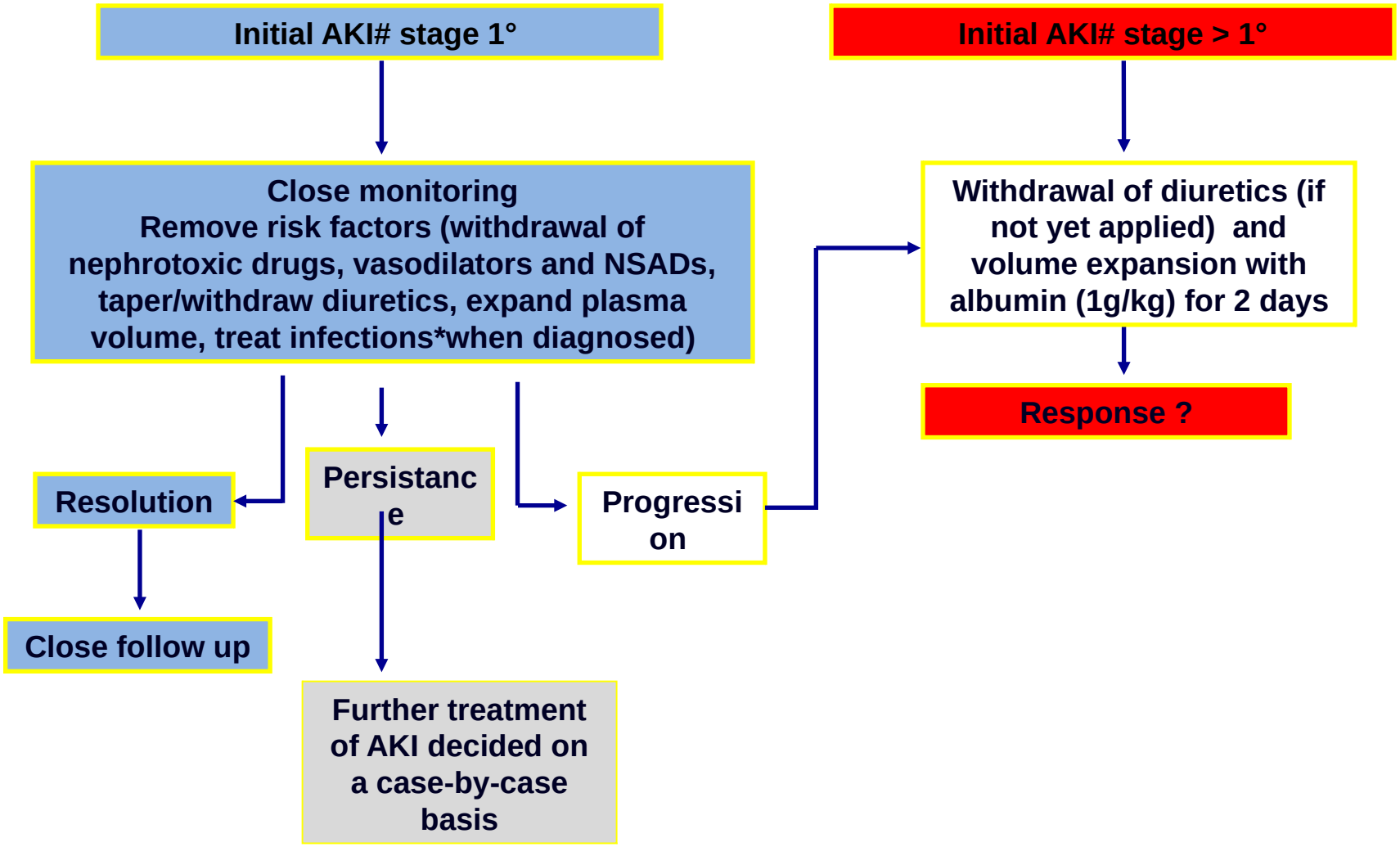
- 1.5 g kg soon and than 1 g/kg at day 3
- 1 g/kg soon and than 1 g/kg the next day

Effects of albumin infusion on morbility and mortality due to SBP

Outcome variable	Cefotaxime (n° = 63)	Cefotaxime plus albumin (n° = 63)	P
Renal failure n° (%)	21 (33%)	6 (11%)	< 0.002
Death in hospital n° (%)	18 (29%)	6 (10%)	< 0.01
Death at 3 months n° (%)	26 (41%)	14 (22%)	< 0.03

P. Sort et al. N. Engl. J. Med. 1999 ; 341 : 403-409.

Algorithm for AKI management in patients with cirrhosis



#= AKI at the first fulfilling of KDIGO criteria

P. Angeli et al. J. Hepatol. 2015 ; 62 : 968-974

ACLF Grade 1 including AKI (peak stage 2)

Follow up

- The patient received 1 g/kg soon and than 1 g/kg the next day.

Day 2

Creatinine (n.v 59-104)	240 µmol/L
Sodium (n.v 136-145)	127 mmol/L
Potassium (n.v 3.4-4.5)	4.9 mmol/L

PMN on ascitic fluid	761 cells/µL

CRP (n.v 3.4-4.5)	32 mg/L

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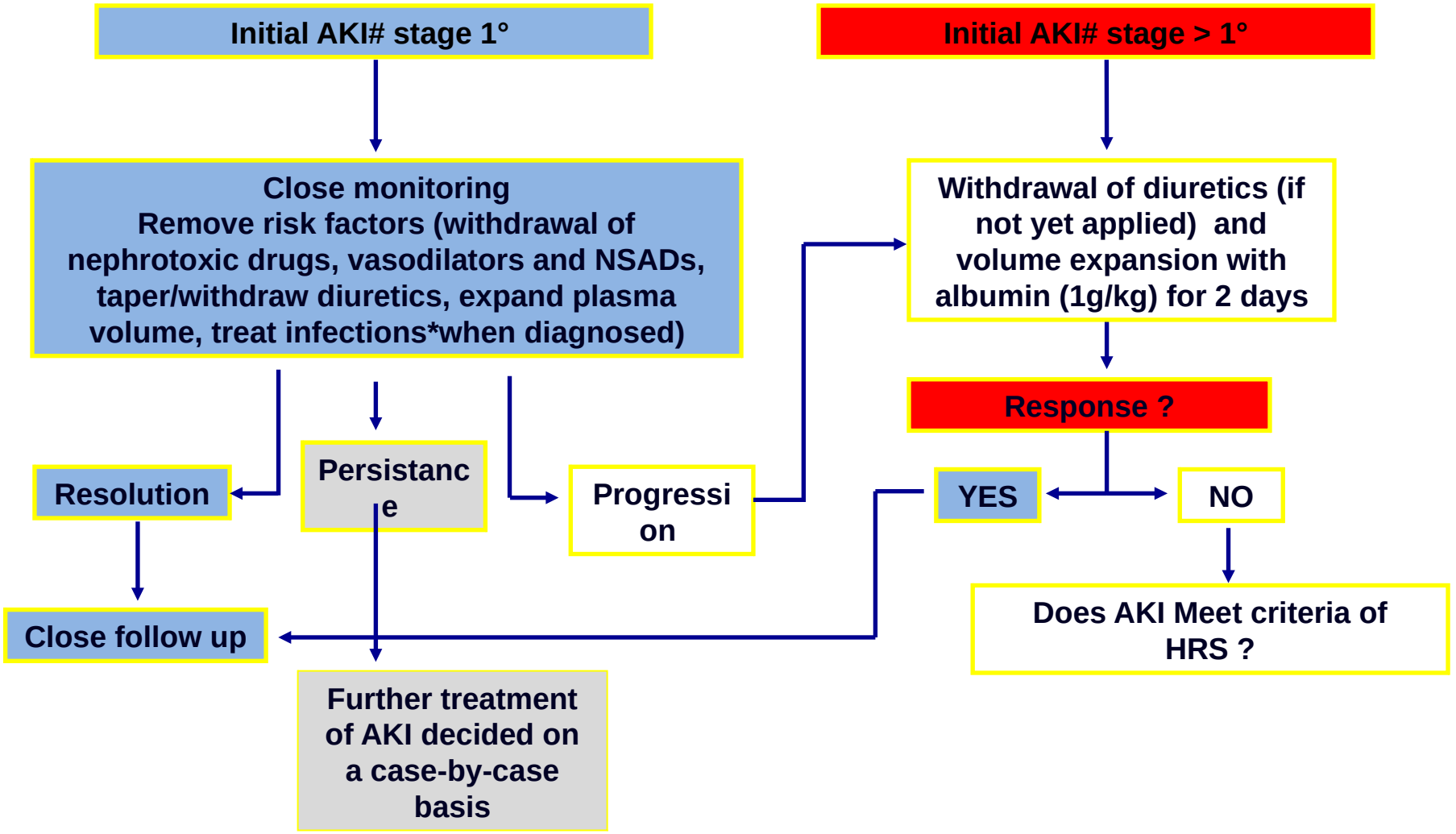

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CRP (n.v 3.4-4.5)	**32 mg/L**

Urinalysis	**Negative**

24 hour urine protein excretion	**140 mg**

Urinary NGAL	**200 µg/g**

What is the diagnosis ?

- Acute Tubular Necrosis (ATN)-Acute Kidney Injury (ATN-AKI)
- Hepatorenal syndrome (HRS)-Acute Kidney Injury (HRS-AKI)

Current diagnostic criteria of HRS

1. Cirrhosis with ascites;

Deleted

3. No sustained improvement of serum creatinine (decrease to a level of 133 µmol/l or less) after at least two days of diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day to a maximum of 100 g/day;
4. Absence of shock
5. No current or recent treatment with nephrotoxic drugs;
6. Absence of parenchimal disease as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography.

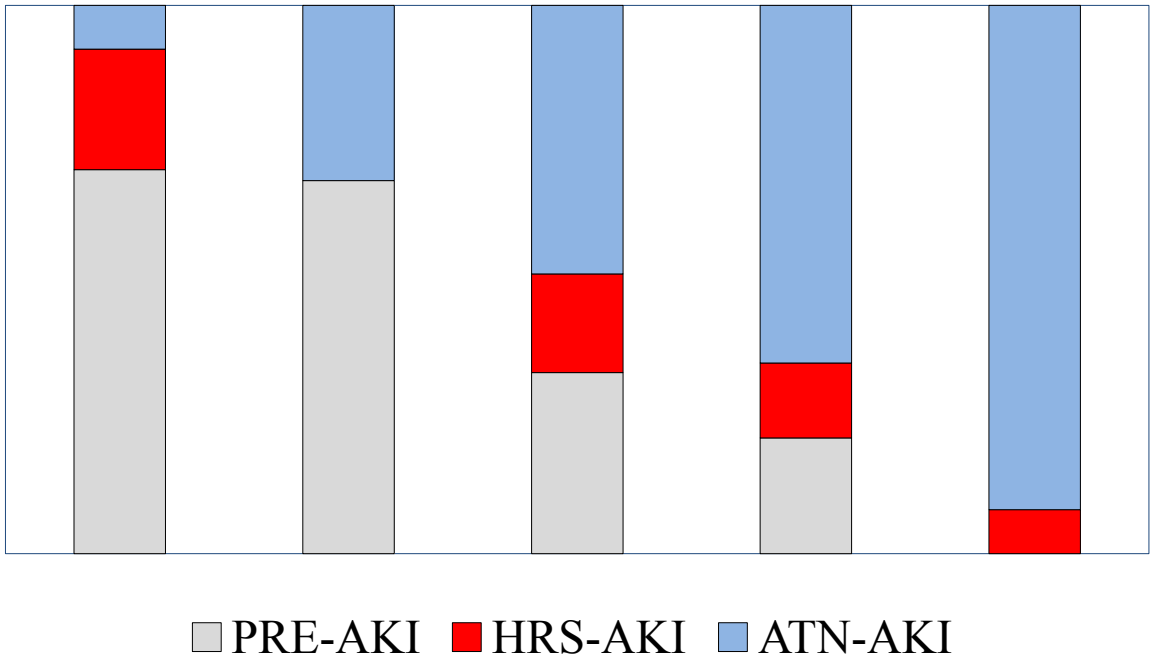
F. Salerno, et al. Gut 2007 ; 56 : 1310-1318.

Values of urinary biomarkers in patients categorized according to the absence or presence of AKI and phenotype of AKI

Biomarkers	No AKI	Prerenal AKI	HRS-AKI	ATN-AKI	P
NGAL (µg/g sCr)	30 (17-41)	36 (26-125)	104 (58-208)	1807 (494-3716)	<0.0001
IL-18 (ng/g sCr)	21 (16-35)	16 (14-36)	18 (10-29)	150 (58-259)	<0.0001
Albumin (mg/g sCr)	3 (1-7)	9 (1-77)	16 (8-46)	324 (53-380)	<0.0001
TFF-3 (µg/g sCr)	582 (367-1665)	2300 (323-2720)	1893 (840-2715)	5810 (4019-14466)	< 0.0001
MCP-1 (µg/g sCr)	0.2 (0.1-1.4)	0.9 (0.2-2.5)	3 (1-6)	4 (1-14)	<0.0001
Ostepontin (µg/g sCr)	1456 (715-3210)	2914 (1847-8382)	5471 (2959-11983)	83337 (4019-14466)	< 0.0001
Calbindin (µg/g sCr)	71 (26-150)	5 (2-34)	25 (8-58)	118 (37-324)	0.010
GST-TT (µg/g sCr)	3 (1-16)	3 (1-7)	4 (2-21)	50 (9-169)	0.012
KIM-1 (µg/g sCr)	0.5 (0.3-1.4)	0.5 (0.1-1.1)	1.2 (0.5-2.8)	1.7 (0.9-5.1)	0.015
Cistatin C (µg/g sCr)	24 (12-435)	21 (15-53)	27 (10-47)	115 (39-1552)	0.023

X. Ariza et al. Plos One 2015 ; 10 [Epub ahead of print]

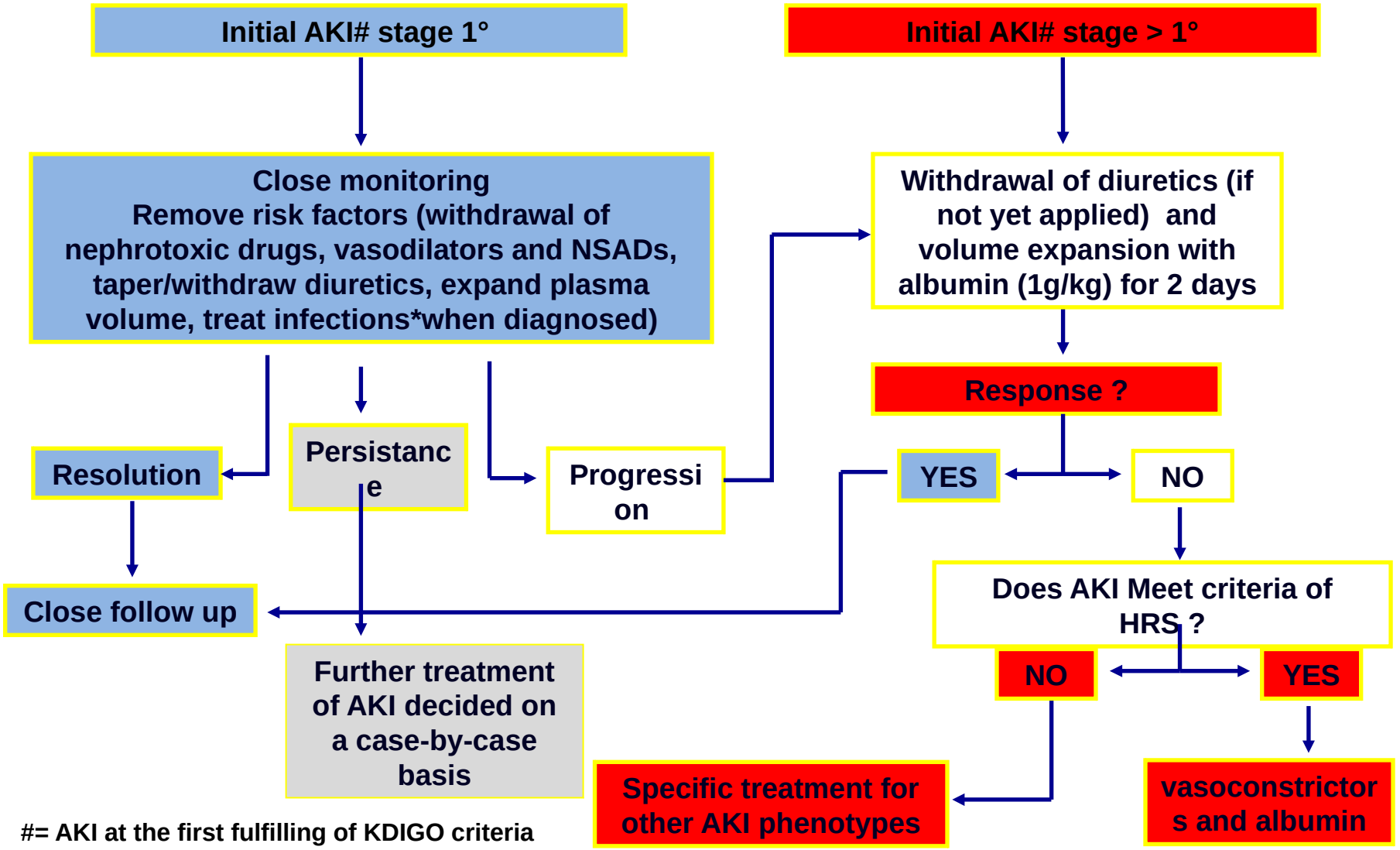
Percentage of patients with prerenal- (PRE-), hepatorenal syndrome (HRS-), and acute tubular necrosis- (ATN-) AKI by the number of biomarkers of structural injury above their optimal cutoff for the diagnosis of ATN



JM. Belcher et al. Hepatology 2014 ; 60 : 622-632

ACLF Grade 1 Including HRS-AKI (peak stage 2)

Algorithm for AKI management in patients with cirrhosis



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Follow up

The patient was treated as follows:

- Albumin 40 g/day
- Terlipressin 2 mg/day continuous i.v. infusion
- Meropenem (1 g b.i.d.)
- Daptomycin (450 mg/48 hours)

Follow up

- After 7 days of treatment with antibiotics, a further paracentesis documented normalization of PMN count → antibiotics were withdrawn and prophylaxis with norfloxacin started

- Terlipressin was increased to 3 mg/24 hours and renal function recovered to baseline after 8 days –

  - The patient was listed for transplantion and discharged home.

Follow up

- The patient is regularly followed up within the Care Management Programme, she required 2 further paracenteses for the control of ascites and she was not re-admitted into hospital for other complications.
- She is on the waiting list. Her MELD and MELD Na scores are, actually, 21 and 23 respectively.