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DHAKA, BANGLADESH
4th International Hepatology Conference
DHAKA 2016

Kidney Diseases in Liver Cirrhosis

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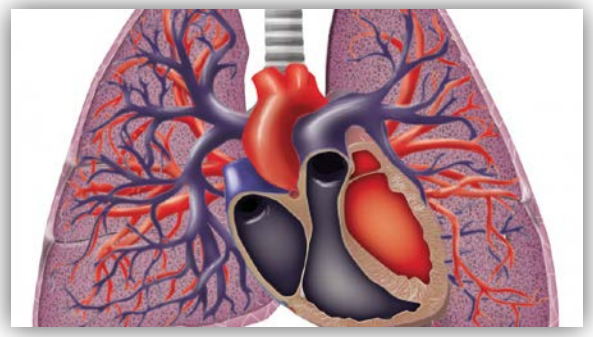
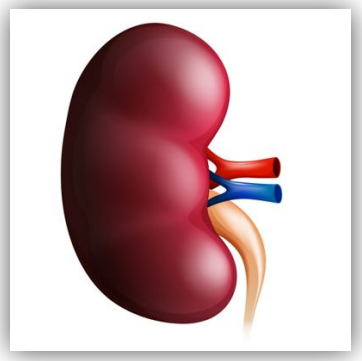
Pathomechanism of AKI in cirrhosis

Effective hypovolemia

Noradrenaline
Angiotensin
Vasopressin

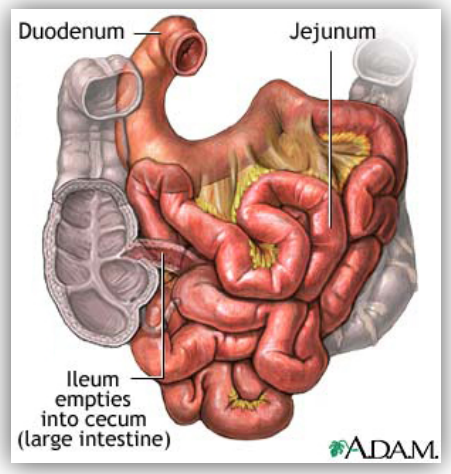


Vasoconstriction



Hypoperfusion
Hypercreatinemia (AKI)
Sodium and water retention

Vasodilatation



Physiological factors regulating renal perfusion/function

Arterial tone
a. afferens

Angiotensin II
Norepinephrine
Vasopressin

Vascular autoregulation

Reduced synthesis of kallikrein and PG-E_2
Increased synthesis of ET-1

Cardiac output (CO)

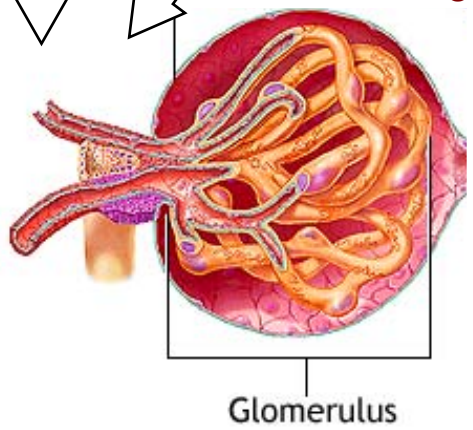
Portal cardiomyopathy

Mean arterial pressure (MAP)

Splanchnic arterial vasodilatation

Intraabdominal pressure (IAP)

Abdominal Compartment Syndrome (ascites)



Definition of Acute Kidney Injury (AKI) according to AKI Network (AKIN)

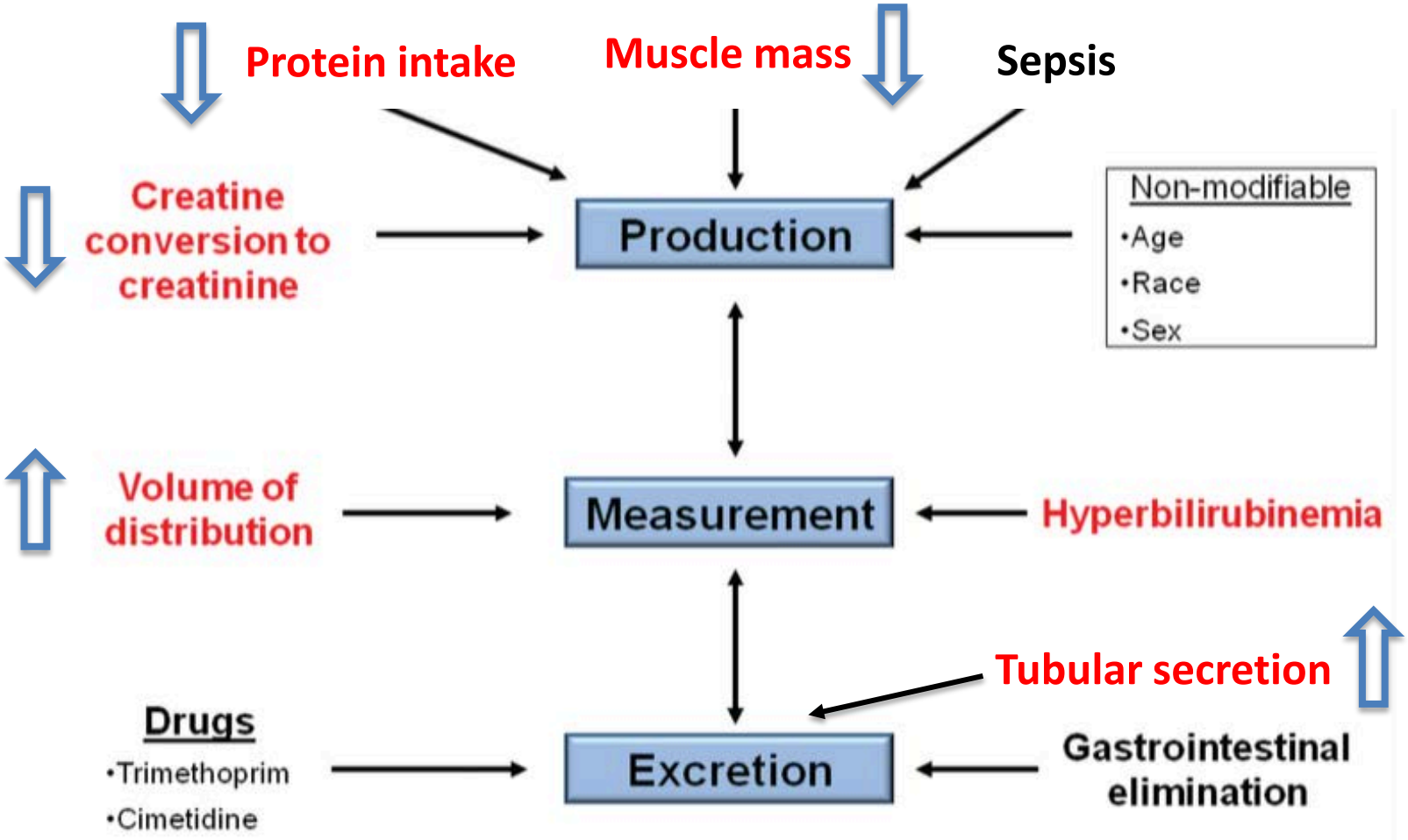
Stage	Increase of creatinine level / 48 hrs
1	↑ 0.3 mg/dl **OR** ↑ 1.5-2 x baseline
2	≥ 2-3 x baseline
3	↑ 0.3 mg/dl if baseline ≥4mg/dl **OR** > 3 x baseline **OR** If renal replacement therapy was started

Modified by IAC

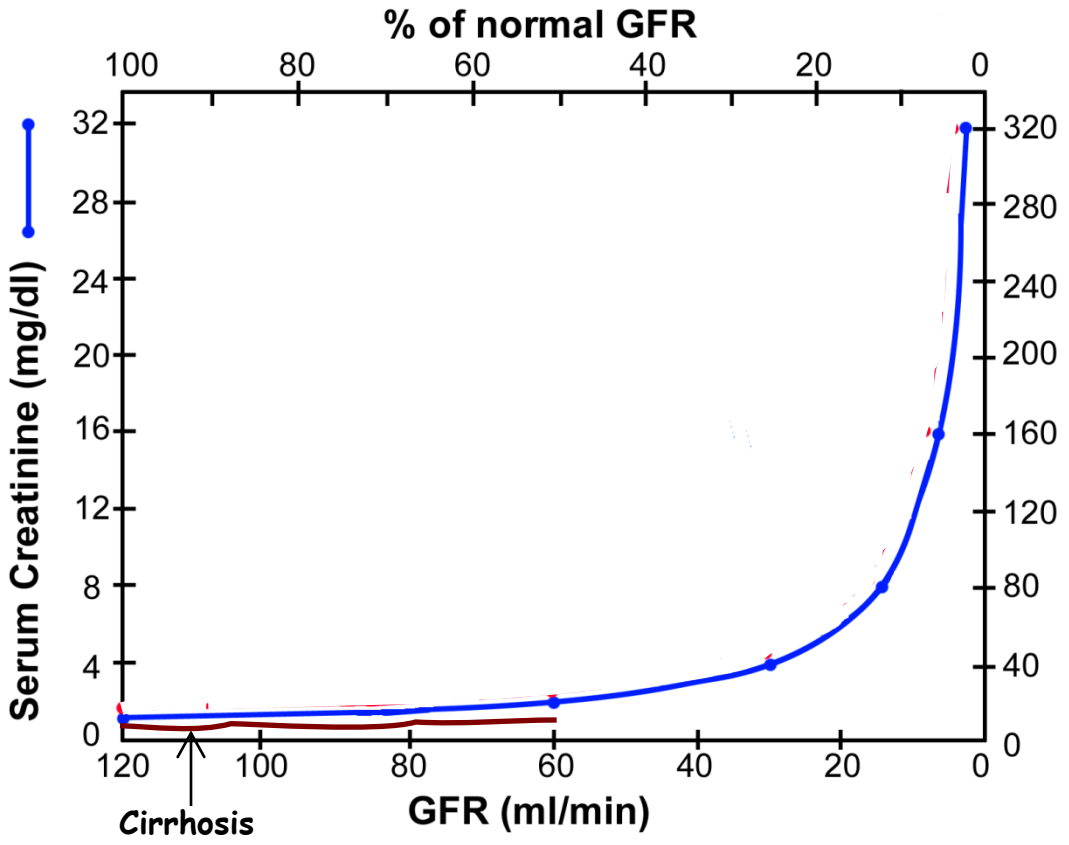
Known or presumed to have occurred within the **prior 3 months**

Single value of sCr is not sufficient to diagnose AKI

Extra-renal influences on creatinine levels in cirrhosis



Relationship between serum creatinine level (S_{cr}) and GFR



- Creatinine overestimates GFR in cirrhosis

Dennen P, Douglas I, Anderson R,: Acute Kidney Injury in the Intensive Care Unit: An update and primer for the Intensivist. *Critical Care Medicine* 2010; 38:261-275.

Creatinine ≥ 1.5 mg/dl in cirrhosis

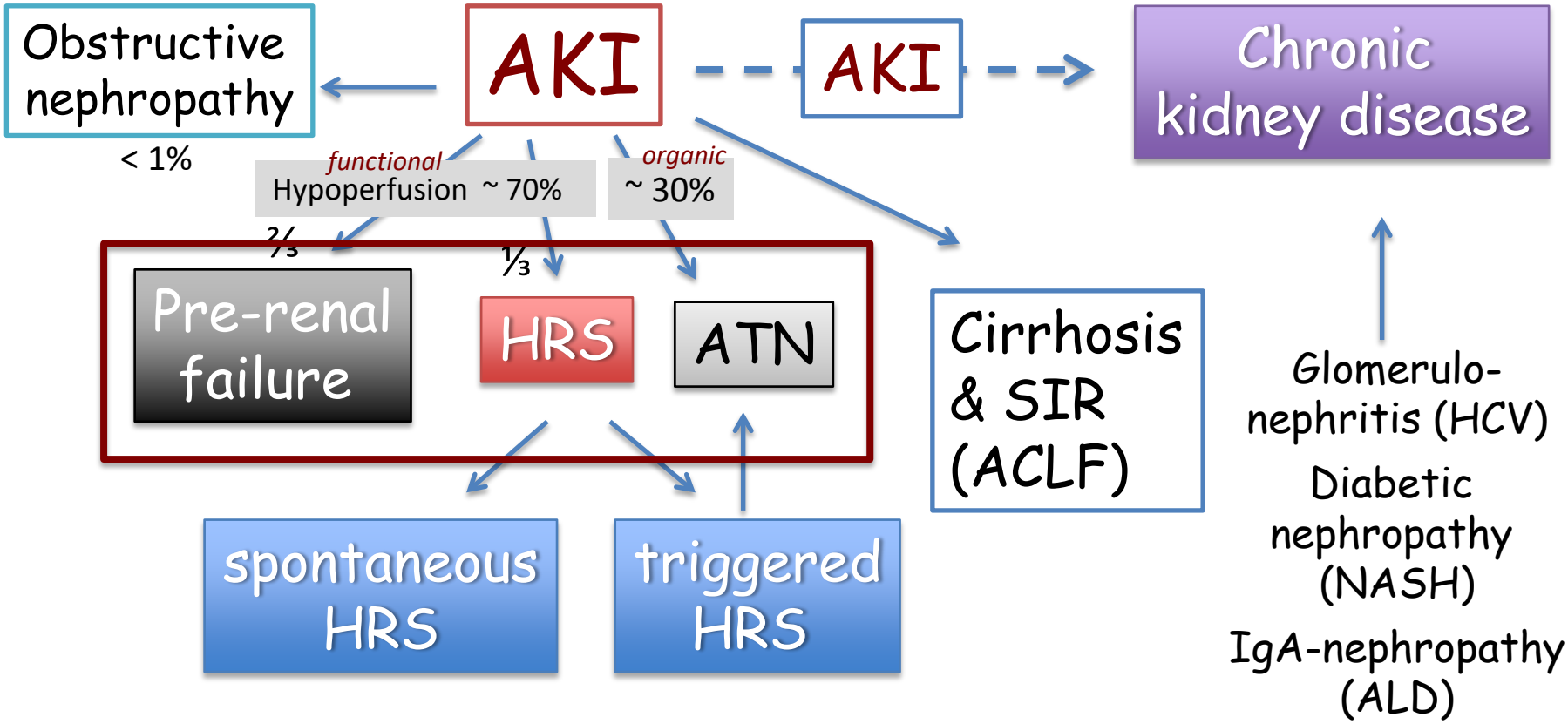
11%	GI bleeding
34%	Spontaneous bacterial peritonitis
17%	Other bacterial infection
40-49%	Critically ill patients hospitalized in ICU

24% in outpatients with cirrhosis within one-year of the first episode of ascites

26-47% *in-patients* (mostly AKIN stage 1)

Cardenas A et al. Hepatology 2001; 34: 671
Carvalho GC et al. Ann Hepatol 2012; 11:90
Fagundes et al. J Hepatol 2013; 59: 474
Piano S et al. J Hepatol 2013; 59: 482

Hepatorenal diseases



HRS: Hepatorenal syndrome; ATN: acute tubular necrosis,
ACLF: acute-on-chronic liver failure

Garcia-Tsao G et al. Hepatology 2008; 48: 2064

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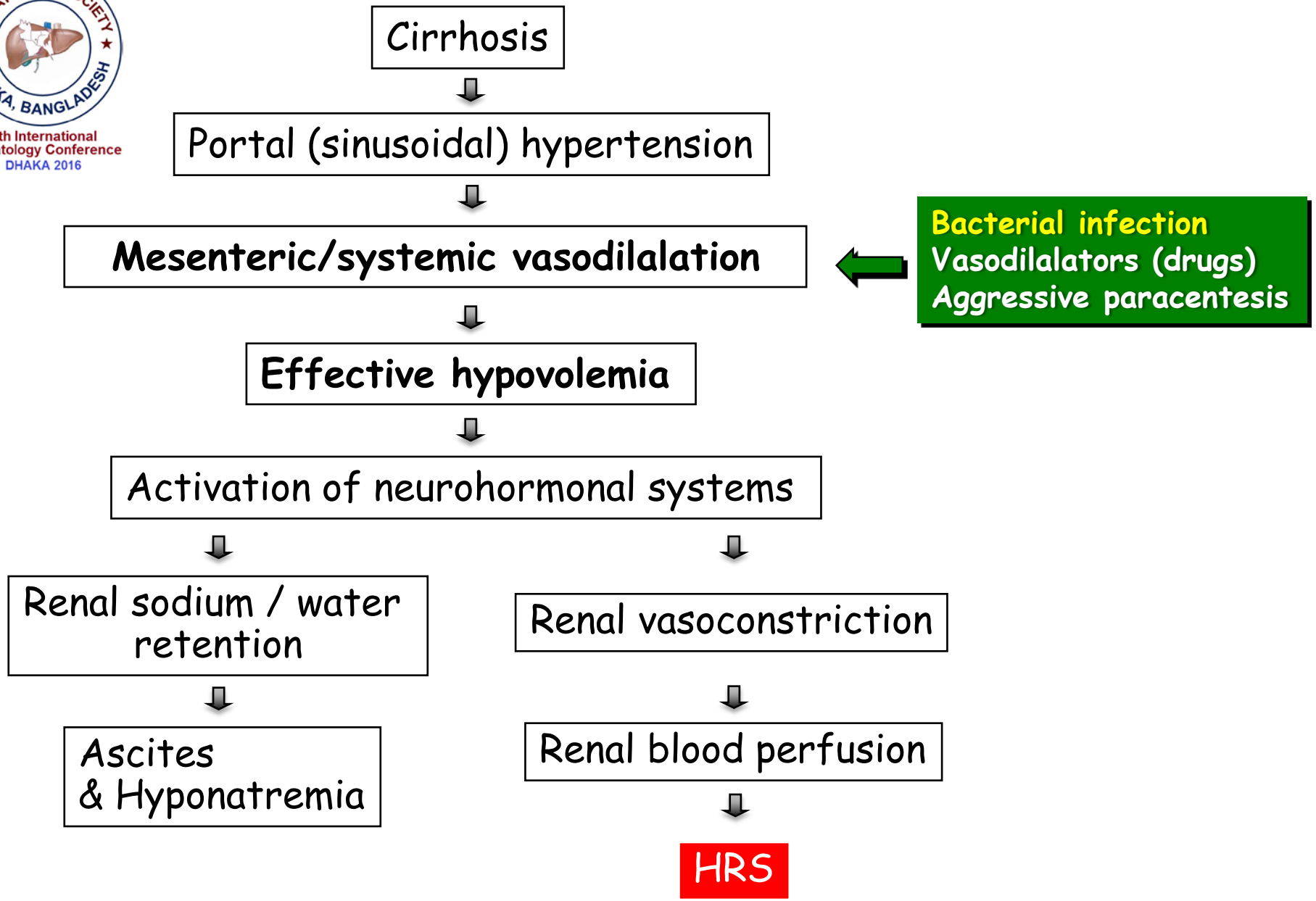

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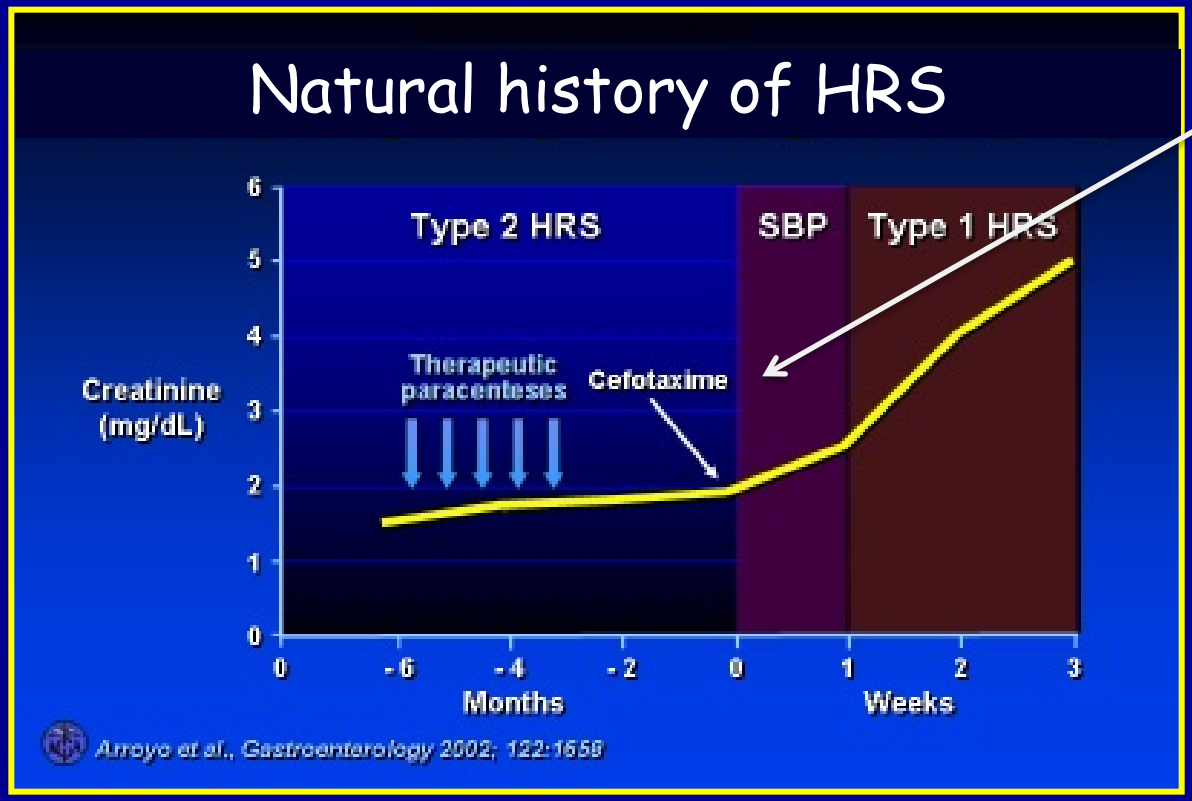
Typical scenario:

Diuretic-resistant ascites → SBP → HRS-1



Antibiotic & **albumin** day 1 and 3

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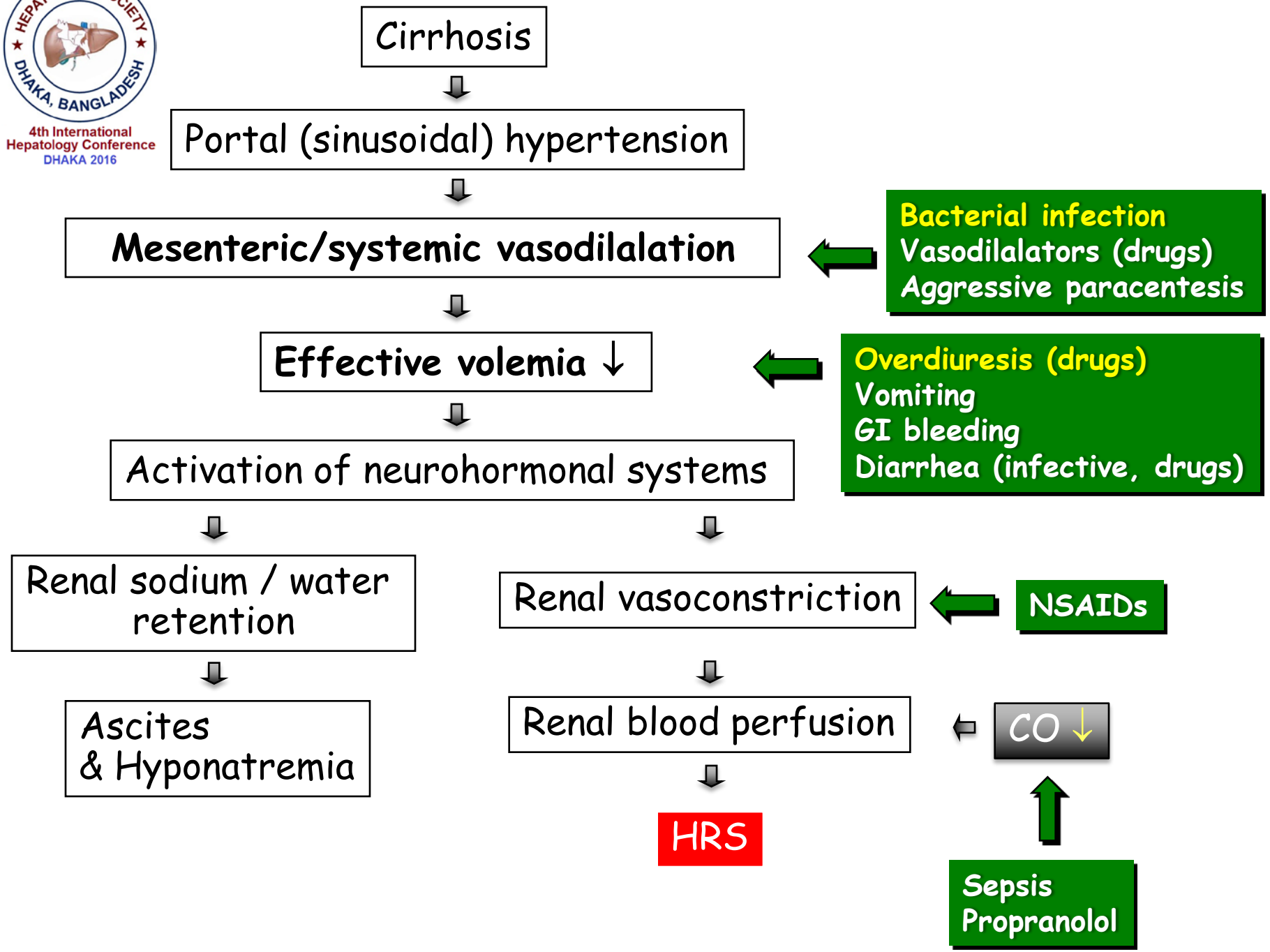


Hepatorenal syndrome
Diagnostic criteria

- **Diagnosis of AKI according to IAC-AKIN criteria**
- **Cirrhosis & ascites**
- No improvement (sCr <1.5 mg/dl) after at least 2 days of diuretic withdrawal and plasma volume expansion with albumin 1g/kg/24 h (max. 100 g)
- Absence of shock (septic or hemorrhagic)
- Absence of parenchymal kidney disease (urine protein <500 mg/24 h and/or erythrocytes < 50 hpf)
- No current or recent use of nephrotoxic agents

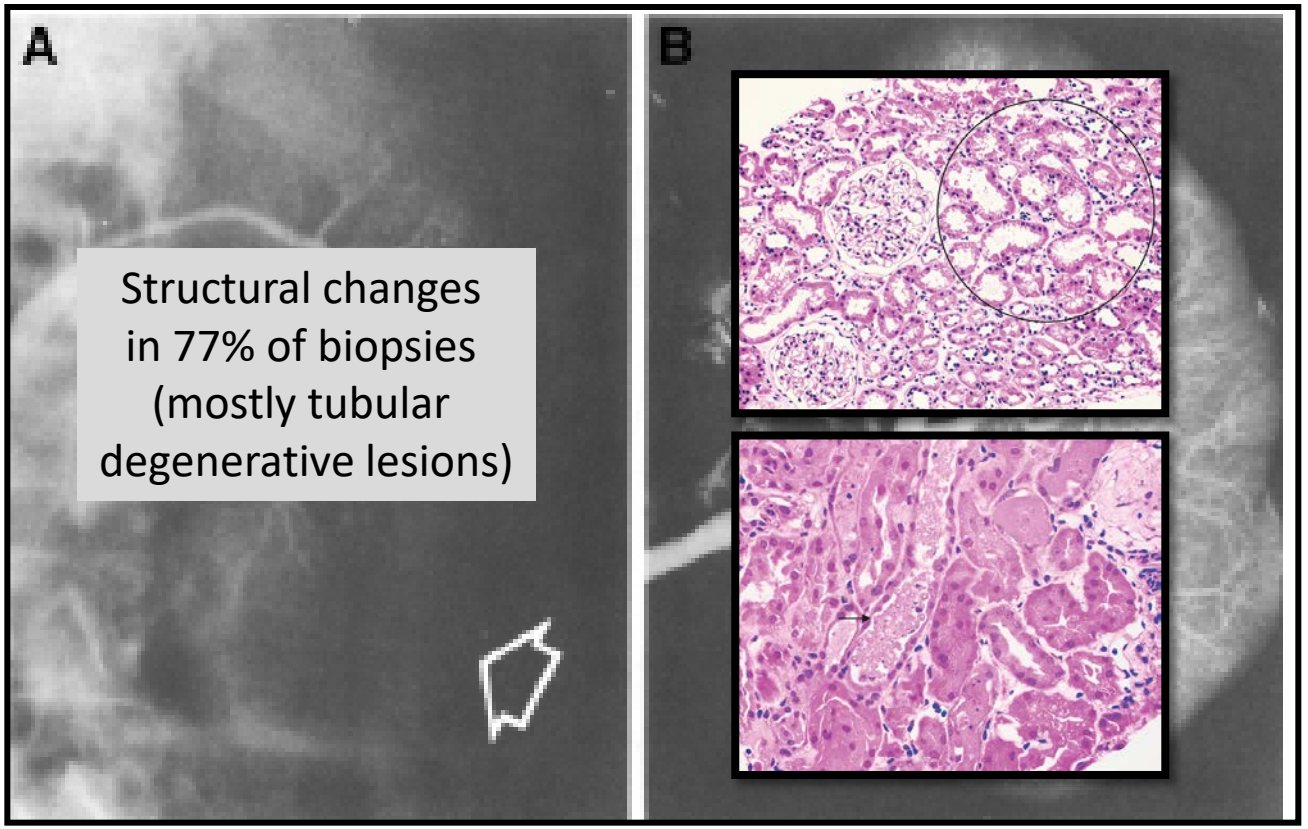
Urine volume < 400 ml/24 h is not obligatory

Hepatorenal syndrome (HRS)

In HRS the pathology exclusively regards the renal vascular system

End-stage cirrhosis

Post-mortem



Russ KB et al. J Clin Transl Hepatol 2015, 3, 195

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Acute kidney injury

- Diuretics
- Diarrhea

- SBP (other infection)
- Paracentesis

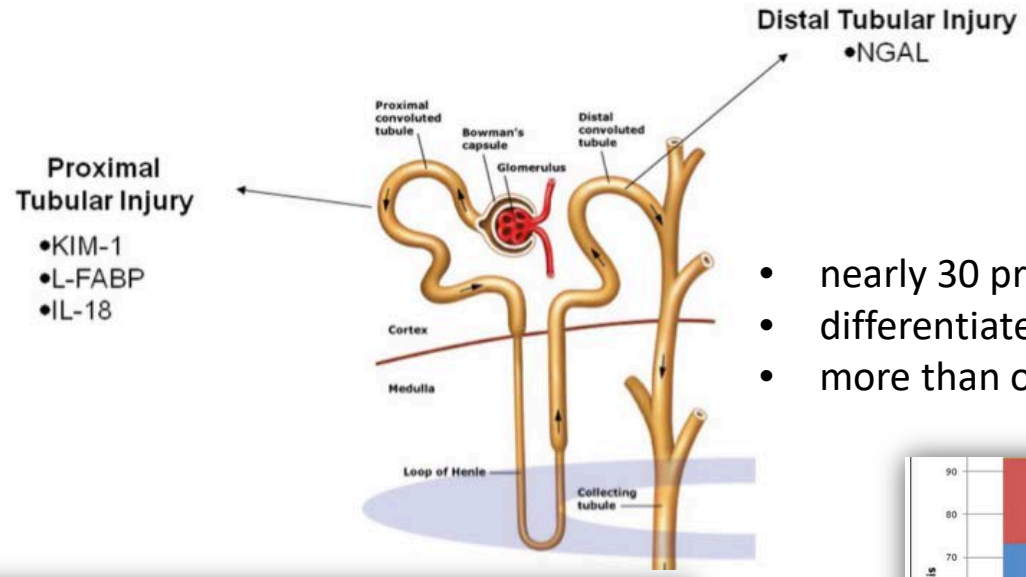
- Unrecognized AKI
- Septic shock
- Hemorrhagic shock
- Nephrotoxic drugs (NSAIDs, aminoglycosides)
- Radiological contrasts

Prerenal azotemia → HRS-1 → Acute tubular necrosis

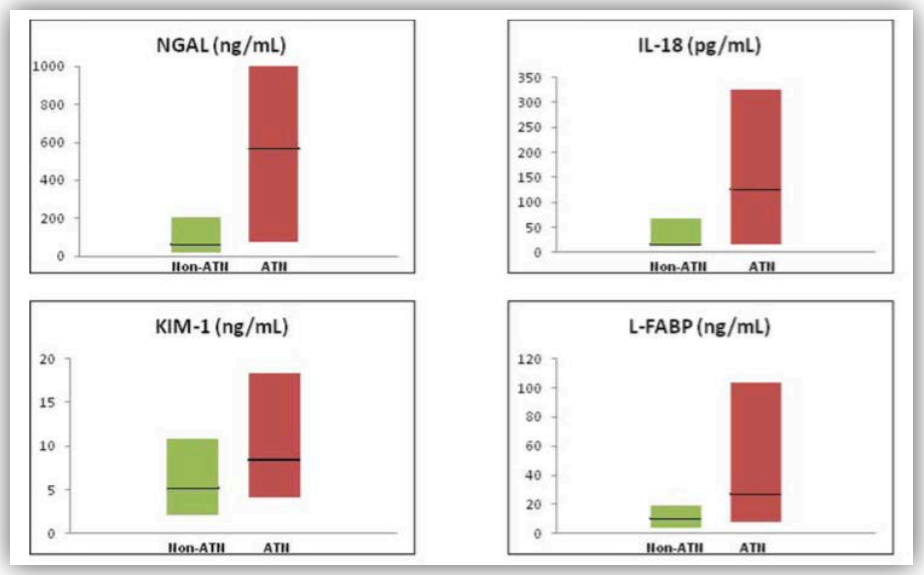
Degree of renal hypoperfusion

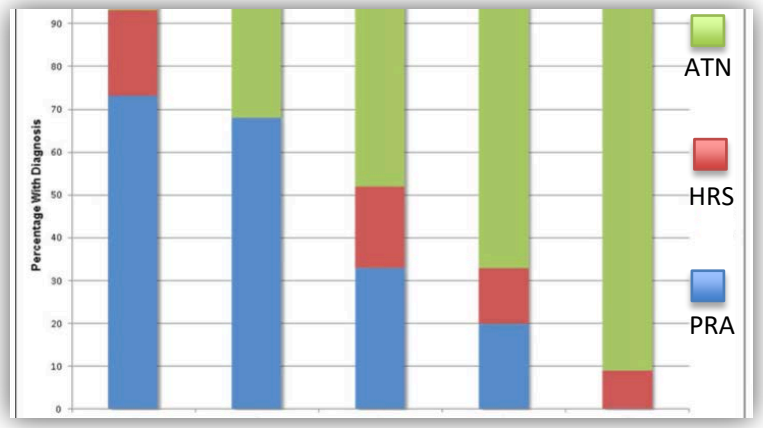
U_{Osm} > 500 mOsm/kg FENa < 1%	U_{Osm} > 500 mOsm/kg FENa < 1%	U_{Osm} < 350 mOsm/kg FENa > 2%
Urine exam No casts	Urine exam No casts	Urine exam Casts granular/epithelial
Volume expansion → sCr normalization	Volume expansion → No sCr normalization	Renal biopsy ?

Biomarkers of tubular necrosis



- nearly 30 primarily tubular markers
- differentiate well pre-renal azotemia from ATN
- more than one marker should be used



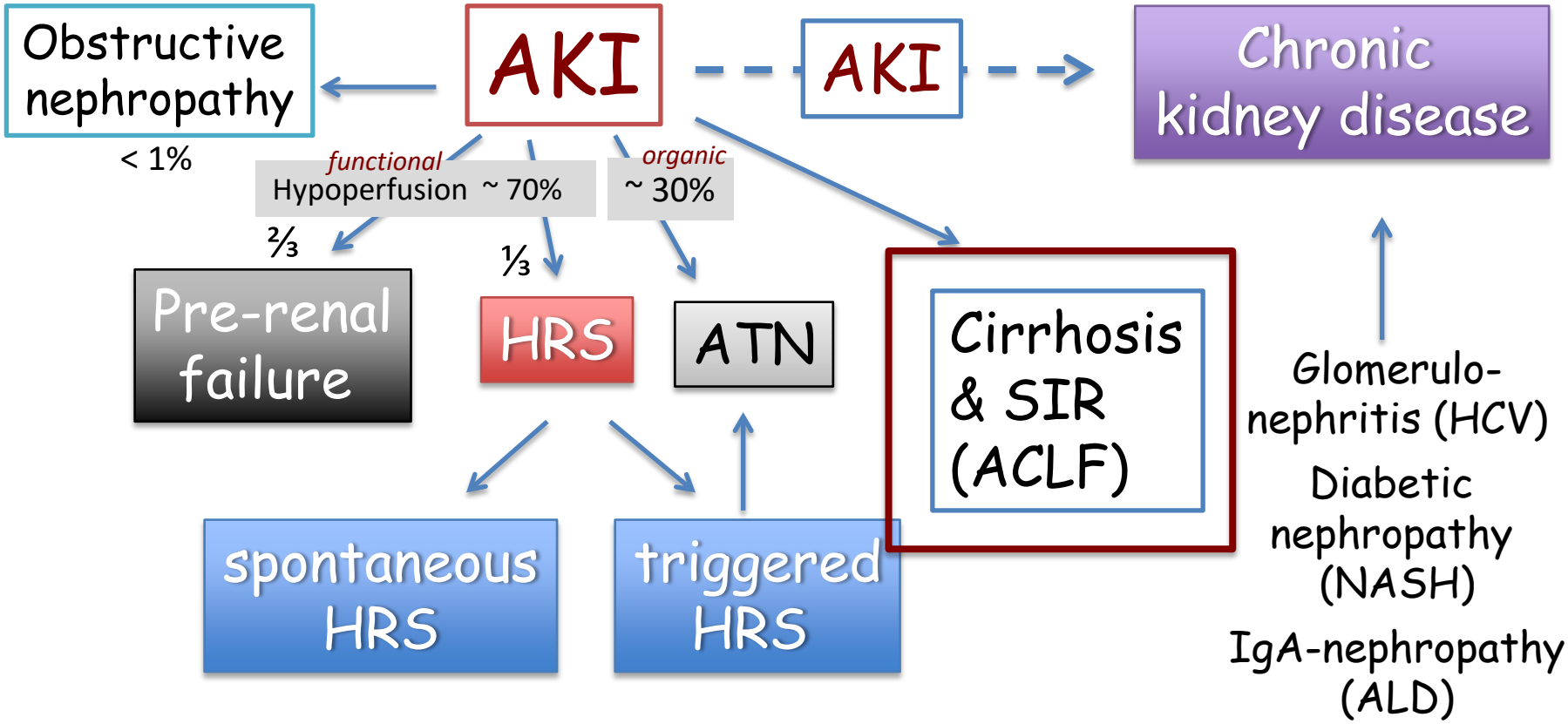


Results above Cutoff

Number of tests	0	1	2	3	4
Number of patients	*44*	*19*	*21*	*15*	*11*

Belcher JM et al. Hepatology 2014; 60: 622

Hepatorenal diseases



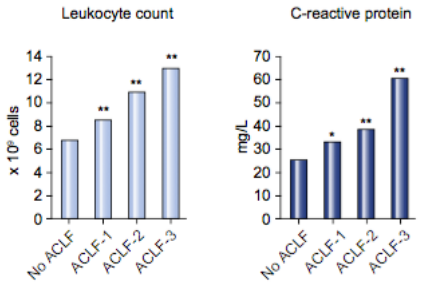
HRS: Hepatorenal syndrome; ATN: acute tubular necrosis,
ACLF: acute-on-chronic liver failure

Garcia-Tsao G et al. Hepatology 2008; 48: 2064

AKI in acute-on-chronic liver failure (ACLF)

Multiorgan failure

- **Kidney**
- Cerebral
- Circulatory
- Respiratory
- Coagulation



IL-1,6,8
TNFα

SIR & oxidative stress

Liver cirrhosis +

- alcoholic hepatitis
- sepsis
- reactivation of HBV infection
- acute hepatitis A or E
- PVT
- ischemia
- drug-induced liver injury

Degree of SIR correlates with number of organ failures

- Another mechanism of AKI (≠hypoperfusion)
- Another treatment (albumin, PTX, N-acetylocysteine??)

Organ system	Score = 1	Score = 2	Score = 3
Liver, bilirubin (mg/dl)	<6	6-≤12	>12
Kidney, creatinine (mg/dl)	<2	2-<3.5	≥3.5 or renal replacement
Brain, grade (West-Haven)	0	1-2	3-4
Coagulation, INR	<2.0	2.0-<2.5	≥2.5
Circulation, MAP (mmHg)	≥70	<70	Vasopressors
Respiratory PaO_2/FiO_2	>300	≤300 and >200	≤200
or SpO_2/FiO_2	>357	>214 and ≤357	≤214

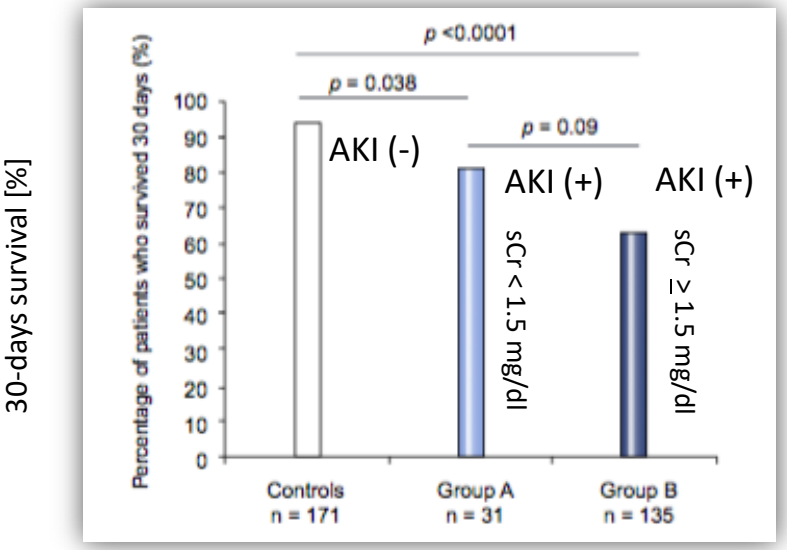
Arroyo V. et al. J Hepatol 2015; 62: 131

AKI in cirrhosis - prognosis

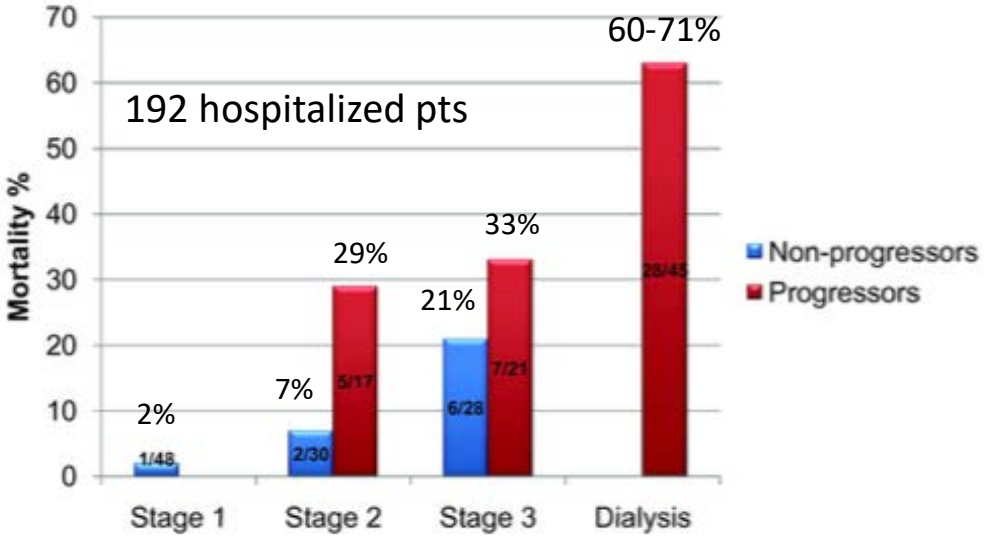
In patients with sCr > 1.5 mg/dl

- higher probability of being transferred to intensive care unit
- longer hospitalization
- higher short-term mortality

MELDScore = 10* [(**0.957*** *ln* **sCr**) + (**0.378** * *ln* **Bilirubin**) + **1.12** **ln* **INR**)] + 6.43

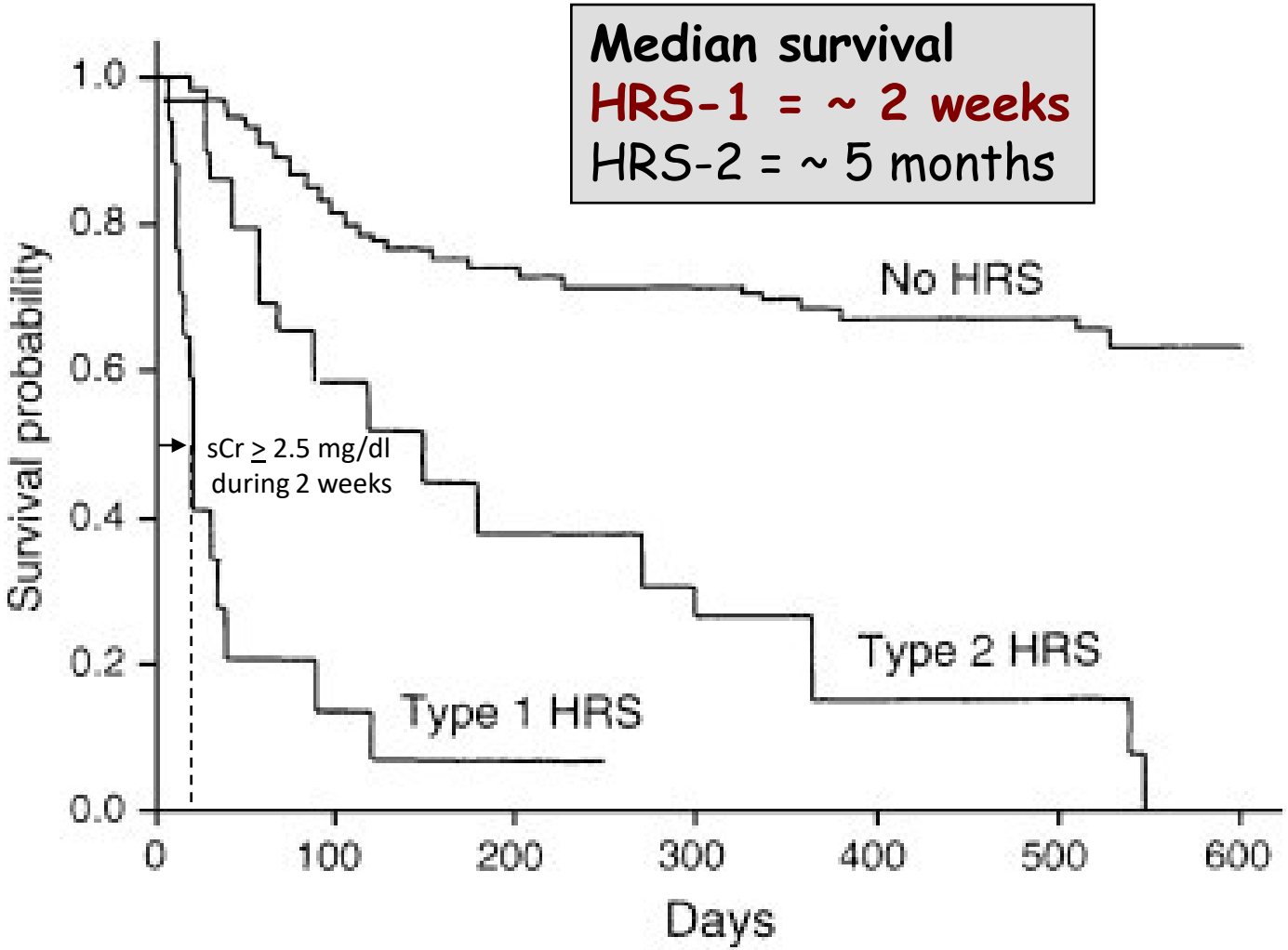


Survival is influenced not only by the stage of renal dysfunction but also by the progression on follow-up



Belcher JM et al. Hepatology 2013; 57:753
Wong F et al. J Hepatol 2015; 62: 739

Survival of patients with liver cirrhosis without HRS, with HRS-2 and HRS-1



Gines i wsp. Lancet 2003, 362, 1819.

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General management principles in case of increase of creatinine level

- ✓ **Withdrawal of diuretics**

  Withdrawal of potentially nephrotoxic drugs, vasodilators or NSAIDs (review drug chart including OTC drugs)

- ✓ **Plasma volume expansion**

  Albumin iv 1 g/kg/24 hr (max. 100 g)* or blood in case of GI bleeding (re-evaluation after 2 days)

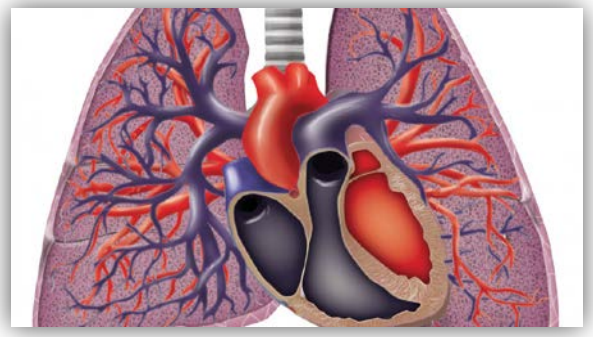
- ✓ **Antibiotic** (bacterial infection?)
- ✓ **Urine analysis** (*leukocytes?, casts?, erythrocytes?)*
- ✓ **Ultrasound of kidneys**

* monitored by central venous pressure

Treatment of AKI in cirrhosis (pre-renal, HRS, ATN)

Effective hypovolemia

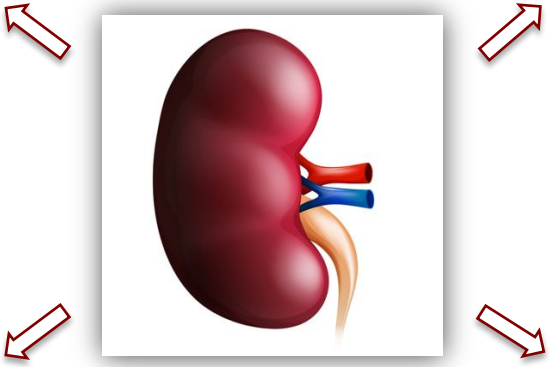
Norpinephrine
Angiotensin
Vasopressin



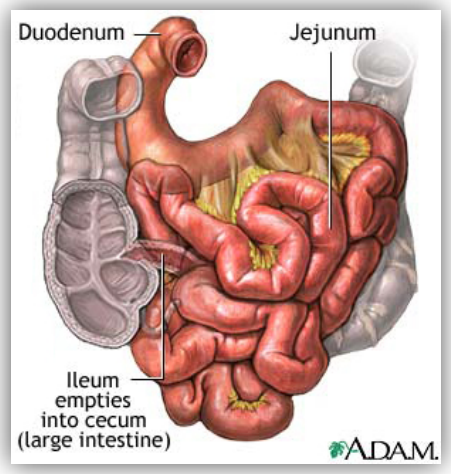
Volume expander (albumin)

Vasoconstriction

Vasodilatation

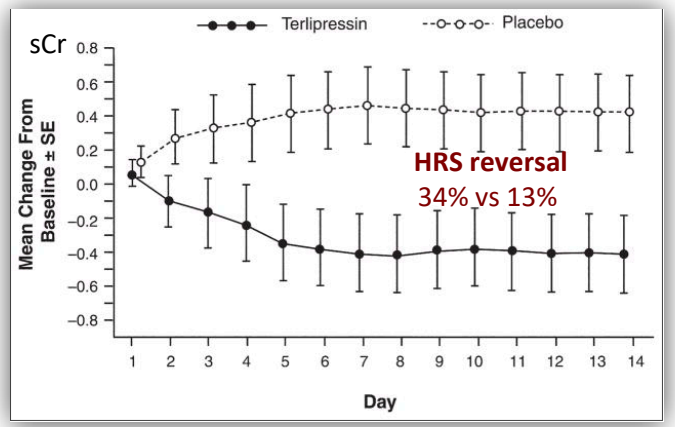


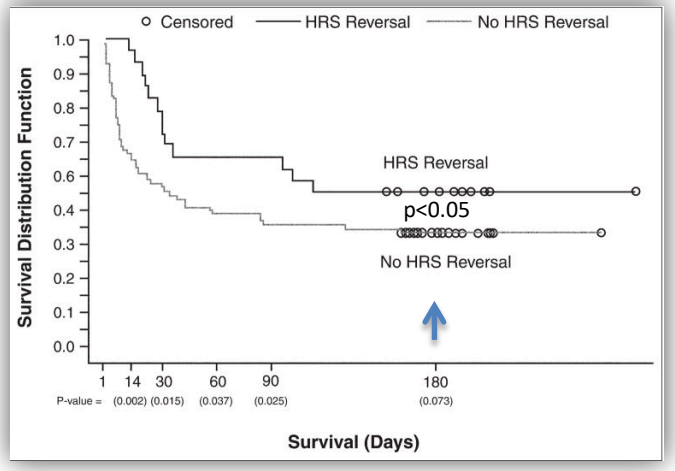
Splanchnic vasoconstrictor (terlipressin, norepinephrine, octreotide)



HRS Treatment
terlipressin & albumin

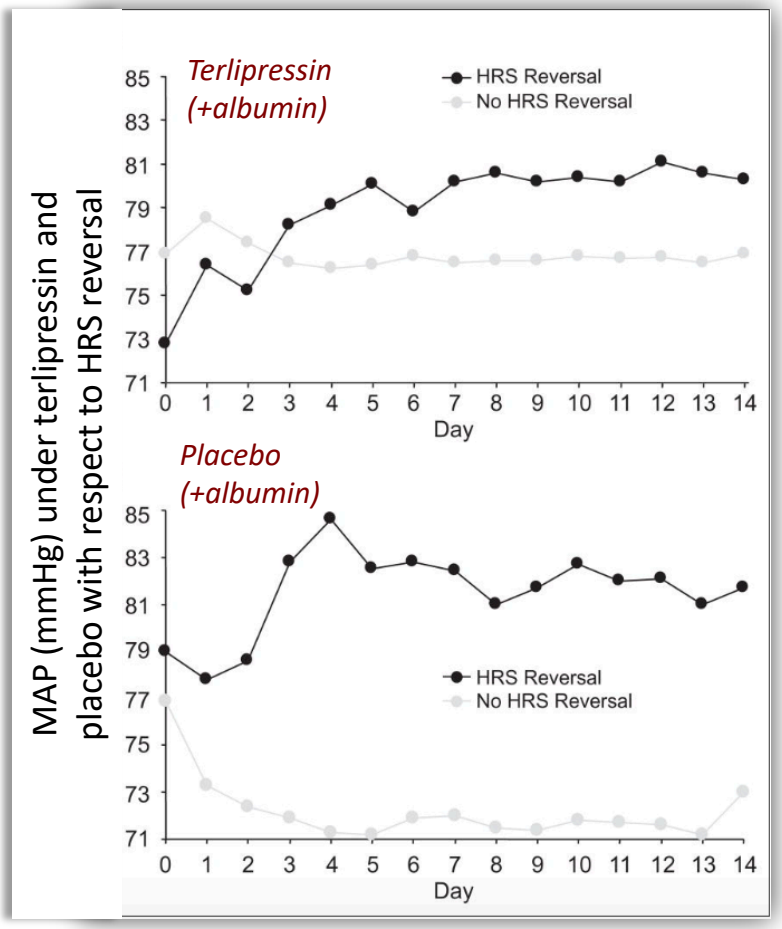
Efficacy of terlipressin in HRS-1:
HRS reversal, survival





Sanyal AJ et al. Gastroenterology 2008; 134: 1360

Single predictor of HRS-1 reversal:
was baseline serum creatinine, importance of MAP



Boyer TD et al. J Hepatol 2011; 55: 315

Acute Kidney Injury
Treatment

Pre-renal azotemia → HRS-1 → Acute tubular necrosis

Degree of renal hypoperfusion

Vascular system repletion (albumin, crystalloids)

Vasoconstrictor & albumin

Renal replacement therapy

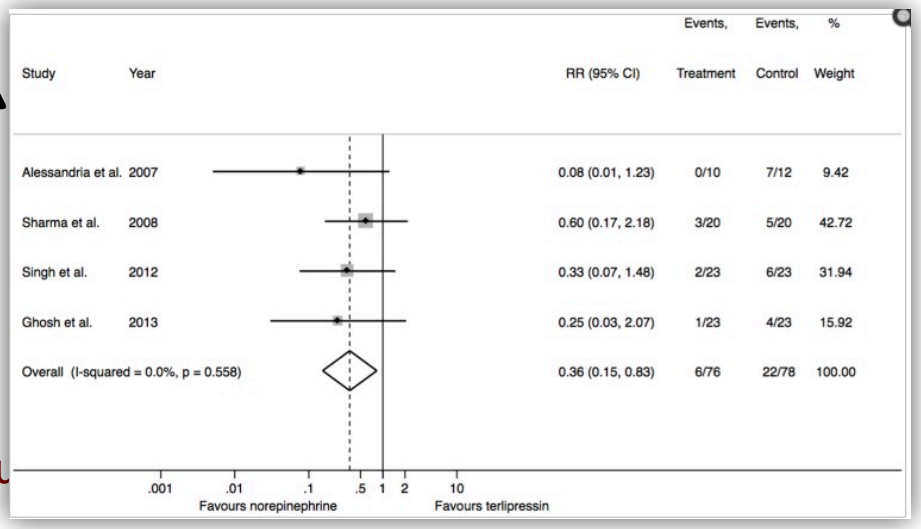
No response ~ 50%

1. Normal perfusion (e.g. ACLF)
2. Chronic renal disease
3. Severe injury (ATN)

Which vasoconstrictor is the best?

Meta-analysis: 4 studies; 154 patients with HRS

Norepinephrine
(n=76)



RESULTS

Reversal of HRS: 44/76 (**74%**)
30-day mortality: 36/76 (**47%**)
Side effects: 6/76 (**7.9%**)

Norepinephrine requires continuous i.v. infu

Nassar Junior AP et al. PLoS One, 2014, 9

RCT: 49 patients with HRS

MID + OCT + ALB
(n=22)

TER + ALB
(n=27)

RESULTS

Reversal of HRS: 6/21 (**28.6%**) 19/27 (**70.4%**) p=0.01

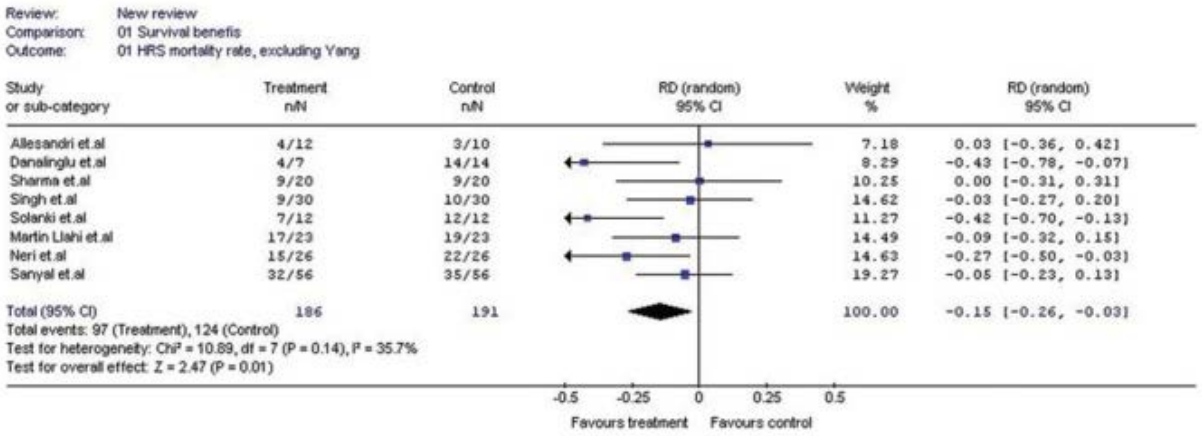
Cavallin M et al. Hepatology, 2015, 62, 567

HRS Treatment
terlipressin & albumin

Meta-analysis:
8 RCTs; 378 pts HRS-1

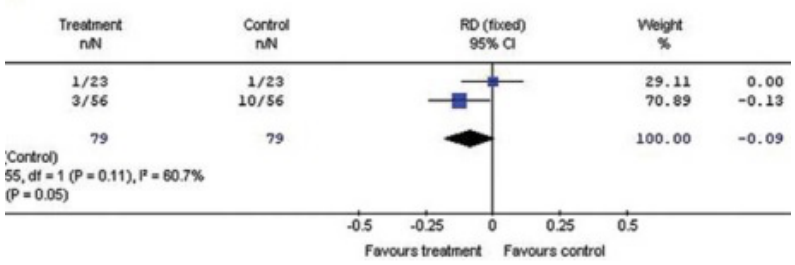
All causes mortality (3 months)

↓ 15%



Mortality due to HRS alone (3 months)

↓ 9%



Response to treatment: 40-60% (mean recovery time 7 days)
Early relapse after response: 5-10%

Hiremath SB et al. Indian I Pharmacol 2013; 45:54
Gluud LL et al. Hepatology 2010; 51: 576

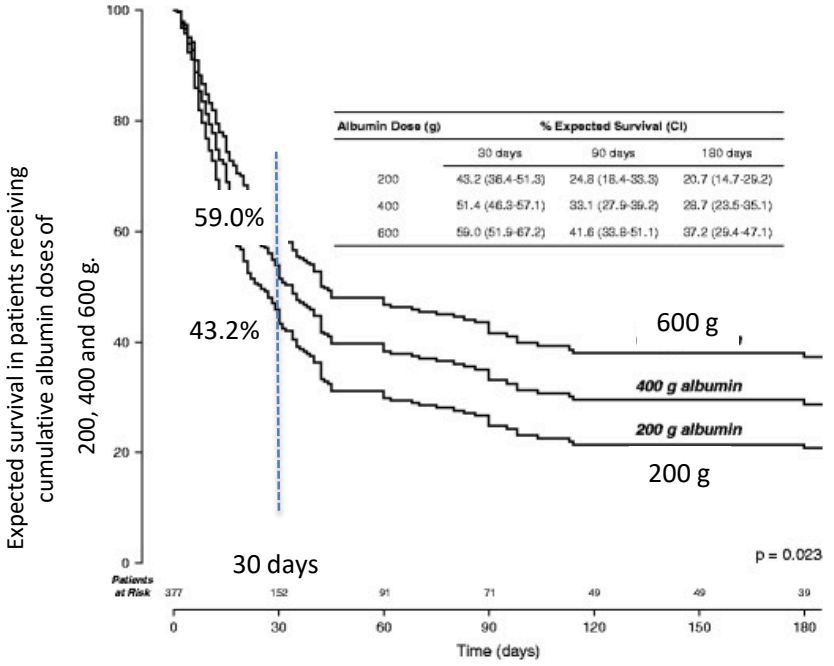
Treatment
role of albumin

Non-randomized study

	TER & ALB	vs	**TER alone**
Reversal of HRS:	77%	vs	25%

Ortega R et al. Hepatology 2002; 36: 941

- Meta-analysis of 8 clinical studies comprising 547 patients with HRS-1
- Pooled reversal of HRS was 49.5%
- Neither **survival nor reversal of HRS** was influenced by vasoconstrictor type/dose or treatment duration



Salerno F et al. BMC Gastroenterology 2015; 15: 167

Hepatorenal syndrome

Management of non-responders to TER & ALB

- **Dialysis**

  Conclusions: *Justified as bridge to liver transplantation or while awaiting reversal of an acute liver failure or ACLF (e.g., alcoholic hepatitis).*

  Classical indications: *Severe volume overload, metabolic acidosis, hyperkalemia, symptomatic uremia*

- **Extracorporeal liver assist devices**: Helios (FPSA) and MARS

  Conclusions: *Improve encephalopathy, sCr and bilirubin level but do not improve short-term survival*

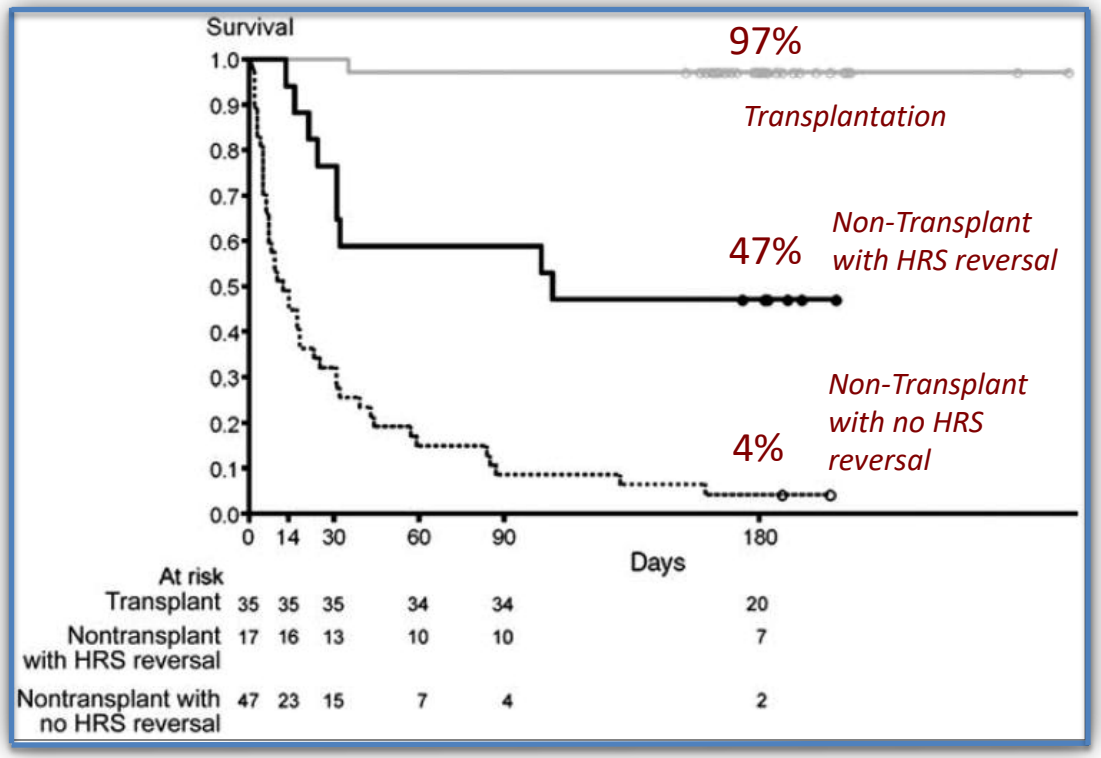
- **TIPS**

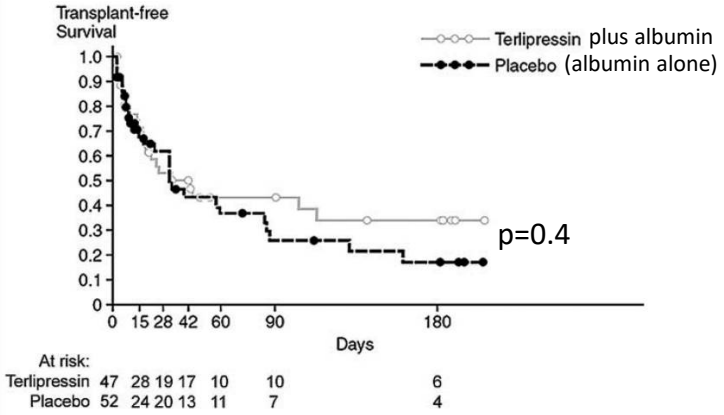
  Conclusions: *reduces portal hypertension and ascites, effect on central volemia, improves indirectly renal function* ***but*** *patients with AKI too sick to undergo TIPS (encephalopathy)*

Kribben et al. Gastroenterology 2012
Banares et al. Hepatology 2013

Liver transplantation (LT)
HRS-1

99 pts with HRS-1 treated with **TERLIPRESSIN** or **PLACEBO**
35% underwent LT





Boyer TD et al. Liver Transp. 2011; 17: 1328

Key points

- Patients with liver cirrhosis have natural tendency to develop AKI that is assoc. with poor prognosis
- Definition of HRS-1 has changed according to AKIN, but still is based on exclusion criteria and creatinine level that is imperfect indicator of renal function in cirrhosis
- HRS is not the unique, and probably also not the commonest form of AKI in patients with cirrhosis
- AKI is potentially reversible disease but type of therapy depends on type of renal failure

Key points

- The standard treatment of HRS is vasoconstrictor combined with albumin (+ withdrawal of diuretics)
- The goal of therapy is to reverse in a very short time window the kidney failure before it leads to irreversible structural renal damage and death
- An estimated 40 to 60 % of patients respond to the combination therapy with reversal of kidney failure
- HRS-1 signals the need for immediate LT, which is **the only definitive treatment**

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