MÁSTER EN HEPATOLOGÍA

UAM Universidad Autónoma de Madrid

Universidad de Alcalá

“Síndrome hepatorenal: forma clásica y en ACLF. Insuficienca renal en el paciente en UCI. Diálisis en el paciente con cirrosis”

Pere Ginès

Hospital Clínic de Barcelona. Universitat de Barcelona. Institut d’Investigacions Biomèdiques August Pi-Sunyer (IDIBAPS), CIBERehd, Barcelona

IDIBAPS Institut D'Investigacions Biomèdiques August Pi i Sunyer

CLÍNIC BARCELONA Hospital Universitari

Universitat de Barcelona

Disclosure of interests

I disclose the following financial relationship(s) with a commercial interest:

Mallinckrodt, Novartis, Sequana Medical, Gilead,

Grifols, Martin Pharmaceuticals, Intercept, Echosens

CASE VIGNETTE

63-yr male with Alcohol-related Cirrhosis and no other relevant diseases

First admission: Ascites/edema and Hepatic Encephalopathy 6 months earlier

Second admission: Skin infection in left lower extremity associated with transient AKI stage 1B, likely due to HRS 2 months earlier

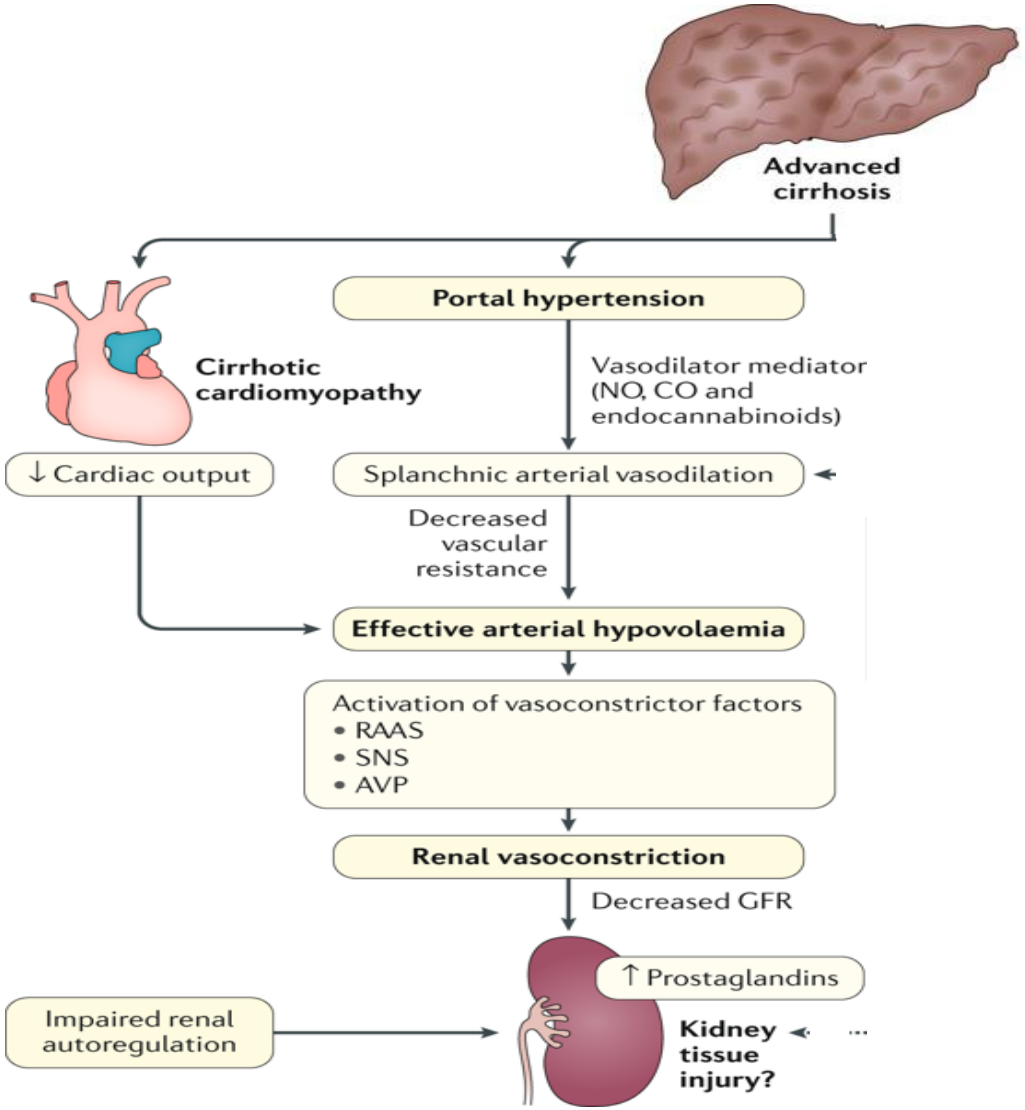
Last labs: bili 1.4 mg/dL, albumin 33 g/L, PT 49%, AST 36 IU/mL, creatinine 0.9 mg/dL, Child B 7 and MELD 14, urine sodium 6 mEq/L (without diuretics).

Ultrasound: cirrhotic liver, patent portal vein, splenomegaly, ascites

Upper GI endoscopy: no esophageal varices

Patient was admitted to the Unit for increased ascites and edema and worsening kidney function with serum creatinine of 6.2 mg/dL.

DECOMPENSATED CIRRHOSIS. HEMODYNAMIC AND INFLAMMATORY BACKGROUND



Ginès, et al. Nat. Rev. Dis. Primers.2018
Ginès and Schrier New Engl J Med 2009

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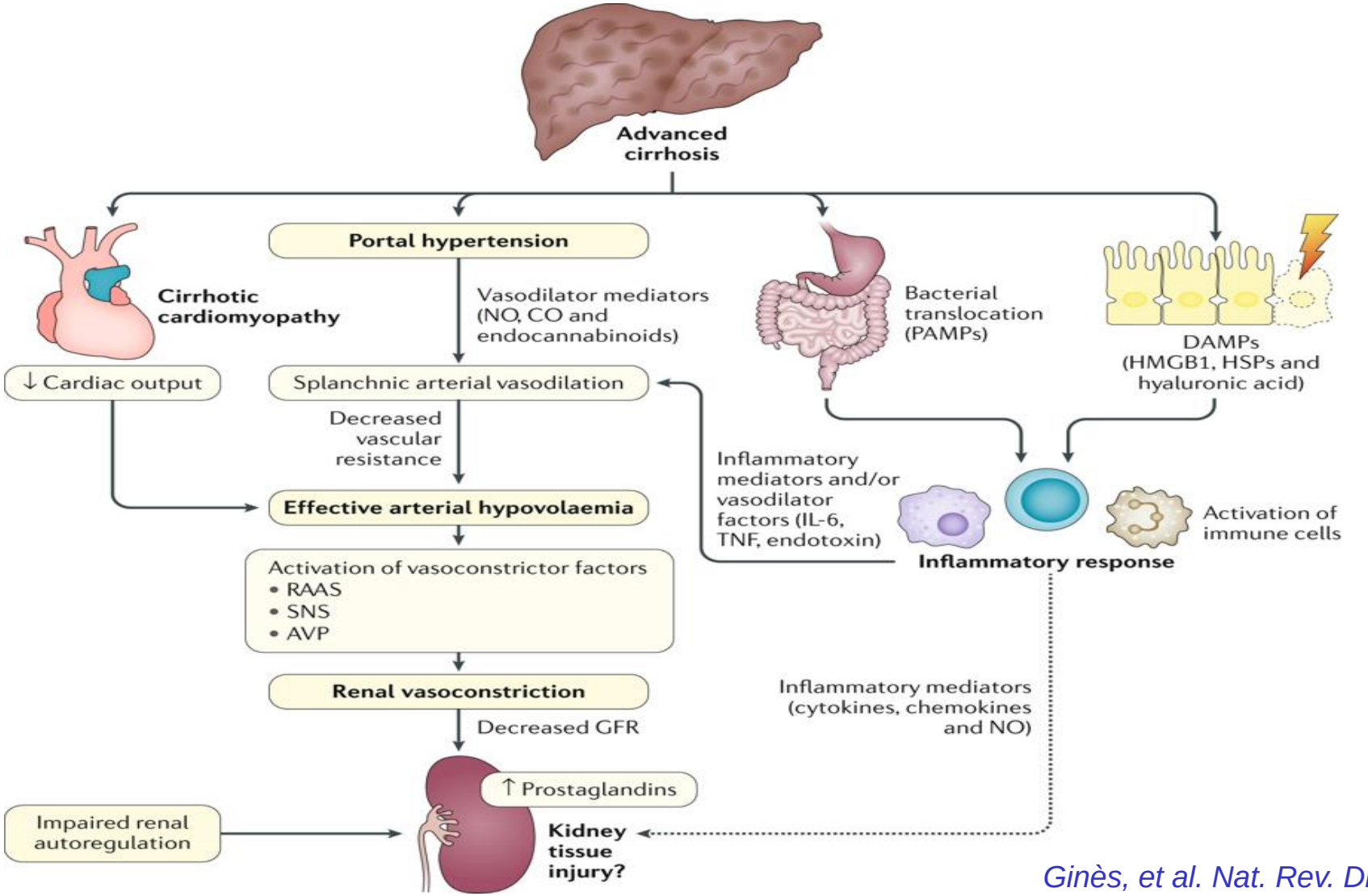

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HEPATORENAL SYNDROME-ACUTE KIDNEY INJURY

Diagnostic criteria

- Cirrhosis with ascites

- Diagnosis of AKI (increase in serum creatinine ≥ 0.3 mg/dL within a short time period – ideally <7 days, but practically < 3 months)

- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g/kg bw) or blodd in case of bleeding or saline in case of dehydration

- Absence of shock or recent use of nephrotoxic drugs (NSAIDs,…)

- No signs of structural kidney injury

Definition of type-1 HRS

Impairment of kidney function defined by >100% increase in serum creatinine to >2.5 mg/dl within <2 weeks

MAIN ETIOLOGIES OF AKI IN CIRRHOSIS

1. Hypovolemia-induced AKI (27-50%)
2. Acute Tubular necrosis (14-35%)
3. Hepatorenal syndrome (15-43%)
4. Nephrotoxicity (NSAIDs, antibiotics, contrast media,..)
5. Acute parenchymal diseases (IgA glomerulonephritis,..)
6. Combined

KIDNEY BIOMARKERS IN CIRRHOSIS

Potential usefulness

Help in differential diagnosis of AKI (ATN vs HRS)

Provide information on kidney outcomes

Provide prognostic information

Provide information on reversibility after transplantation

KIDNEY BIOMARKERS IN CIRRHOSIS

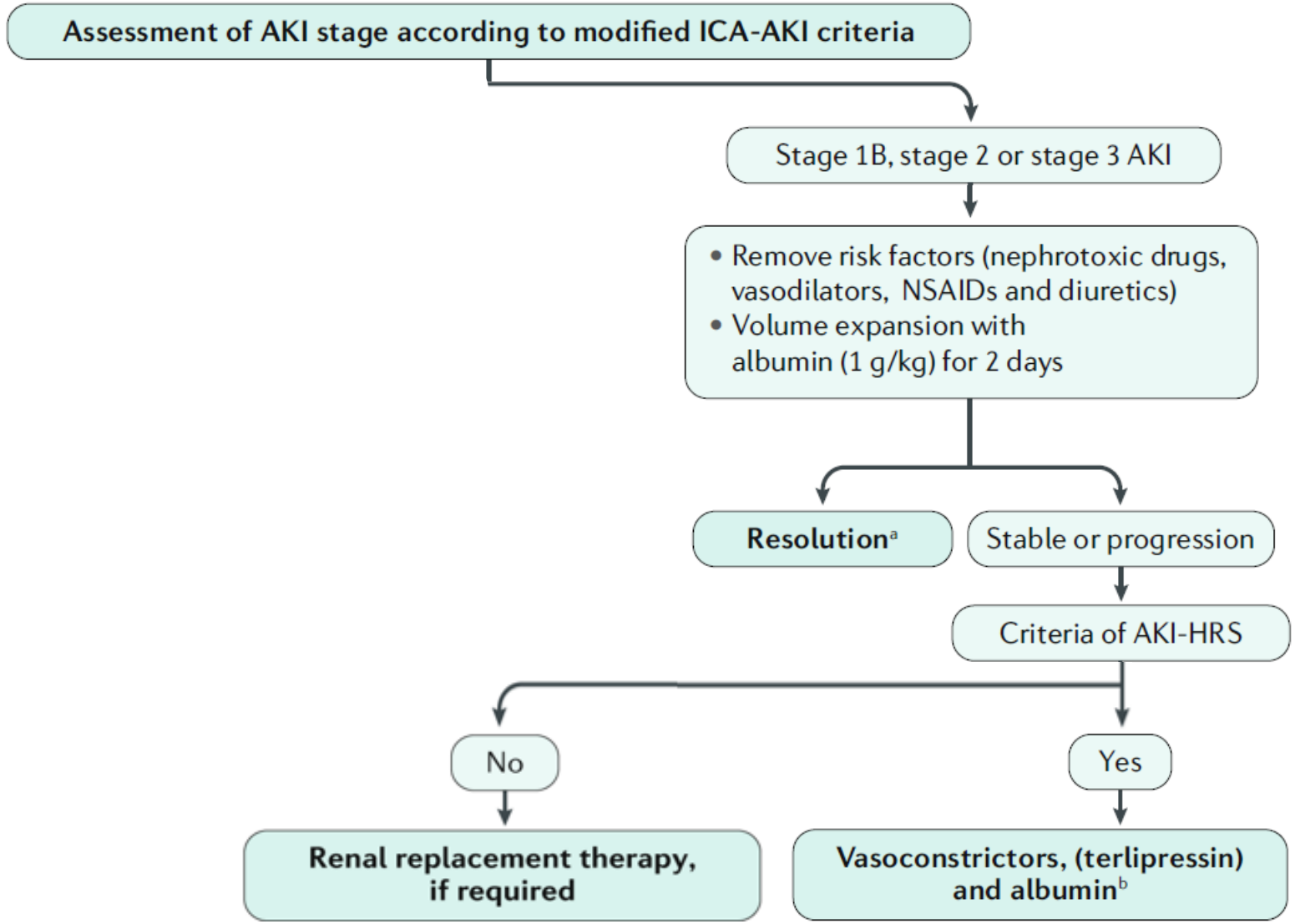
Urine NGAL for diagnosis of ATN vs other types of AKI

Author (year)	Patients included			Day of urine collection	AUROC ATN vs other	Cut-off value	Sn/Sp (%)*
	AKI (n)	HRS (n)	ATN (n)				
Fagundes (2012)	84	33	11	AKI diagnosis	NA	194 µg/g	91/82
Verna (2012)	52	20	15	AKI diagnosis	0.86	110 ng/mL	88/85
Belcher (2014)	76	16	39	median 2 days after AKI diagnosis	0.78	365 ng/mL	NA
Ariza (2015)	39	12	15	AKI diagnosis ±1 day	0.95	294 µg/g	92/89
Huelin (2019)	320	93	39	AKI diagnosis and day 3**	0.87	220 µg/g	88/85
Allegretti (2021)	161	55	49	AKI diagnosis	0.76	244ug/g creat	71/76

*Sensitivity/Specificity

** Urine was collected at diagnosis of AKI and at day 3. Values shown in the table are those of day 3.

ALGORITHM FOR MANAGEMENT OF AKI IN CIRRHOSIS



Adapted with permission from European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis *J. Hepatol.* **69**, 406–460 (2018)

Ginès et al., Nat.Rev.Dis.Primers,2018

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MANAGEMENT OF HEPATORENAL SYNDROME

Current Guidelines

- Terlipressin in combination with albumin should be considered the first line therapeutic agent for AKI-HRS, continous iv infusion starting at 2 mg/day.

EASL Clinical Practice Guidelines, J Hepatol, 2018

- Terlipressin and albumin first line therapy for AKI-HRS, preferably as continous iv infusion starting 2 mg/day. Use other vasoconstrictors if terlipressin is not available

AASLD Clinical Practice Guidance Hepatology 2022

“TIPS” FOR MANAGEMENT OF HRS-AKI WITH TERLIPRESSIN AND ALBUMIN

- Make sure patient meets criteria of HRS-AKI

- Start with terlipressin 2 mg/day as continuous iv infusion

- Add albumin 1 g/kg ev the first day and continue with 20-40 g/day. Confirm patient has no contraindications to albumin infusion and monitor CVP, if possible. If CVP > 16 mmHg stop albumin and continue terlipressin

- Look several times per day for side effects, particularly ischemic (fingers, toes, tongue, skin, scrotum..) and pulmonary edema

- Monitor efficacy of treatment with serum creatinine. Effect is slow. If there is no response (decrease in serum creatinine <25% from peak value) increase terlipressin dose (2mg/day) every 48 hours up to a dose of 12 mg/day.

RECOMMENDATIONS OF THE EUROPEAN MEDICINES AGENCY ON THE USE OF TERLIPRESSIN IN PATIENTS WITH HEPATORENAL SYNDROME

• In some studies in patients with type-1 HRS, the use of terlipressin has been asociated with an increased risk of respiratory failure and sepsis.

• Terlipressin should be avoided in patients with serum creatinine > 5mg/dL, ACLF grade ≥3, and/or MELD ≥39 unless benefits outweigh the risks.

• Patients with respiratory failure should be stabilized before the start of therapy and patients should be closely monitored during treatment. If patients develop respiratory symptoms, albumin dose should be reduced. If symptoms do not improve, terlipressin should be discontinued.

• Patients should be closely monitored for symptoms of infection.

• Terlipressin should be given as continuous infusion to reduce the risk of adverse events.

RENAL REPLACEMENT THERAPY FOR HEPATORENAL SYNDROME

• RRT should not be used as first-line therapy for HRS-AKI

• There are no good studies assessing the effects of RRT on survival in patients with HRS-AKI; therefore, the effect of RRT on survival is unknown.

• RRT should only be used in non-responders for pharmacological therapy who meet criteria for RRT (hypervolemia, metabolic acidosis, hyperkalemia), particularly in patients who are candidates to transplantation.

• Use of RRT in patients with HRS-AKI not candidates to transplantation should be decided on a case-by-case basis

• Ideally, cases of HRS-AKI (as well as other types of AKI) should be discussed in a “cirrhosis-renal committee” with hepatologists, nephrologists, transplant hepatologists, and ICU physicians.

HEPATORENAL SYNDROME AND ACLF

Independent predictors of 90-day mortality in patients with type-1 hepatorenal syndrome

	HR	95% CI	P
Age (years)	1.05	1.03 – 1.07	<0.001
Leukocytes (cells/mm^3)	1.03	1.12 – 2.02	0.006
ACLF grade	2.06	1.54 – 2.75	<0.001
Response to treatment	0.41	0.29 – 0.60	<0.001

Piano et al., Clin Gastroenterol Hepatol 2018

TAKE-HOME MESSAGES

- The diagnostic criteria of AKI are helpful for early detection of impairment in kidney function. Check serum creatinine frequently particularly in decompensated patients

- Development of AKI-HRS is associated with an impaired prognosis. AKI-HRS should be identified and treated as early as possible. Terlipressin and albumin is the first-line therapy for AKI-HRS. Check treated patients regularly for possible side effects of therapy, particularly ischemic effects, respiratory symptoms, and sepsis. Do not overuse albumin.

- Rapid identification of the etiology of AKI is very important to start specific therapy. Urine NGAL is helpful in the differential diagnosis between ATN and HRS and guiding prognosis.

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ciberehd
Centro de Investigación Biomédica en Red
Enfermedades Hepáticas y Digestivas

IDIBAPS
Institut D'Investigacions Biomèdiques August Pi i Sunyer

Fondo de Investigación en Salud
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*iCrea
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