BANNER UNIVERSITY MEDICAL CENTER

Phoenix, November 15, 2019

HEPATORENAL SYNDROME: VASOCONSTRICTORS, BIOMARKERS, AND BEYOND

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Disclosure of interests

PERE GINÈS

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

Mallinckrodt, Novartis, Sequana Medical, Gilead,

Grifols, Martin Pharmaceuticals, Intercept, Echosens

OUTLINE

- Definition and prevalence of AKI in cirrhosis
- Staging and main etiologies of AKI
- Diagnosis and management of Hepatorenal syndrome
- Algorithm for diagnosis and management of AKI in cirrhosis

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ACUTE KIDNEY INJURY IN CIRRHOSIS

International Club of Ascites (ICA-AKI) definition

Increase in sCr ≥0.3 mg/dL (≥26.5 µmol/L) within 48 h; or increase of >50% from baseline which is known, or presumed, to have occurred within the prior 7 days. Values up to the previous 3 months can be used as baseline

Examples:

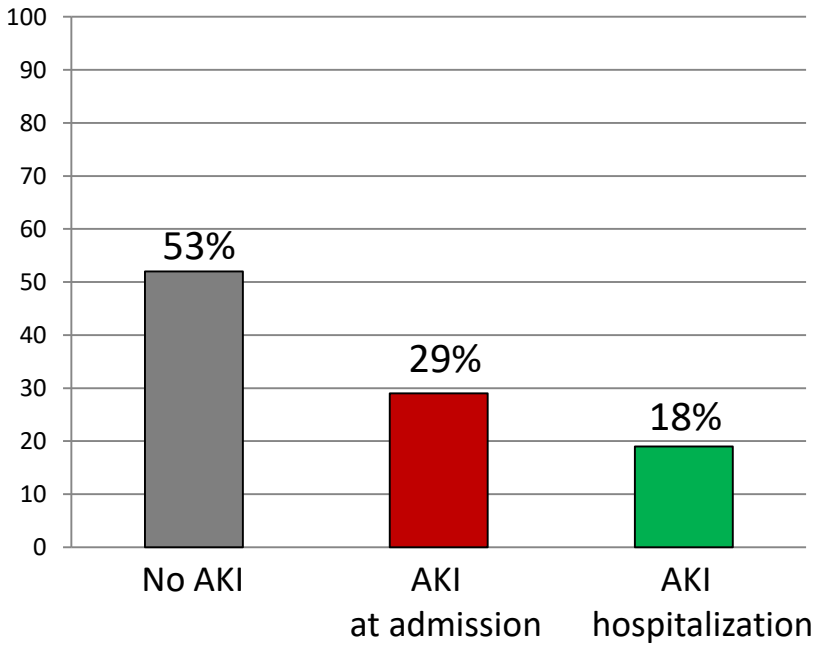
Baseline	AKI	Diagnosis
0.7 mg/dL	2.6 mg/dL	AKI
0.9 mg/dL	1.2 mg/dL	AKI
1.8 mg/dL	3.2 mg/dL	AKI on CKD
------	2.5 mg/dL	AKI or CKD?

Angeli P et al , J Hepatol 2015

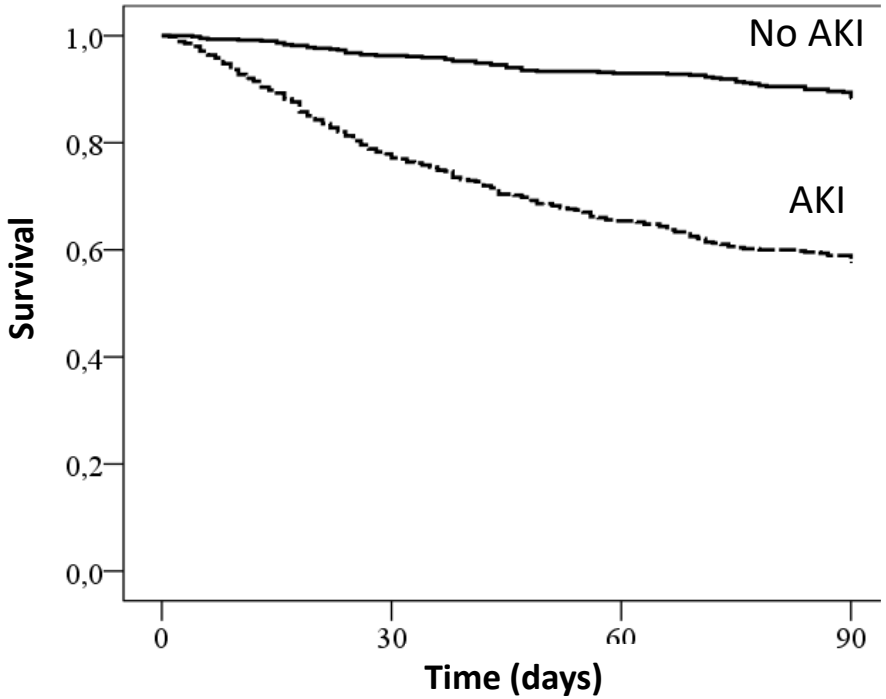
PREVALENCE OF AKI AND PROGNOSIS

Hospitalized patients with decompensated cirrhosis (n=1155)

Prevalence



Survival



Huelin P. et al, Clin Gastroenterol Hepatol 2017

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International Club of Ascites (ICA-AKI) definition

Staging of AKI

Stage AKI	CRITERIA
Stage 1 **68%**	increase in sCr ≥0.3 mg/dL (26.5 mmol/L) or an increase in sCr ≥1.5-fold to twofold from baseline **Stage 1A** sCr at diagnosis: < 1.5 mg/dL **20%** **Stage 1B** sCr at diagnosis: ≥ 1.5 mg/dL **48%**
Stage 2 **19%**	increase in sCr >two to threefold from baseline
Stage 3 **13%**	increase of sCr >threefold from baseline or sCr ≥4.0 mg/dL (353.6 mmol/L) with an acute increase ≥0.3 mg/dL (26.5 mmol/L) or initiation of renal replacement therapy

Angeli P et al , J Hepatol 2015

NEW CATEGORIZATION OF AKI-STAGE 1

Serum creatinine value at diagnosis of AKI

	AKI-1A (SCr < 1.5mg/dl)	AKI-1B (SCr ≥ 1.5mg/dl)	p value
AKI resolution	75	50	< 0.001
AKI progression	13	38	< 0.001
Type of AKI			
Hypovolemia/HRS/ATN	47/11/3	28/33/12	
Associated ACLF	22	75	< 0.001
3-month mortality	29	57	< 0.001

Values are percentages

Huelin et al, Clin Gastroenterol Hepatol 2017

EASL Clinical Practice Guideliness, J Hepatol 2018

MAIN ETIOLOGIES OF AKI IN CIRRHOSIS

- **HYPOVOLEMIA-INDUCED** *(diuretics, GI bleeding, diarrhea)*.
- **HEPATORENAL SYNDROME**
- **ACUTE TUBULAR NECROSIS** *(shock, nephrotoxic drugs, other)*.
- **NON-STEROIDAL ANTIINFLAMMATORY DRUGS** *(NSAIDs)*
- **GLOMERULONEPHRITIS**
- **MISCELLANEOUS/UNKNOWN**

PREVALENCE AND ETIOLOGIES OF AKI

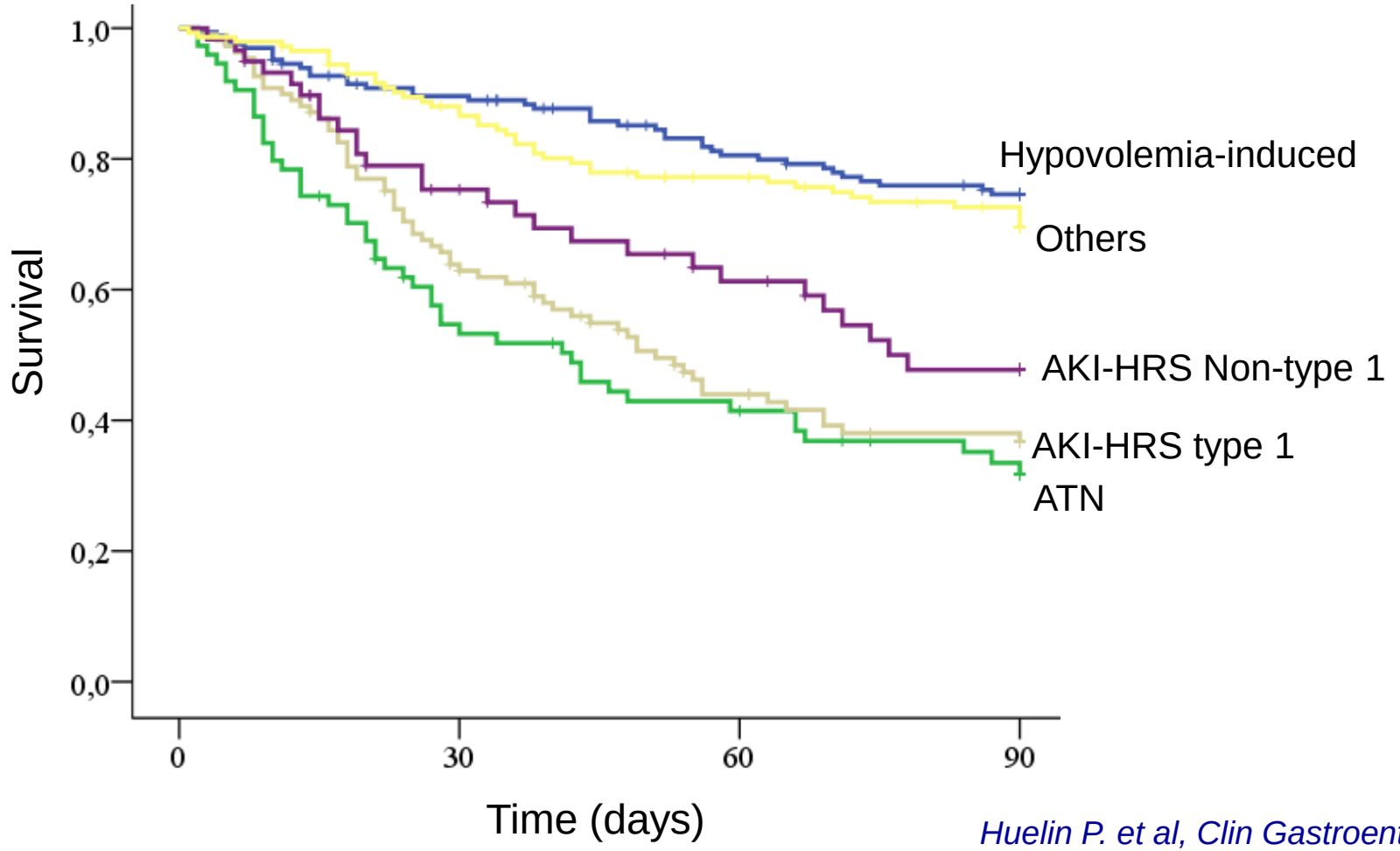
Study	*n*	AKI prevalence (%)	Causes of AKI			Refs
			Hypovolaemia (%)	ATN (%)	HRS (%)	
Fagundes et al., 2013	375	47	35	ND	18	14
Piano et al., 2013	233	27	36	ND	43	18
Belcher et al., 2014	110[a]	ND	50	35	15	10
Alegretti et al., 2015	120[a]	ND	33	29	30	17
Tandon et al., 2017	4,733	36	ND	ND	ND	13
Huelin et al., 2017	547	53	27	14	32	16

All patients with cirrhosis had been hospitalized for complications of the disease. AKI, acute kidney injury; ATN, acute tubular necrosis; HRS, hepatorenal syndrome; ND, not determined.
[a]Studies included only patients with cirrhosis and AKI.

Ginès et al ., Nat Rev Dis Primers 2018

PROGNOSIS OF AKI IN CIRRHOSIS

Relevance of the etiology of AKI



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CLASSICAL DIAGNOSTIC CRITERIA OF HRS

- Cirrhosis with ascites
- Serum creatinine >1.5 mg/dl (>133 mmol/l)
- No improvement of serum creatinine (decrease to a level of ≤1.5 mg/dl) after at least 2 days with diuretic withdrawal and volume expansion with albumin
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease. Parenchymal kidney disease is indicated by proteinuria (>500 mg/day), microhaematuria (>50 red blood cells per high- power field) and/or abnormal renal ultrasonography

NEW DIAGNOSTIC CRITERIA OF AKI-HRS

- Cirrhosis with ascites

- Diagnosis of AKI according to International Club of Ascites- Acute Kidney Injury (ICA- AKI) criteria

- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin

- Absence of shock

- No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides or iodinated contrast media)

- No signs of structural kidney injury. Structural kidney injury is indicated by proteinuria (>500 mg/day), microhaematuria (>50 red blood cells per high- power field) and/or abnormal renal ultrasonography

KIDNEY BIOMARKERS IN CIRRHOSIS

Potential usefulness

Help in differential diagnosis of AKI (ATN vs HRS)

Provide information on kidney outcomes

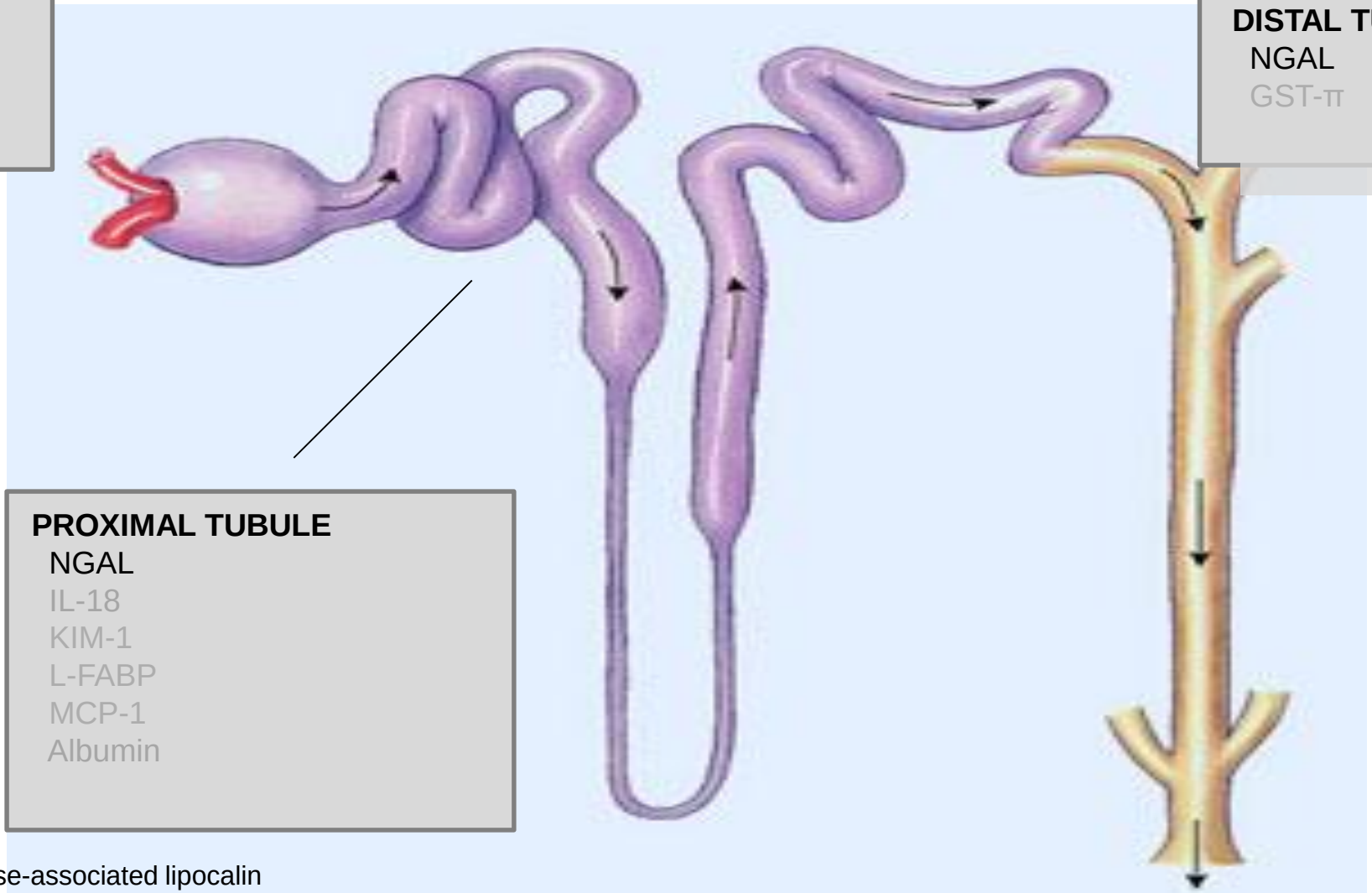
Provide prognostic information

Provide information on reversibility after transplantation

MAIN URINE BIOMARKERS

GLOMERULUS
- Creatinine
- Albumin
- NGAL

DISTAL TUBULE
- NGAL
- GST-π



PROXIMAL TUBULE
- NGAL
- IL-18
- KIM-1
- L-FABP
- MCP-1
- Albumin

NGAL, neutrophil gelatinase-associated lipocalin
IL-18, interleukin-18

Adapted from Koyner et al, Clin J Am Soc Nephrol 2013

DIFFERENTIAL DIAGNOSIS OF AKI IN CIRRHOSIS

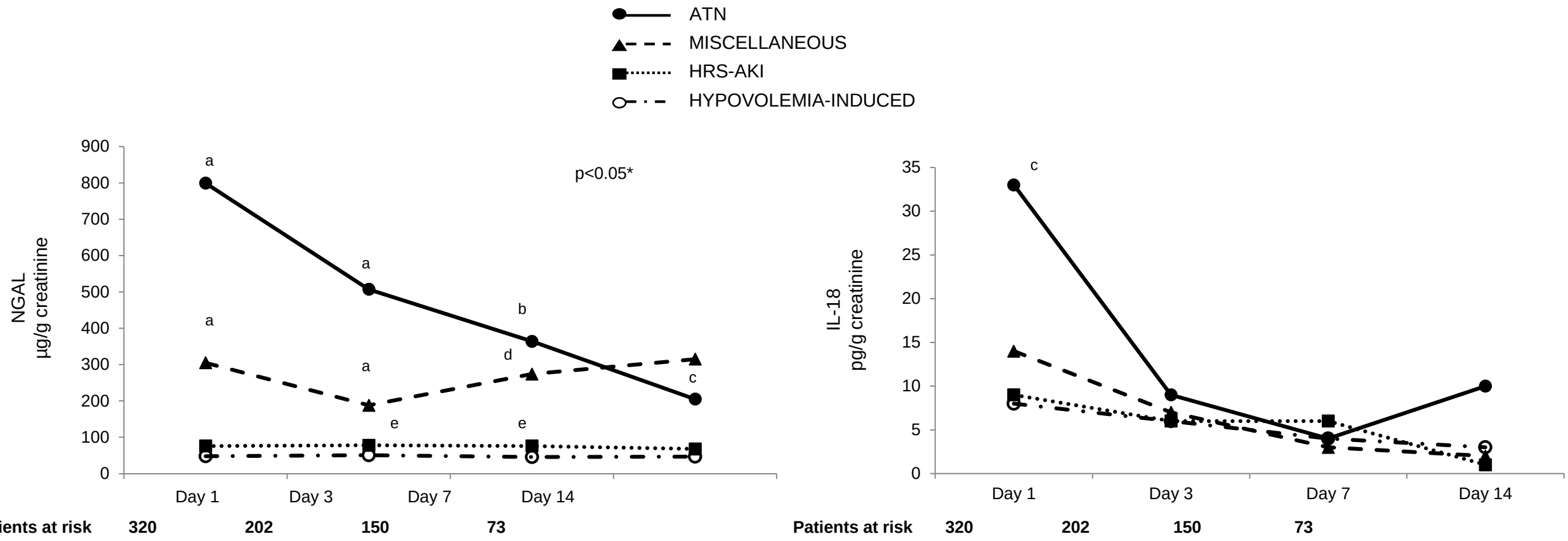
Urine NGAL for diagnosis of ATN vs other types of AKI

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

*Sensitivity/Specificity

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

TIME-COURSE OF URINE NGAL AND IL-18 IN PATIENTS WITH CIRRHOSIS AND AKI



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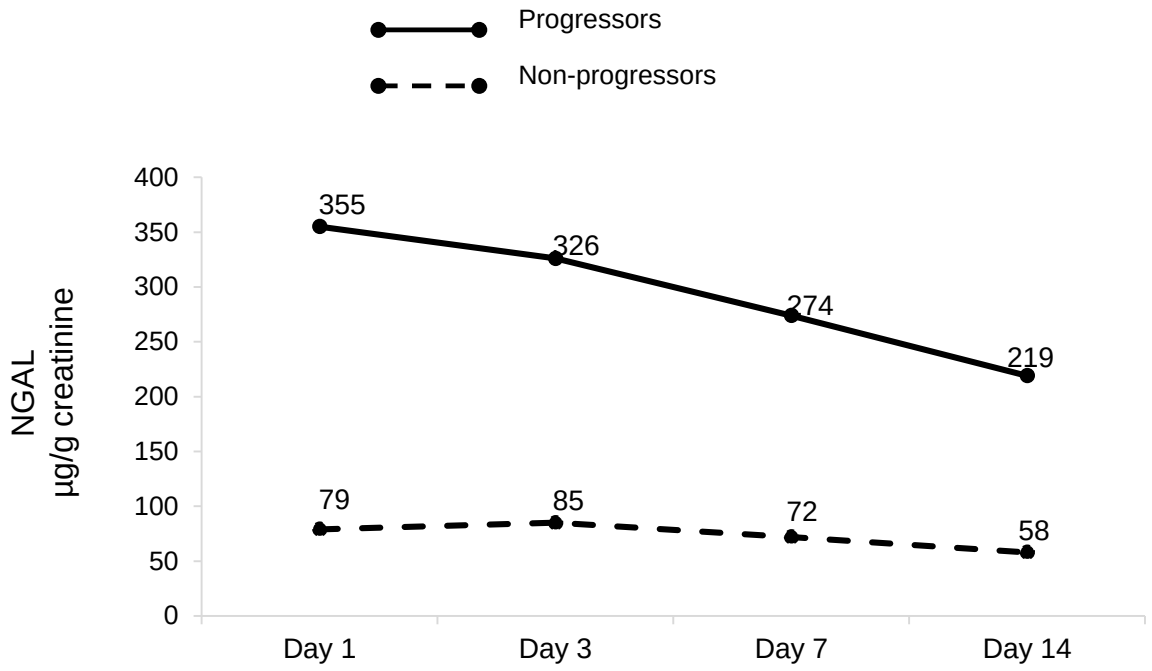
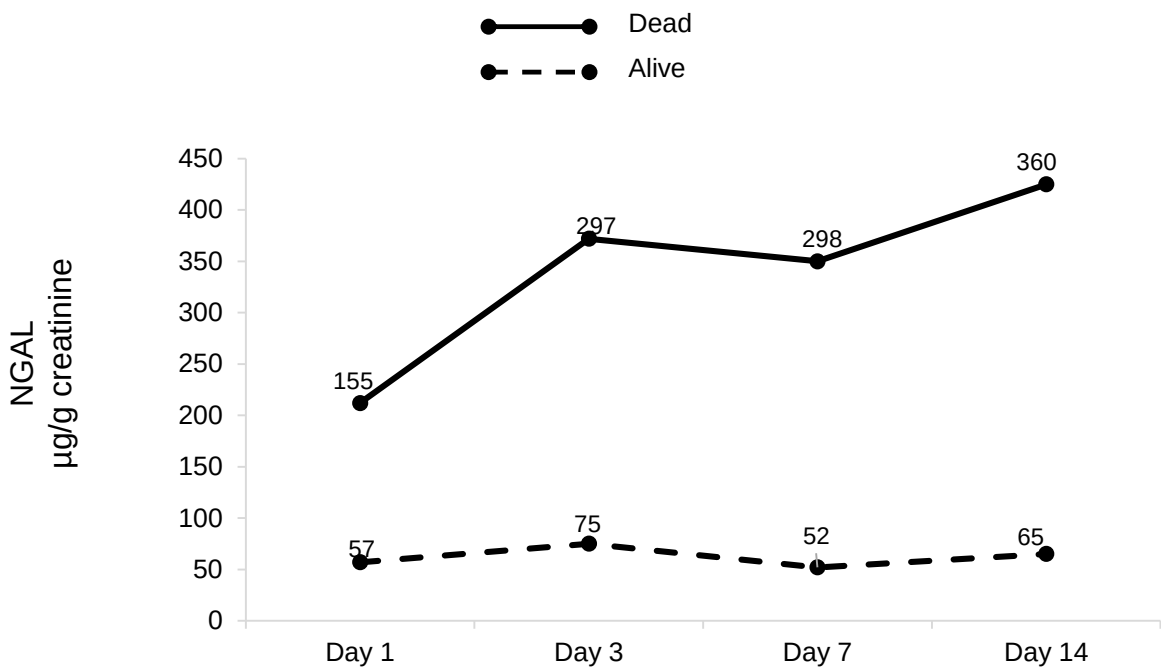


Patients at risk	202	202	142	69



Patients at risk	214	214	96	47

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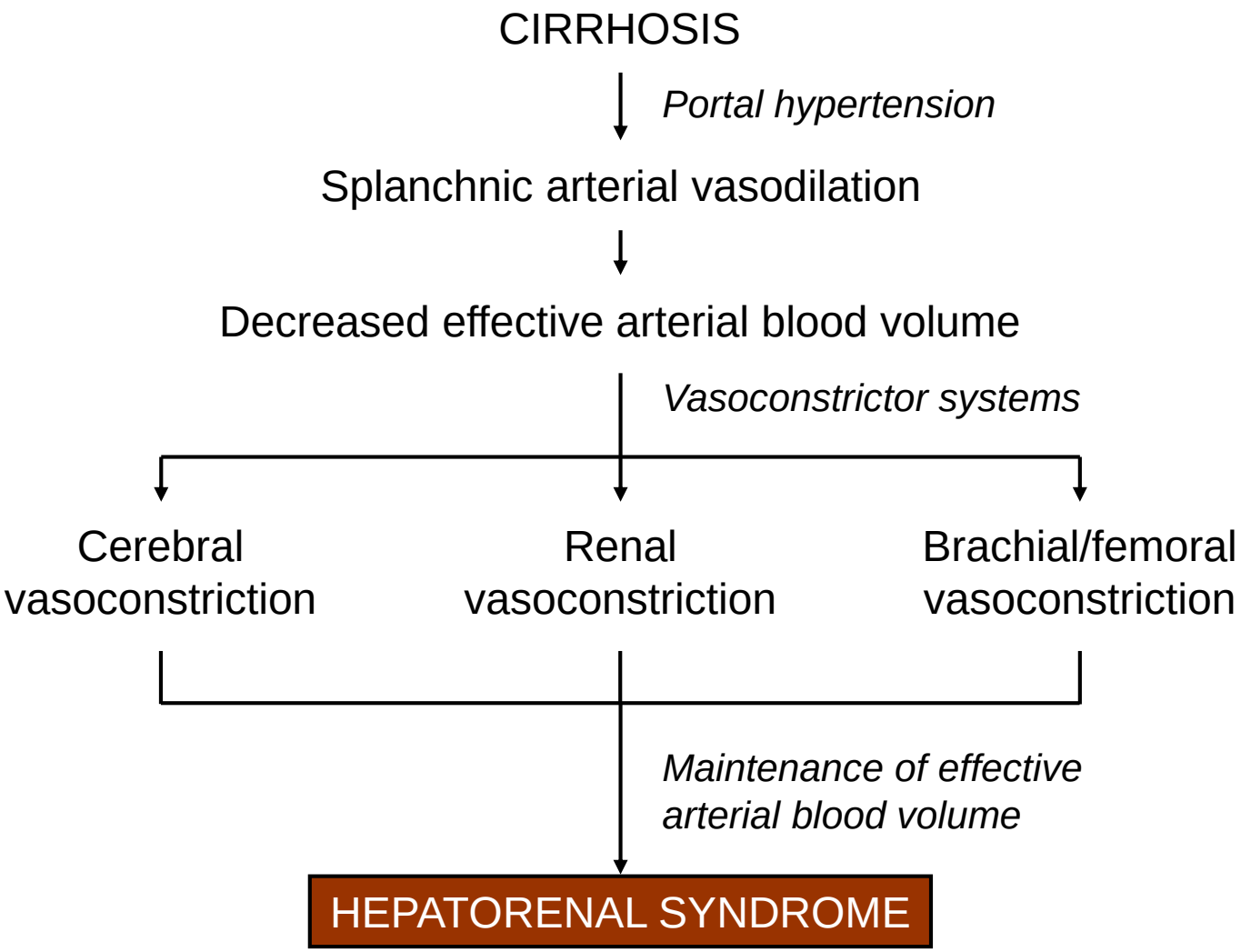
VASOCONSTRICTORS AND ALBUMIN FOR HEPATORENAL SYNDROME



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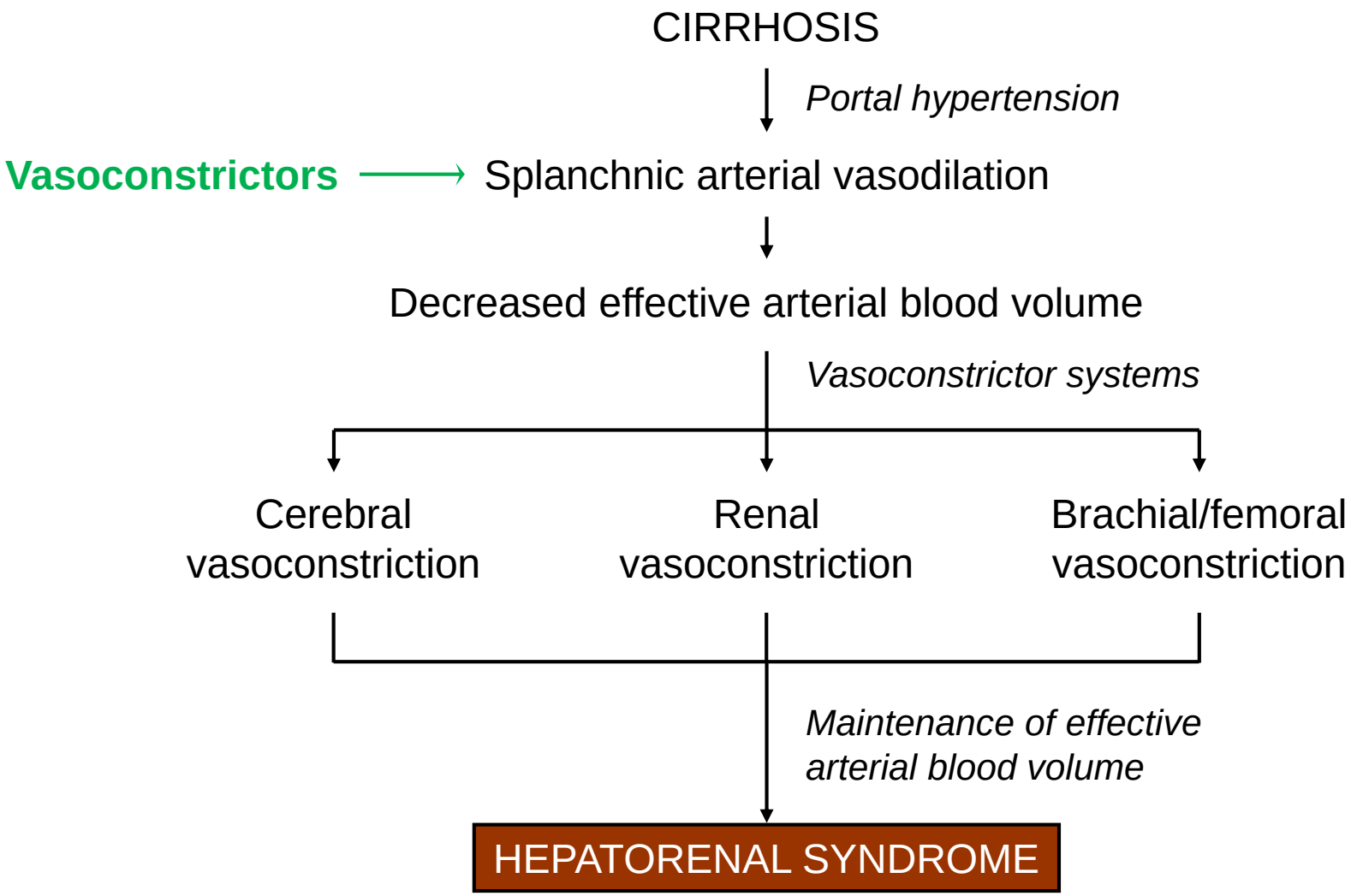

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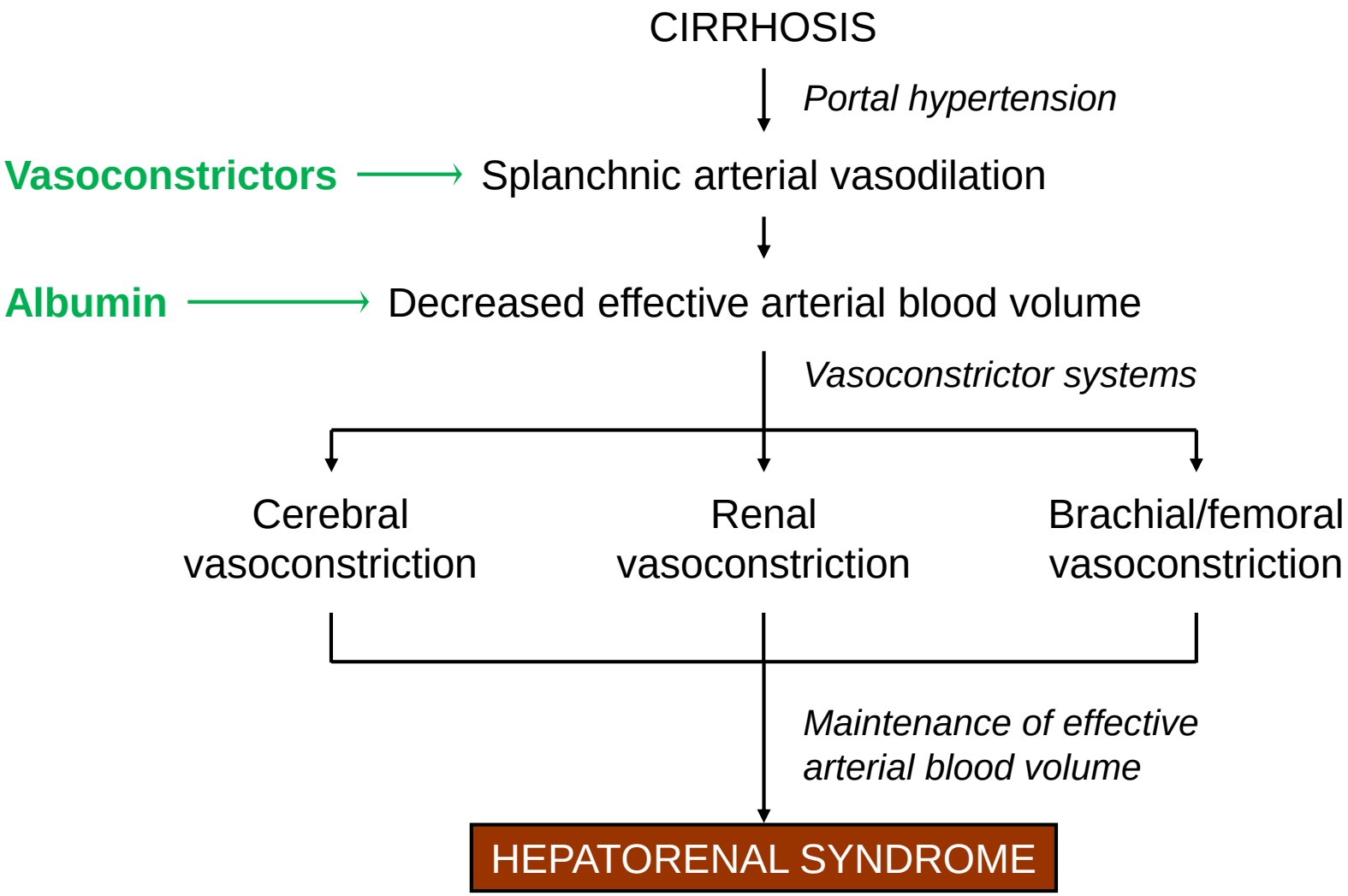


CLINICAL TRIALS ON TERLIPRESSIN FOR HRS

Randomized clinical trial	Treatment response (%)[a]		3-month overall survival (%)		Refs
	Terlipressin	Placebo and/or control	Terlipressin	Placebo and/or control	
Solanki et al., 2003	42	0	42[b]	0[b]	110
Neri et al., 2008	80	19	54	18	109
Martin-Llahi et al., 2008	43.5	8.7	27	19	29
Sanyal et al., 2008	34	13	42.9[c]	37.5[c]	28
Cavallin et al., 2015[d]	55.5	4.8	59	43	103
Boyer et al., 2016	19.6	13.1	57.7	54.5	104

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

MANAGEMENT OF HEPATORENAL SYNDROME

Current Guidelines

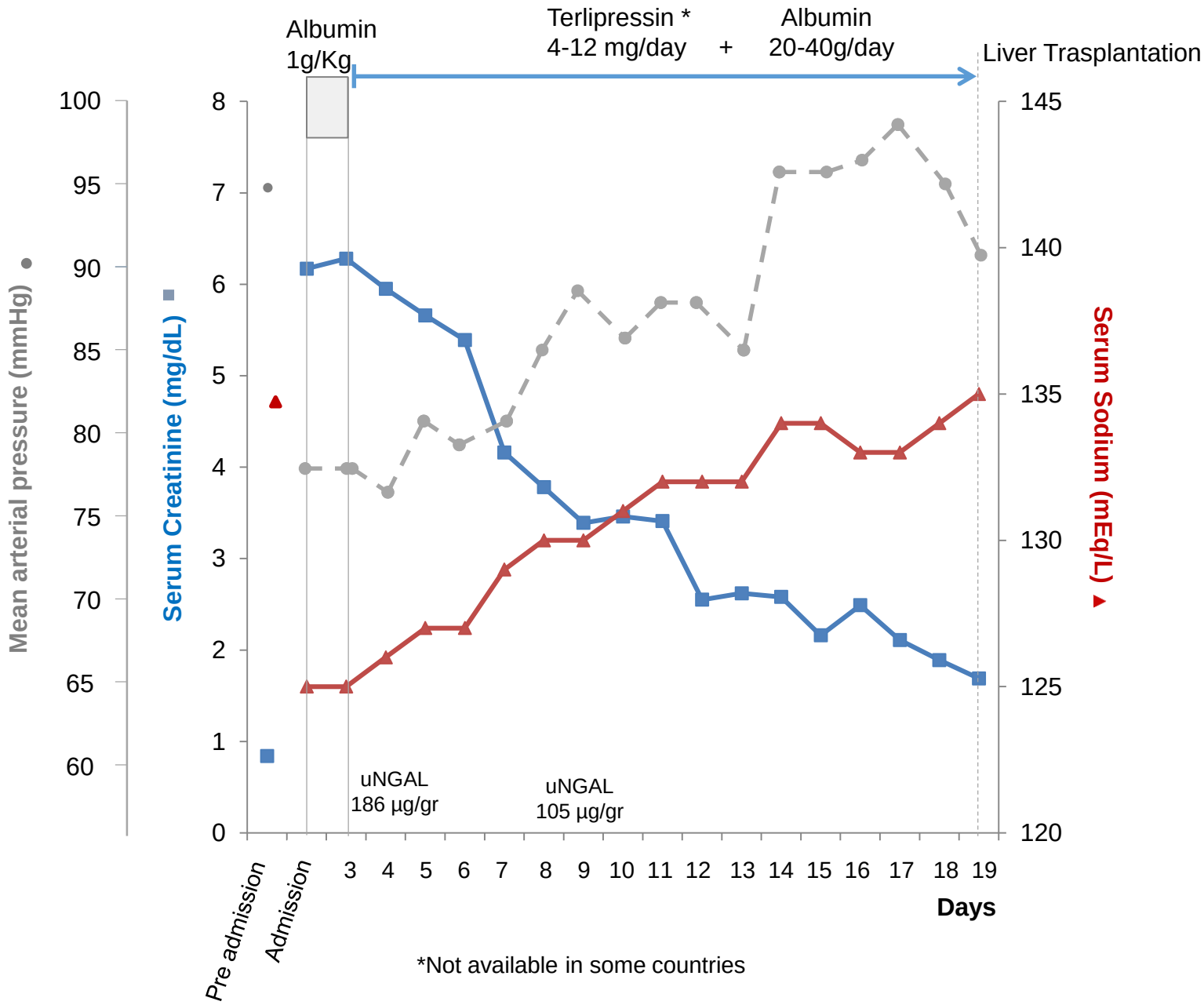
- Terlipressin in combination with albumin should be considered the first line therapeutic agent for type-1 HRS. Use other vasoconstrictors if terlipressin is not available

EASL Clinical Practice Guidelines, J Hepatol, 2010

- Telirpressin and albumin is the first line therapy for AKI-HRS, preferably as continous iv infusion starting at 2 mg/day and increasing up to 12 mg/day, if no response.

EASL Clinical Practice Guideliness, J Hepatol 2018

HRS. CASE DESCRIPTION



*Not available in some countries

MANAGEMENT OF HEPATORENAL SYNDROME

Pros and cons of vasoconstrictor therapy

PROS	CONS
. Pathophysiologically-oriented	. Terlipressin not available in all countries
. Administration simple	. ICU required for norepinephrine treatment
. Low cost in Europe (unknown in USA)	in some countries
. Allows transplant without RRT in responders	. Ischemic side effects possible (up to 10%)
. Survival likely improved	. MELD score decreases in responders

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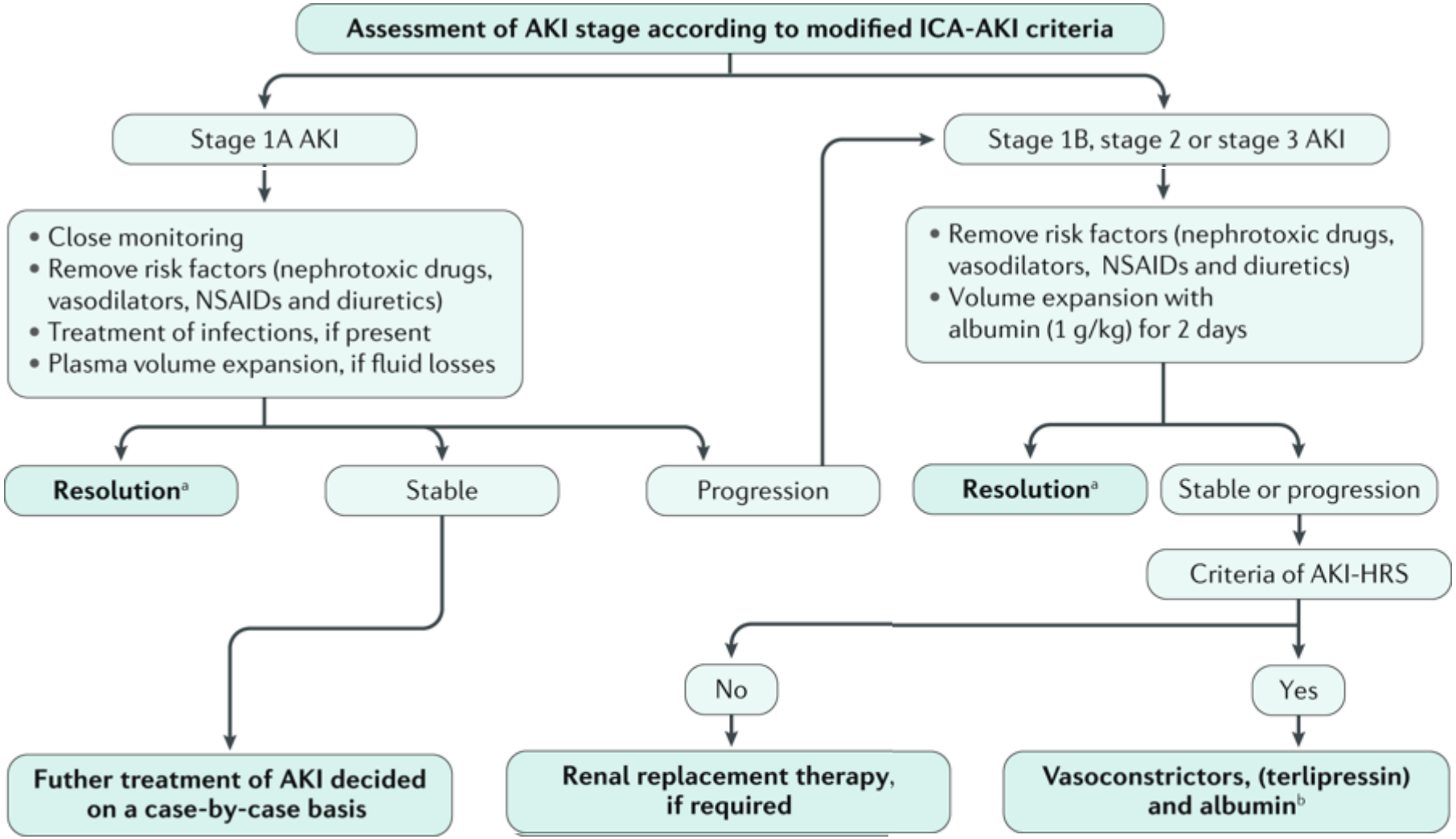
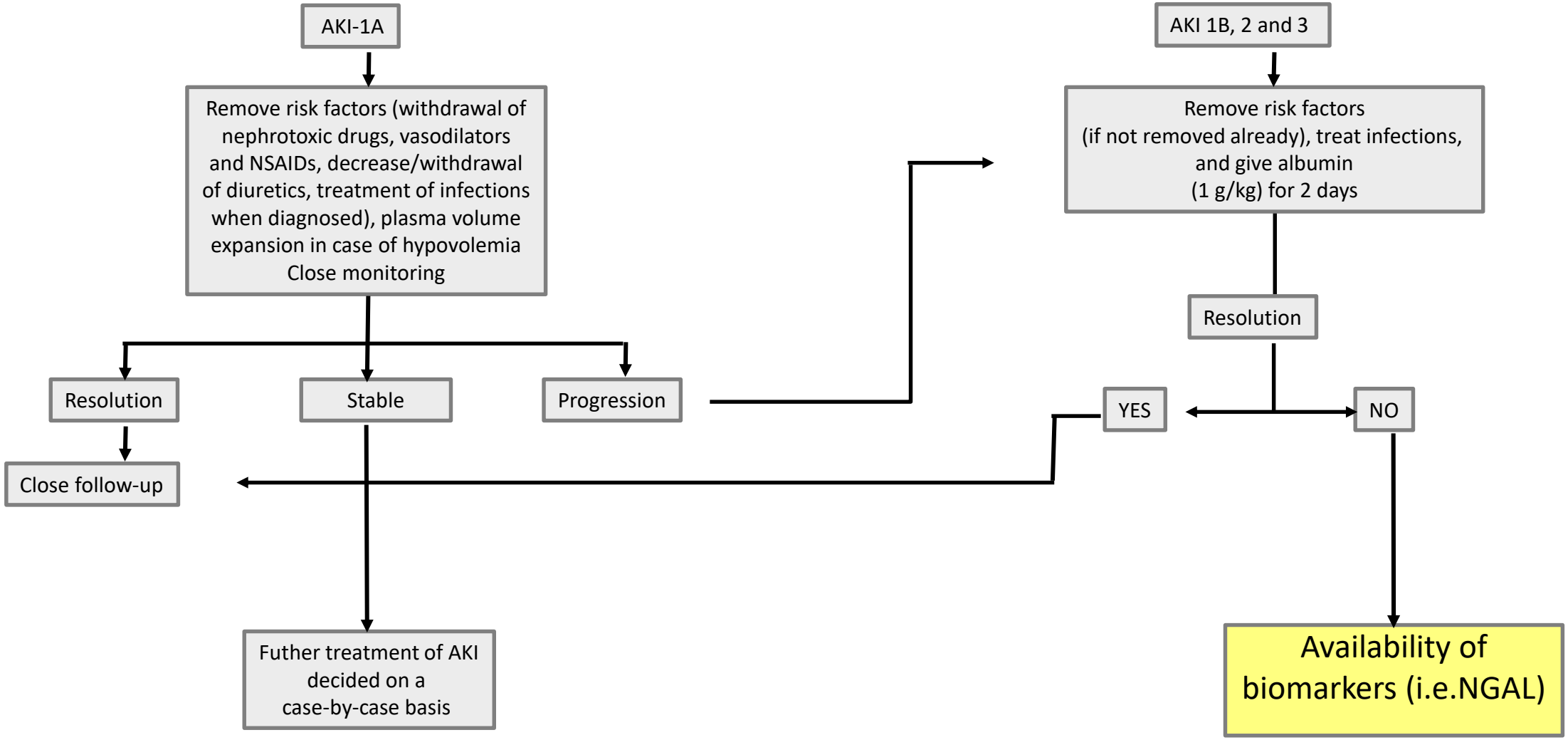
DIAGNOSIS AND MANAGEMENT OF AKI IN CIRRHOSIS



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

PROPOSED ALGORITHM FOR AKI DIAGNOSIS AND MANAGEMENT



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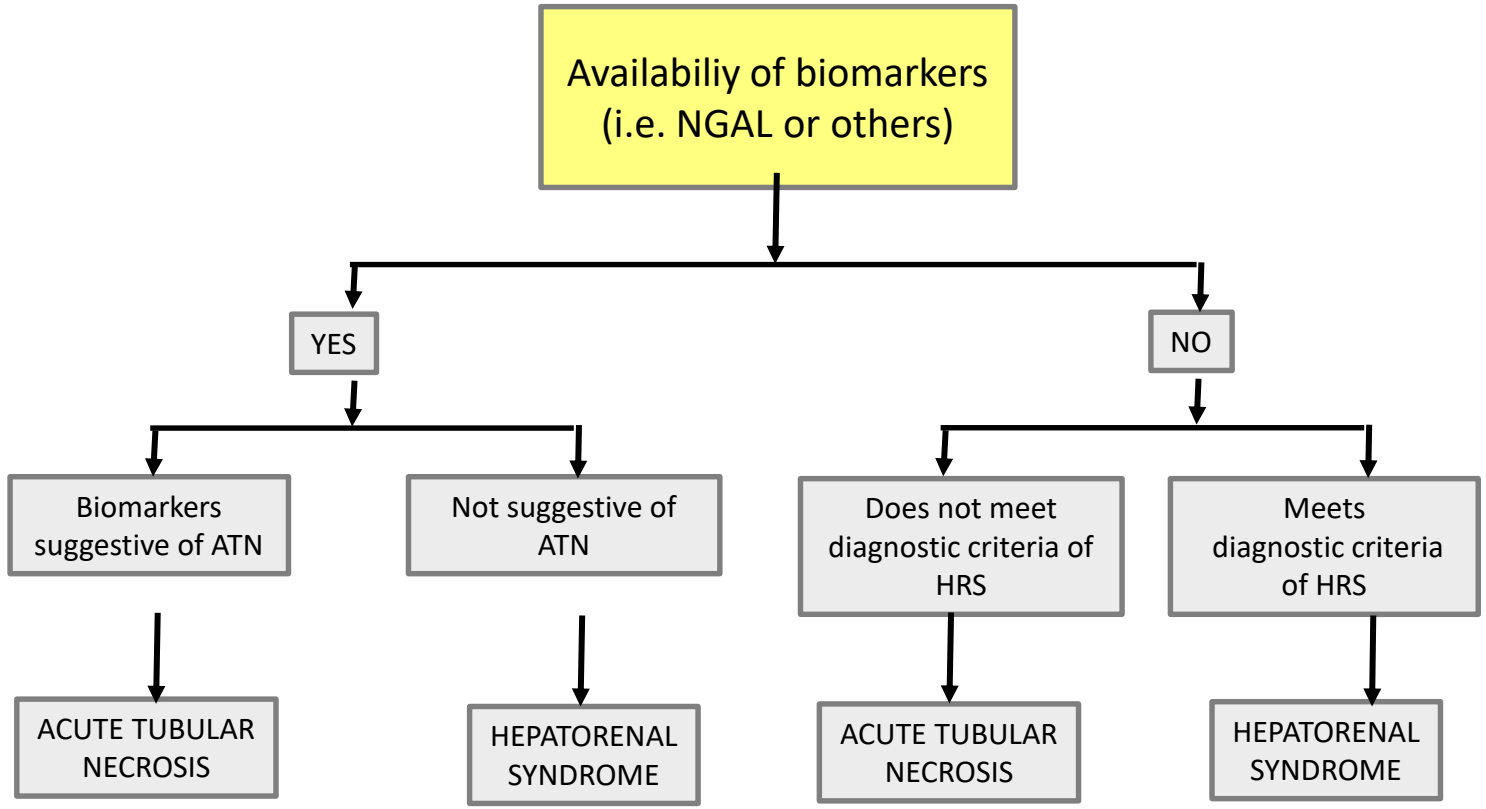

TAKE-HOME MESSAGES

- The new diagnostic criteria of AKI are helpful for early detection of impairment in kidney function
- Categorization of patients with AKI stage 1 into 1A and 1B identifies subgroups with very different kidney and patient outcomes
- Development of AKI is associated with an impaired prognosis. Etiology of AKI is an important determinant of prognosis, mortality being higher for hepatorenal syndrome and acute tubular necrosis vs hypovolemia-induced AKI
- Rapid identification of the etiology of AKI is very important to start specific therapy, particularly terlipressin for patients with AKI-HRS. Kidney biomarkers are helpful in the differential diagnosis between ATN and HRS.

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FREEDOM FOR POLITICAL PRISONERS IN SPAIN!!

19 politicians in prison (for an average of 10 years each) or in exile

Many others awaiting trials

... just for organizing
a referendum

While the former dictator is still honored