Acute Kidney Injury in Patients with Cirrhosis

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REVIEW ARTICLE

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Acute Kidney Injury in Patients with Cirrhosis

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Outline

- Background
- Definitions of AKI and HRS
- Pathophysiology
- Assessment of kidney function
- Diagnostic workup and Management
- Treatment of HRS-AKI
- Prevention of AKI
- Conclusions

Background

- **AKI: 50%** of hospitalized patients with cirrhosis and in 58% of this patients in ICU.

- Hepatorenal syndrome (HRS): renal hypoperfusion due to **renal vasoconstriction**.

- AKI etiology in cirrhosis patients
  - Hypoperfusion from **hypovolemia: 50%**
  - Intrinsic causes (e.g., ATN) : 30%
  - **HRS: 15 - 20%**
  - Postrenal obstruction: < 1%

Definitions of AKI and HRS

- KDIGO-AKI:
  - SCr >= 0.3 mg/dl (26.5 μmol/L) within 48 hrs
  - SCr >= at least 1.5 times the baseline level within 7 days
- HRS: **No threshold value** for the SCr level (1.5 mg/dl), earlier **woman, elderly, sarcopenia**.
- **HRS-AKI (Type 1): SCr >= 2.5 mg/dl** (221.0 μmol/L) **within 2 weeks.**
- HRS-CKD (Type 2): chronic course, > 2 weeks
- **Urine output criteria**: sensitive, **poor prognosis**.

Table 1. Definitions of Acute Kidney Injury (AKI) and the Hepatorenal Syndrome (HRS) in Patients with Cirrhosis.*

Variable or Definition	International Ascites Club, Salerno et al.[7] (2007)	Acute Disease Quality Initiative, Nadim et al.[8] (2012)	International Club of Ascites, Angeli et al.[9] (2015)	Angeli et al.[10] (2019)
Baseline serum creatinine level	—	—	Serum creatinine measured in previous 3 mo; in patients with >1 value within previous 3 mo, the value closest to time of hospital admission should be used; in patients without a previous serum creatinine value, the value on admission should be used as baseline	Similar to 2015 definition[9]
AKI	—	Increase in serum creatinine ≥0.3 mg/dl within 48 hr or increase ≥1.5 times baseline level	Increase in serum creatinine ≥0.3 mg/dl within 48 hr or increase ≥1.5 times baseline level, which is known or presumed to have occurred within previous 7 days	Absolute increase in serum creatinine ≥0.3 mg/dl within 48 hr or≥1.5 times baseline level or urinary output <0.5 ml/kg/hr in 6 hr
AKI stage	—	Stage 1: increase in serum creatinine ≥0.3 mg/dl or ≥1.5–2 times baseline level Stage 2: increase in serum creatinine >2–3 times baseline level Stage 3: increase in serum creatinine >3 times baseline level or ≥4.0 mg/dl with an acute increase ≥0.5 mg/dl or initiation of renal-replacement therapy	Similar to 2012 definition[8]	Similar to 2012 definition[8]
HRS	Cirrhosis with ascites Serum creatinine >1.5 mg/dl with no improvement (decrease ≤1.5 mg/dl) after at least 2 days of diuretic withdrawal and volume expansion with albumin (1 g/kg/day, maximum of 100 g/day) Absence of shock No current or recent treatment with nephrotoxic drugs Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria >50 red cells/high-power field, or abnormal renal findings on ultrasonography	Similar to 2007 definition[7]	Similar to 2007 definition,[7] except for removal of serum creatinine >1.5 mg/dl and inclusion of AKI diagnosis according to KDIGO serum creatinine criteria (i.e., increase in serum creatinine ≥0.3 mg/dl within 48 hr or ≥1.5 times baseline level)	Similar to 2015 definition,[9] except for addition of urinary output <0.5 ml/kg/hr for ≥6 hr as a criterion for AKI; suggestion of HRS-AKI with FeNa of <0.2% (FeNA <0.1% highly predictive)

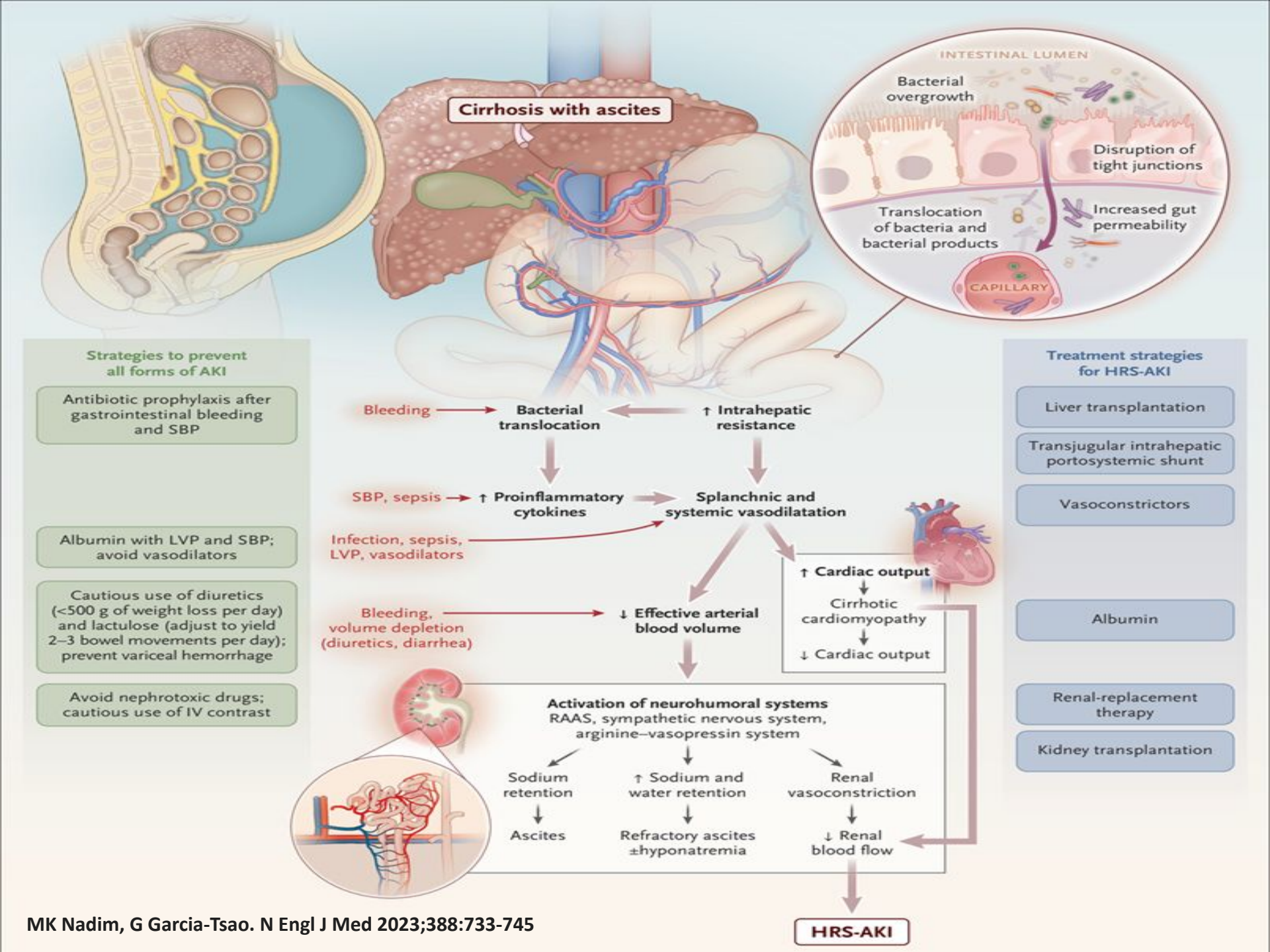
HRS type 1	Rapid, progressive renal failure, defined by doubling of initial serum creatinine (to a level >2.5 mg/dl) in <2 wk	A specific form of AKI	—	HRS-AKI: absolute increase in serum creatinine ≥0.3 mg/dl within 48 hr or increase in serum creatinine >1.5 times baseline level; or urinary output <0.5 ml/kg/hr for 6 hr
HRS type 2	Serum creatinine increased from 1.5 to 2.5 mg/dl, with steady or slowly progressive course; typically associated with refractory ascites	A specific form of CKD	—	HRS-CKD: eGFR <60 ml/min/1.73 m^2 for ≥3 mo in the absence of other (structural) causes HRS-AKD: eGFR <60 ml/min/1.73 m^2 for <3 mo in the absence of other (structural) causes or <50% increase in serum creatinine with last outpatient value within previous 3 mo as baseline level
Response to therapy	Complete response (reversal of HRS): decrease in serum creatinine to <1.5 mg/dl Partial response: decrease in serum creatinine ≥50% of pretreatment level, without reaching level of <1.5 mg/dl No response: no decrease in serum creatinine or decrease to <50% of pretreatment level, with final level >1.5 mg/dl Relapse: increase in serum creatinine >1.5 mg/dl after discontinuation of therapy	—	Full response: return of serum creatinine to a level within 0.3 mg/dl of baseline level Partial response: regression of AKI stage, with reduction of serum creatinine to ≥0.3 mg/dl above baseline level No response: no regression of AKI	Similar to 2015 definition[9]

* To convert values for creatinine to millimoles per liter, multiply by 88.4. CKD denotes chronic kidney disease, eGFR estimated glomerular filtration rate, FeNa fractional excretion of sodium, and KDIGO Kidney Disease: Improving Global Outcomes.

Pathophysiology (1)

- **Cirrhosis**: distortion of the liver architecture (fibrosis and nodules) → increased intrahepatic resistance and vascular tone → **portal hypertension** → activation of vasodilators in the splanchnic circulation (the most important: NO) → progressive **splanchnic and systemic vasodilatation**

- **Intestinal dysbiosis**, bacterial overgrowth, and altered tight-junction proteins → increased of **bacterial translocation** → vasodilatation → reduction in the effective arterial blood volume → activation of neurohumoral systems(**RAAS, sympathetic, and arginine–vasopressin systems**)



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Pathophysiology (2)

- Activation of neurohumoral systems (RAAS, sympathetic, AVS) -> Na, water retention and ascites formation -> dilutional hyponatremia.

- Progressive vasodilatation -> vasoconstrictive systems (mainly **renin and angiotensin**) → renal vasoconstriction → renal hypoperfusion

- **Cirrhotic cardiomyopathy**: A relative decrease in cardiac output(C.O.) in this high C.O. HF → decreased renal perfusion.

Pathophysiology (3)

- **HRS-AKI**: reduced renal blood flow → decrease in GFR and a prerenal type that does **not respond to volume expansion**.

- Mechanism of renal vasoconstriction in patients with cirrhosis
  - **decrease production** of vasodilators (**prostaglandins**)
  - **local release** of vasoconstrictors such as **endothelin**

- Precipitating factors
  - rapid fluid loss (e.g., diuresis or GI bleeding)
  - worsening vasodilatation by drugs (e.g., ACEI)
  - systemic inflammatory response (e.g., infection)

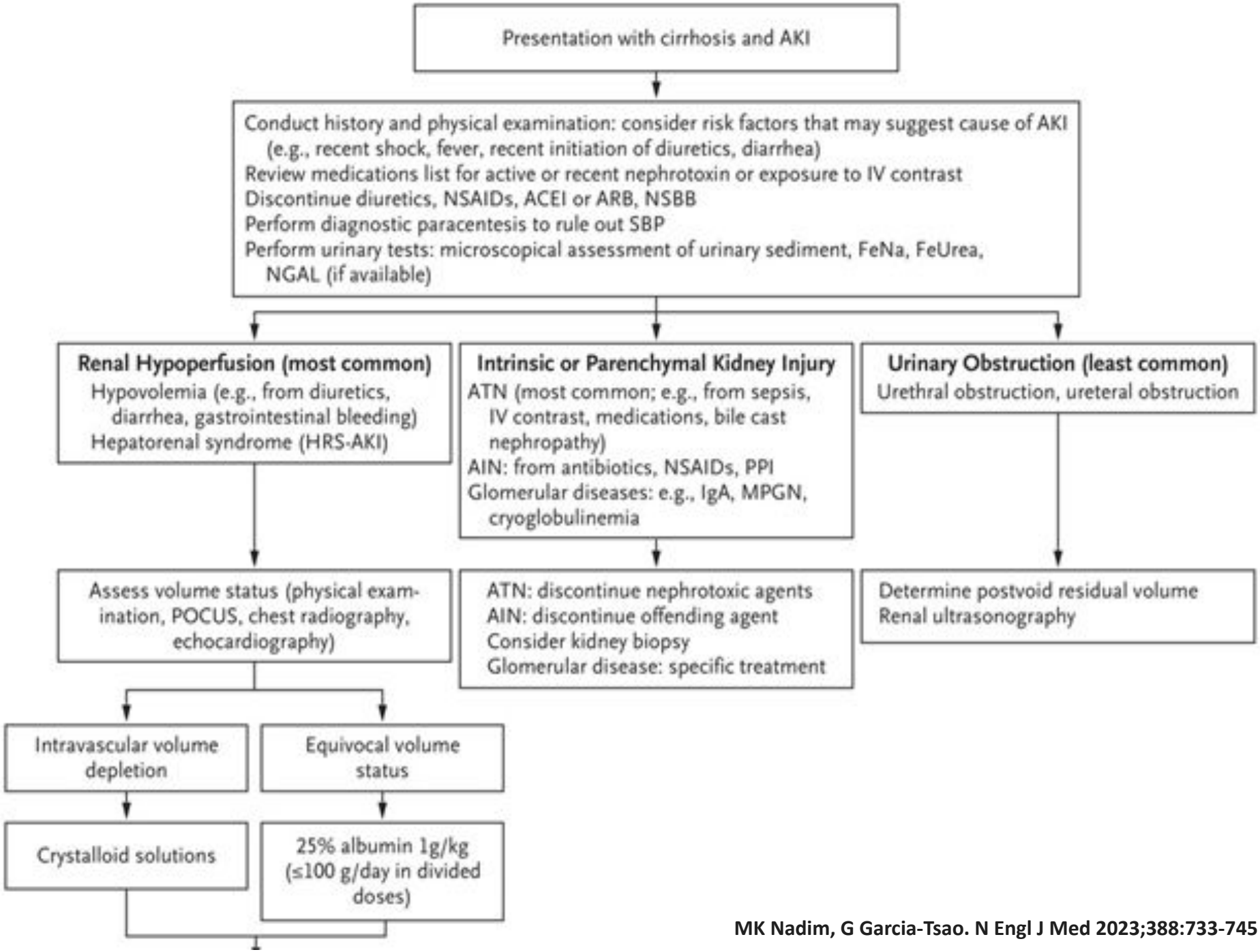
Assessment of Kidney Function

- The serum creatinine(Scr) level: overestimate
  - **decreased production**: liver disease, protein calorie malnutrition, and muscle wasting)
  - **dilutional effect**: fluid overload, ascites
- 24 hrs-CCr : collection error or increased tubular secretion of Cre as the GFR declines
- EGFR based on Cre and/or Cystatin C
  - **overestimate** the true GFR by **10 to 20 ml**
  - especially in eGFR < 40 and/or ascites

Diagnostic Workup and Management

- HRS-AKI (from ATN)
  - FENa < 0.1%
  - FEUrea < 21%
  - Urine albumin < 44 mg/dl
  - **Urine NGAL -> uncertain cut-off value**
- Discontinue the nephrotoxic agents: diuretics, vasodilators, nonselective beta-blockers, NSAIDs
- Treat/rule out infection: SBP
- **Volume expansion**: crystalloids vs. albumin

  → **24 - 48 hrs**, in hypo/euvolemic patients
- Paracentesis + IV albumin: removal < 5 L



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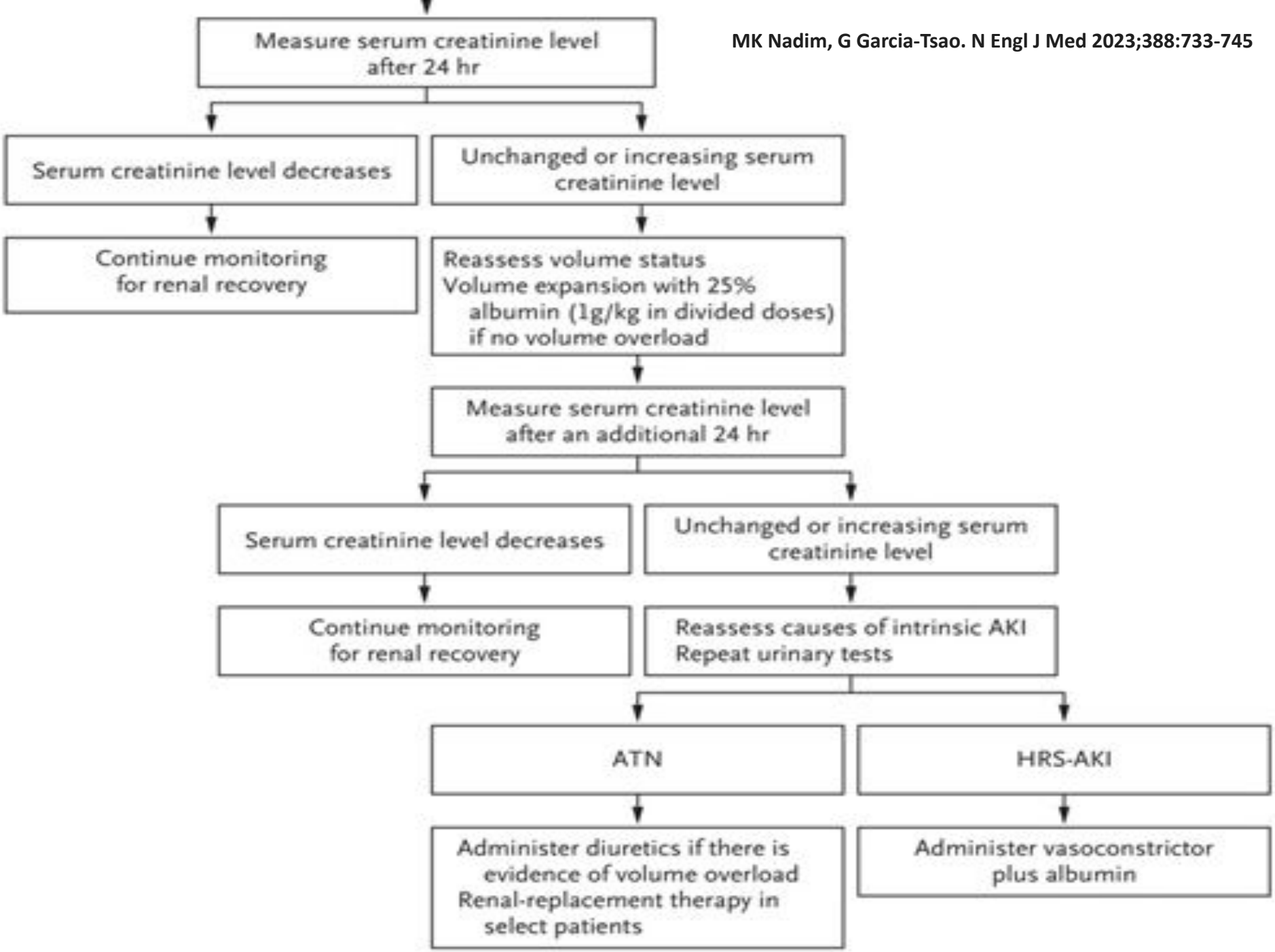

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Treatment of HRS

- Pharmacologic therapy: **Terlipressin + Albumin**
- Transjugular intrahepatic portosystemic shunt (**TIPS**): a pooled response of 93%
- Renal-replacement therapy: AEIOU
- **Liver transplantation: treatment of choice**

Pharmacologic therapy

- Changes in the SCr level correlate inversely with changes in MAP induced by vasoconstrictors.

- Regimen: vasoconstrictor **+ albumin**
  - **Terlipressin** (vasopressin analogue): first-line
    - IV bolus/**Continuous Infusion**: similar efficacy
    - increased incidence of pulmonary edema
  - **Norepinephrine**: similar efficacy with Terli
  - Octreotide + midodrine: low efficacy

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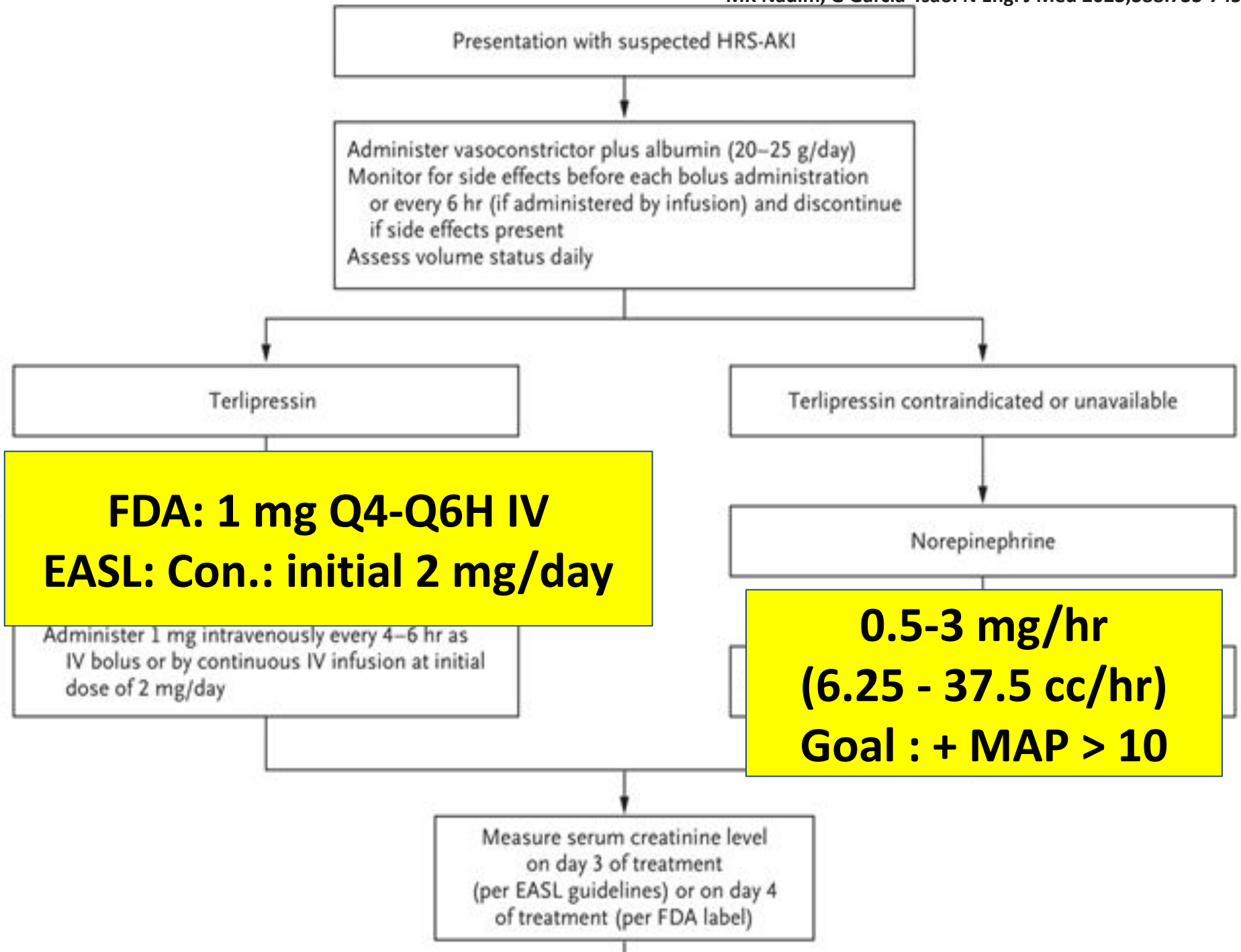

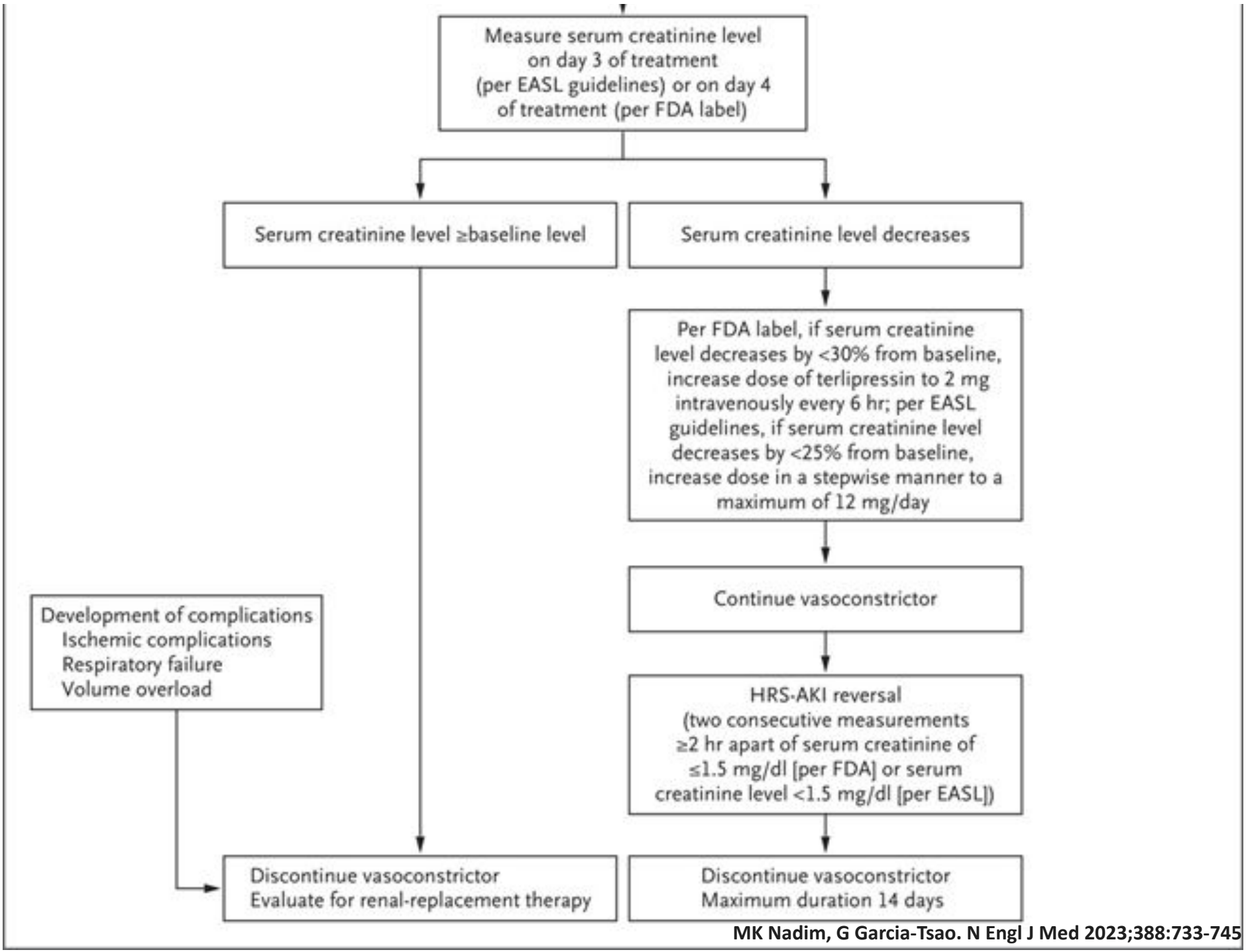

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Liver transplantation

- Simultaneous liver and kidney transplantation
- **Kidney biopsy** may assist in establishing the diagnosis and determining the reversibility of kidney dysfunction and the need for simultaneous liver and kidney transplantation
- Priority to patients with persistent, severe kidney dysfunction **after liver transplantation** to a kidney transplant **within the first year**.

Prevention of AKI

- Diuretics: **BW loss <**1 lb **(0.45 kg)/day**
- Lactulose: dose to defecation BID-TID
- Prevention of variceal hemorrhage
- IV **albumin** infusions: **4 - 6 g/L of ascites**
  - Lower AKI rates and mortality of SBP
  - **No long-term use (increased pulmonary edema)**
- Avoid nephrotoxic agents

  → e.g., beta-lactam antibiotics and **proton-pump inhibitors cause allergic interstitial injury**.

同場加映: 長期白蛋白輸注

- Design: **prospective**, interventional, multicenter, **open-label RCTs in UK**
- **N=777** (380 Albumin : 397 standard care)
- Population: Hospitalized patients with decompensated cirrhosis, acute complications, serum albumin < 3g/dl (**2.32 g/dl in average**)
- Exclusion: advanced HCC associated with a life expectancy of < 8 weeks and the receipt of palliative care.
- Intervention: 20% human **albumin infusion : 100 cc/hr since day 1 to 3**
- Goal: to serum albumin >= 3.5 g/dl within 3 days after admission
- **Follow 15 days**

同場加映: 長期白蛋白輸注

- The primary endpoint was a composite of
  - infection from any cause
  - kidney dysfunction
  - death in hospitalized patients between trial day 3 and day 15
  - the date of discharge (if before day 15)
  - the date on which the patient was MBD (if before day 15)

- **Median dose** of albumin group: **200 g albumin (10g/50cc/bot)**
- **No benefit / superior to standard care** in UK
- Increased pulmonary edema/respiratory failure in albumin group

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ORIGINAL ARTICLE

A Randomized Trial of Albumin Infusions in Hospitalized Patients with Cirrhosis

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*A complete list of the ATTIRE Trial Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Albumin Group (N=380)	Standard-Care Group (N=397)
Mean age — yr	53.8±10.6	53.8±10.7
Female sex — no. (%)	123 (32.4)	104 (26.2)
Admitted to ward — no. (%)	370 (97.4)	384 (96.7)
Admitted to intensive care unit — no. (%)	8 (2.1)	10 (2.5)
Cause of cirrhosis — no. (%)†		
Alcohol	347 (91.3)	350 (88.2)
Hepatitis C	24 (6.3)	35 (8.8)
Nonalcoholic fatty liver disease	26 (6.8)	29 (7.3)
Reason for admission — no. (%)†		
Encephalopathy	80 (21.1)	69 (17.4)
Suspected variceal bleed	52 (13.7)	63 (15.9)
New-onset or worsening ascites	236 (62.1)	281 (70.8)
Infection — no. (%)		
Diagnosis of infection at randomization by site medical team	98 (25.8)	113 (28.5)
Use of antibiotics	195 (51.3)	199 (50.1)

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Serum albumin level — no. (%)		
<20 g/liter	61 (16.1)	60 (15.1)
20–25 g/liter	207 (54.5)	224 (56.4)
26–29 g/liter	112 (29.5)	113 (28.5)
Physiological variable — median (IQR)		
Creatinine level — mg/dl	0.75 (0.58–0.97)	0.78 (0.64–1.06)
Bilirubin level — mg/dl	5.70 (2.75–10.47)	5.56 (2.63–9.68)
International normalized ratio	1.6 (1.4–1.9)	1.6 (1.4–1.9)
MELD score — median (IQR)‡	19.6 (15.4–22.9)	19.5 (15.4–23.4)
Baseline organ dysfunction — no. (%)		
Cerebral: grade III or higher hepatic encephalopathy	10 (2.6)	8 (2.0)
Circulatory: mean arterial pressure <60 mm Hg	10 (2.6)	6 (1.5)
Respiratory: Spo_2:Fio_2 ratio		
Grade 0: >357	345 (90.8)	367 (92.4)
Grade 1: >214 to ≤357	29 (7.6)	23 (5.8)
Grade 2: ≤214 or mechanical ventilation	5 (1.3)	5 (1.3)
Renal: creatinine level ≥1.5 mg/dl	36 (9.5)	46 (11.6)

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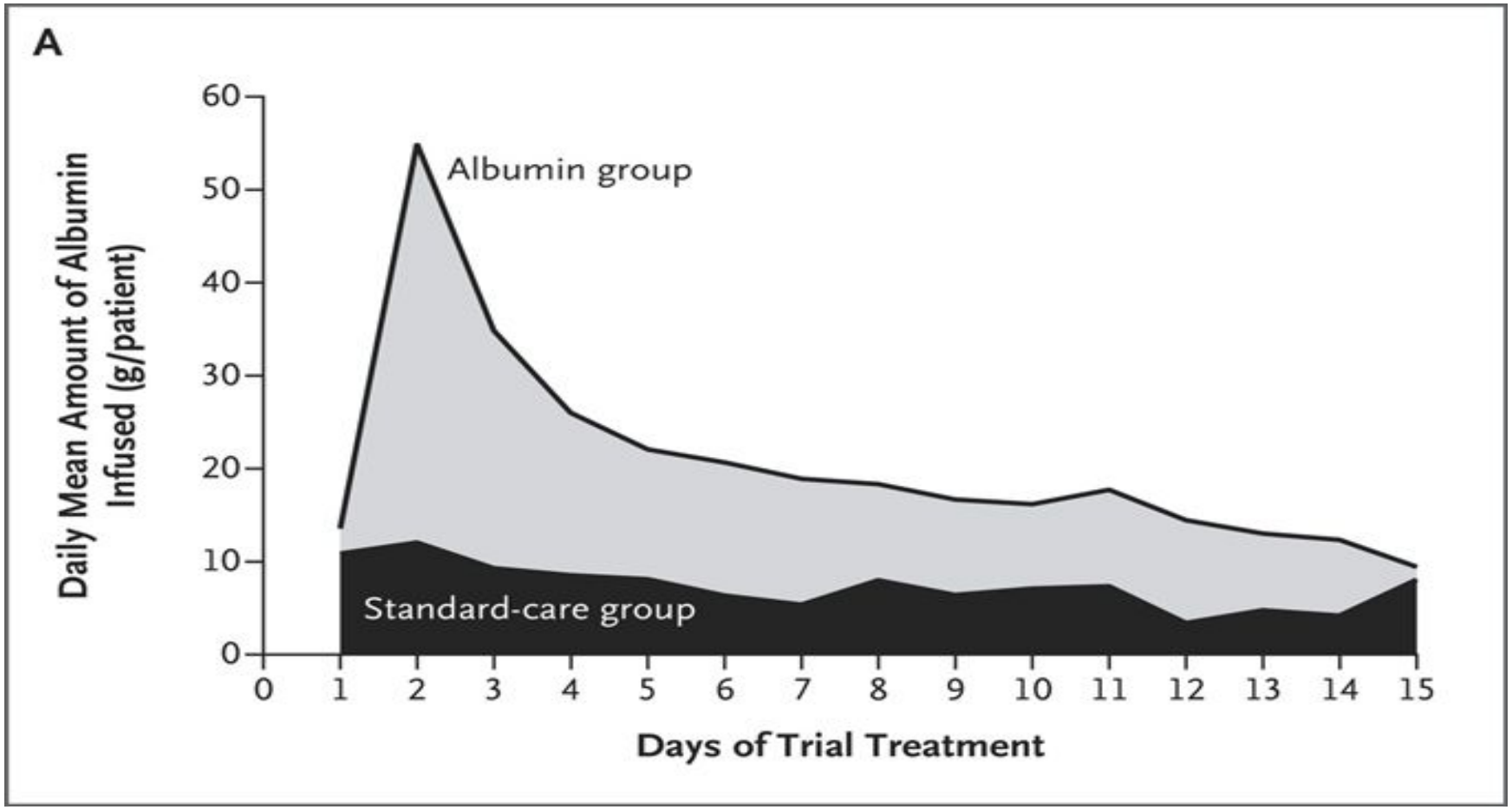

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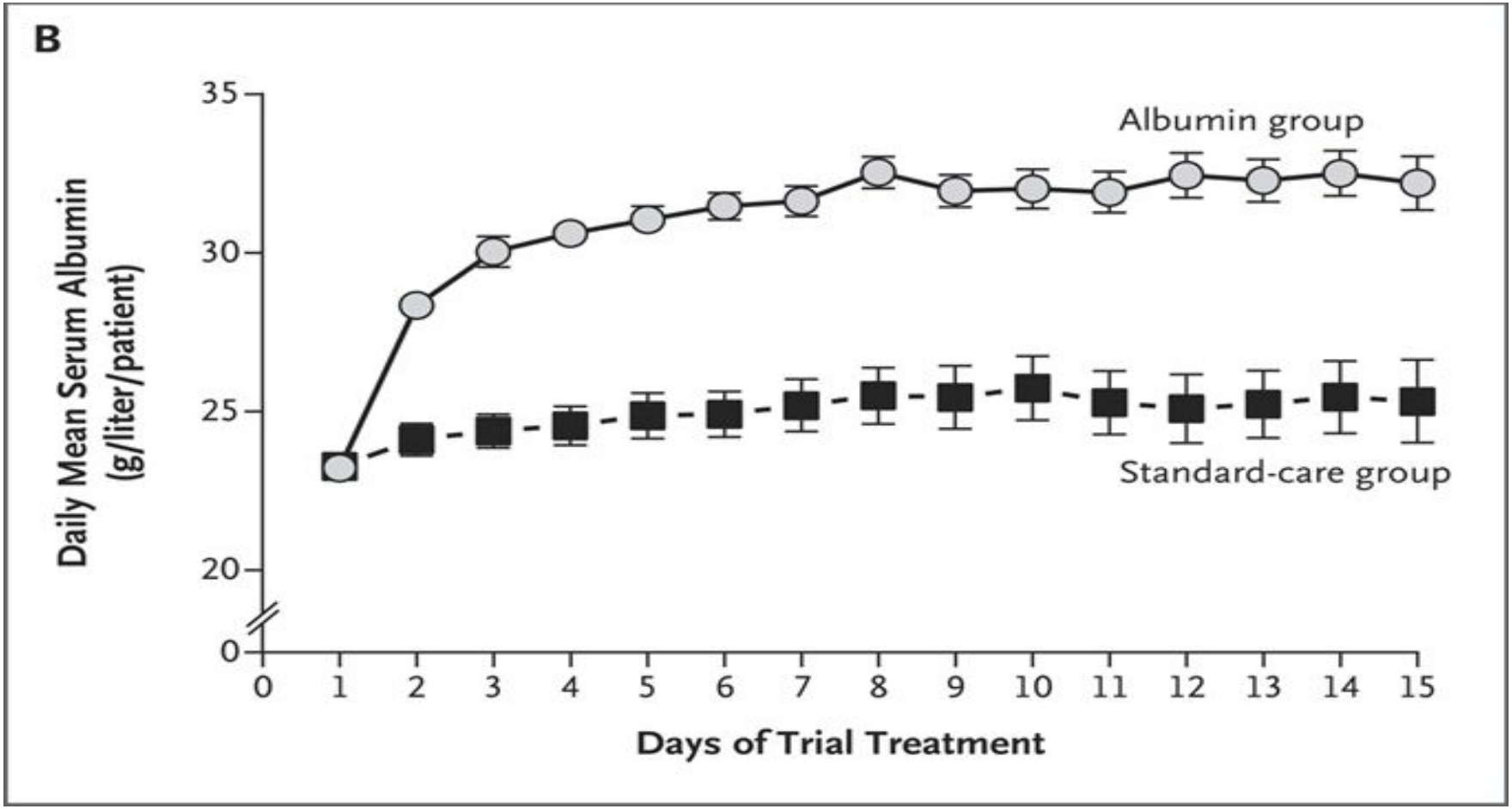

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Table 2. End Points.*

Variable	Albumin Group (N=380)	Standard-Care Group (N=397)	Adjusted Odds Ratio (95% CI)†	P Value
Composite primary end point — no. (%)	113 (29.7)	120 (30.2)	0.98 (0.71–1.33)	0.87
Components of composite primary end point — no. (%)‡				
Incidence of new infection	79 (20.8)	71 (17.9)	1.22 (0.85–1.75)	
Incidence of kidney dysfunction	40 (10.5)	57 (14.4)	0.68 (0.44–1.11)	
Incidence of death	30 (7.9)	33 (8.3)	0.95 (0.56–1.59)	
Death at 28 days	53 (14.0)	62 (15.6)	0.86 (0.57–1.30)	
Death at 3 mo	92 (24.2)	93 (23.4)	1.05 (0.74–1.48)	
Death at 6 mo	132 (34.7)	119 (30.0)	1.27 (0.93–1.73)	
Total median albumin infused per patient (IQR) — g	200 (140–280)	20 (0–120)	143 (127–158)§	

* Unless stated, the time of the end point is during the trial treatment period (15 days after randomization).
† Odds ratios are adjusted for stratification variables, with sites as random intercept terms.
‡ The end points are defined in the original trial protocol.[26]
§ This is the adjusted mean difference between the groups.

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Table 3. Serious Adverse Events.* L China et al. N Engl J Med 2021;384:808-817

Event	Albumin Group (N=380)	Standard-Care Group (N=397)	All Patients (N=777)
		number of events	
Serious adverse event			
Grade 3: severe event	28	11	39
Grade 4: life-threatening event	17	13	30
Grade 5: death	42	48	90
All events	87	72	159
Individual serious adverse events occurring in >1 patient†			
Anemia	1	1	2
Esophageal varices hemorrhage	5	6	11
Gastric hemorrhage	5	4	9
Multiorgan failure	23	31	54
Other infections and infestations: spontaneous bacterial peritonitis	0	5	5
Lung infection	15	8	23
Sepsis	4	3	7
Encephalopathy	4	1	5
Acute kidney injury	2	0	2
Adult respiratory distress syndrome	0	2	2
Hypoxia	1	1	2
Pleural effusion	1	1	2
Pulmonary edema	15	4	19
All serious adverse events that included pulmonary edema or gastrointestinal bleeding‡			
Any pulmonary edema or fluid overload	23	8	31
Any gastrointestinal bleeding	11	13	24

* Patients may have had more than one clinical diagnosis per serious adverse event. A serious adverse event was any new adverse event that was a life-threatening event or resulted in prolongation of an existing hospitalization.
† Serious adverse events are categorized with a single primary event name (graded by two assessors) according to the Common Terminology Criteria for Adverse Events, version 5.0 (2017).
‡ Serious adverse events were labeled by the investigators as involving a primary event but could have involved other contributing events.

Conclusions

- The extent to which the presence of **systemic inflammation** or underlying kidney parenchymal damage **limits the efficacy of treatment** in patients with HRS-AKI remains unknown.

- **Urinary biomarkers**
  - differential diagnosis of AKI
  - guide vasoconstrictor therapy
  - predict the reversibility of AKI after liver transplantation.

- The **amount of albumin** for the prevention and treatment of AKI and HRS-AKI
- Use of **point-of-care ultrasonography** to guide fluid repletion.

Take home messages

- Definition of HRS-AKI (type 1) /CKD (type 2)
- Terlipressin/Norepinephrine + Albumin
- Urinary biomarkers

Thank you!