HUMAN ALBUMIN USE IN INTENSIVE CARE

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Targu Mures – septembrie 2014

Utilizarea albuminei umane la pacientul critic

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Universitatea de Medicina si Farmacie ”Victor Babes” Timisoara

Anestezie si Terapie Intensiva

Targu Mures – septembrie 2014

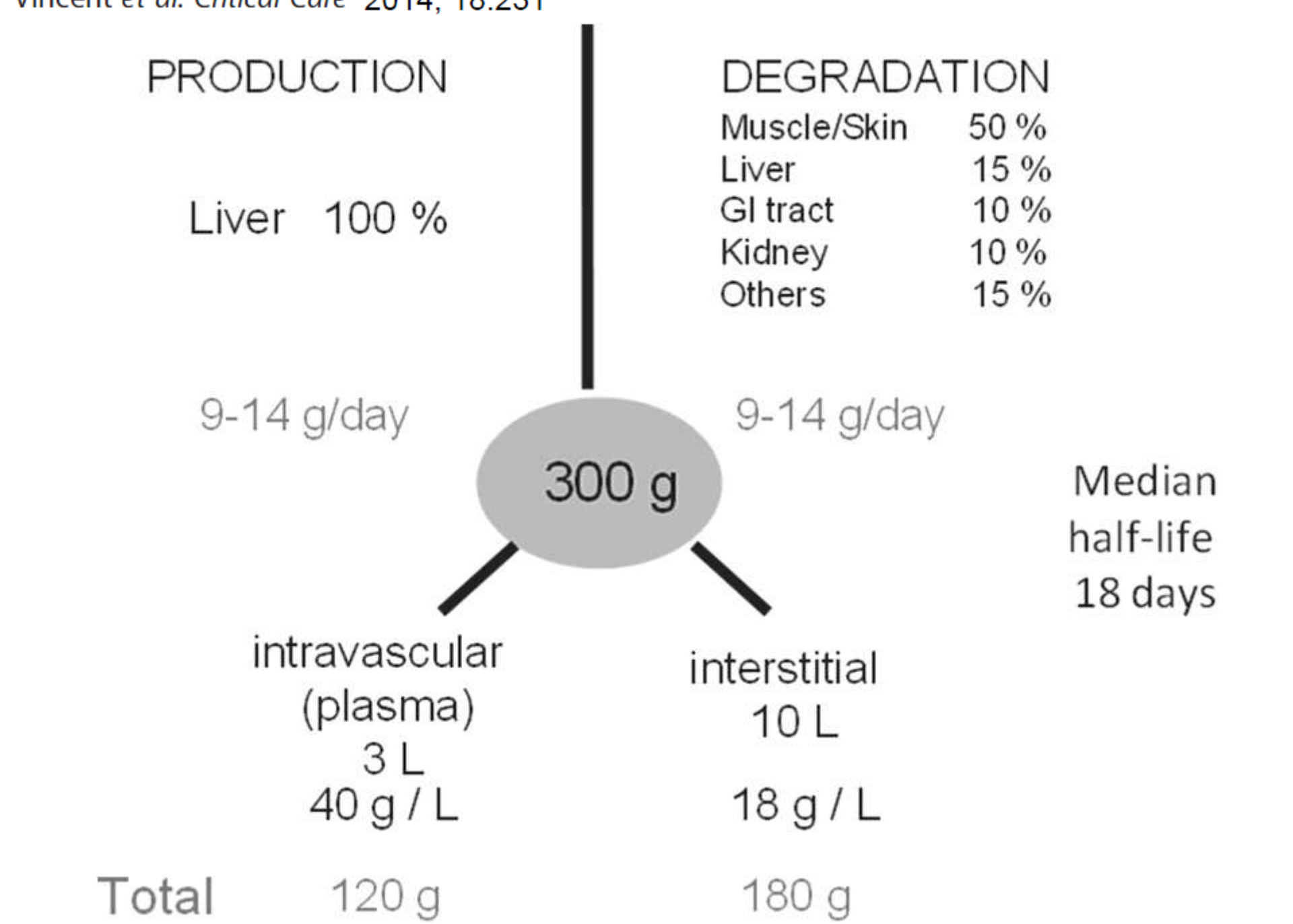

URGENTA

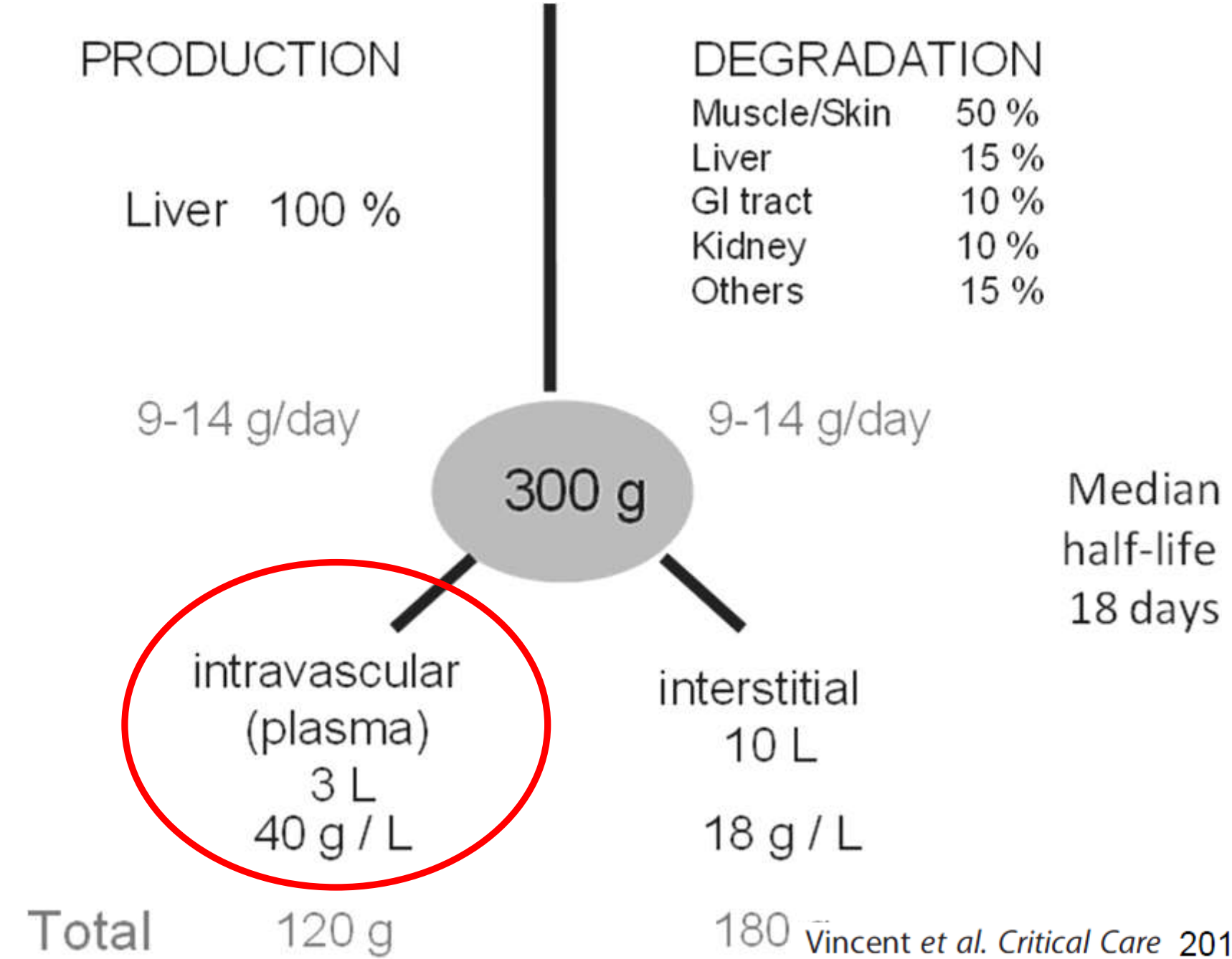
HUMAN ALBUMIN

Human albumin structure

- globular 66 kDa protein, 584 aminoacids
- three homologous domains that form a heart-shaped molecule
- water soluble
- negative charged
- non-glycosilated
- high capacity for binding water

Vincent *et al. Critical Care* 2014, 18:231





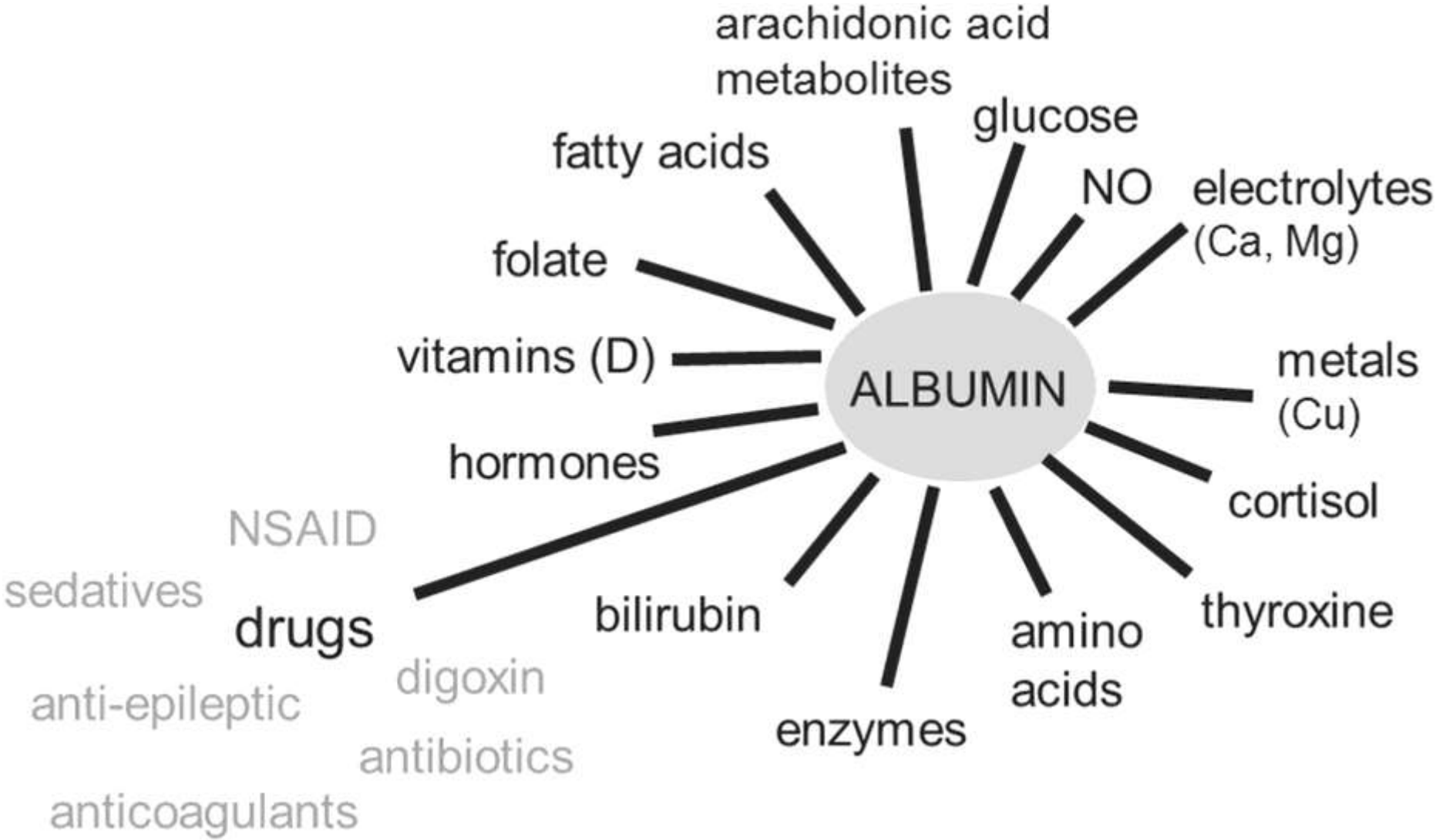
Vincent *et al. Critical Care* 2014, 18:231

Physiological functions of albumin in the plasma

Vascular	• Maintenance of oncotic pressure • Microvascular integrity
Transport	• Hormones (steroids, thyroxine) • Fatty acids • Bile salts • Bilirubin • Ca^{2+}, Mg^{2+}, and other metals (copper, zinc) • Drugs: - warfarin - diazepam
Metabolic	• Acid–base balance • Antioxidant • Anticoagulant

Boldt J. Br. J. Anaesth. 2010;104:276-284

BJA British Journal of Anaesthesia



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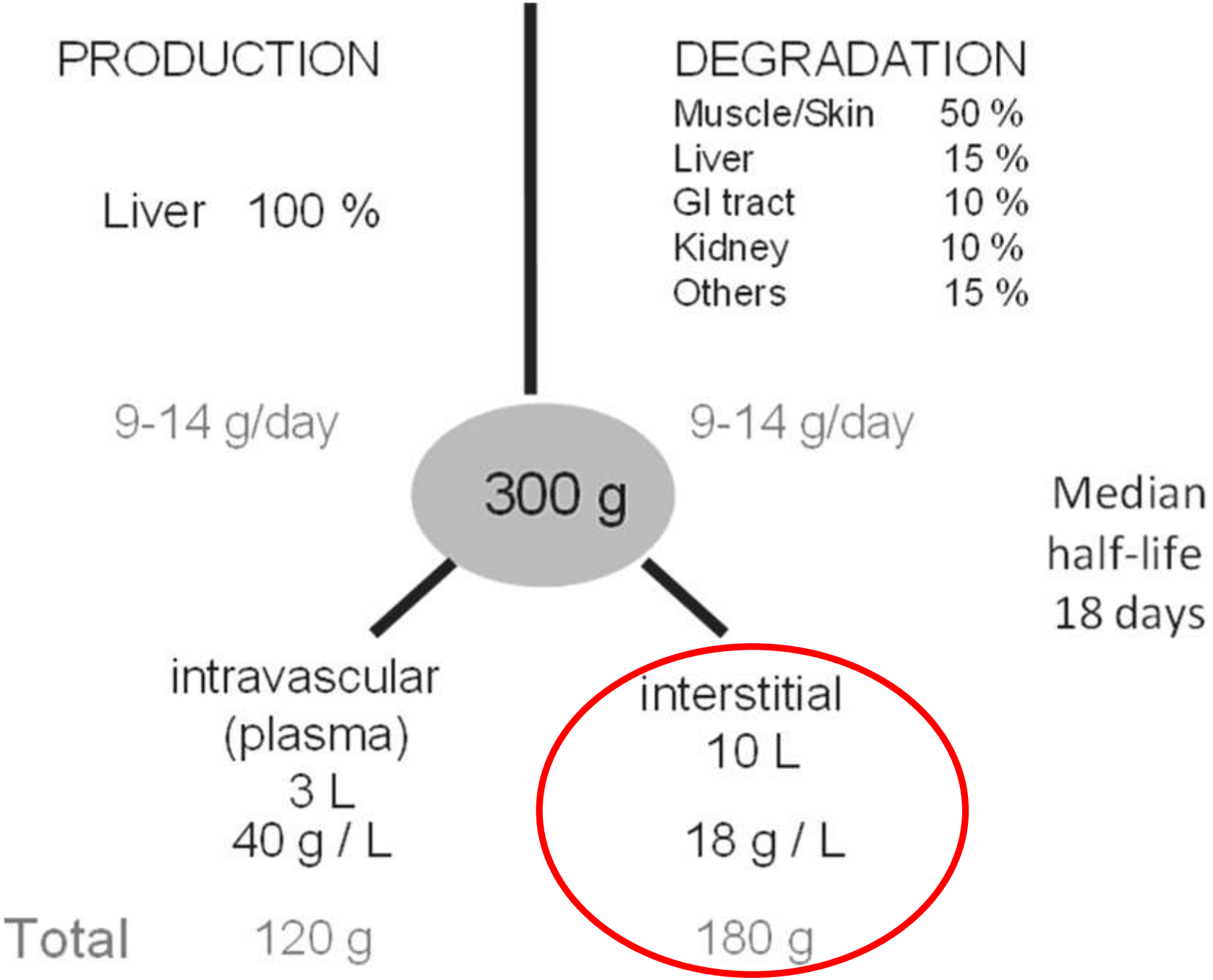

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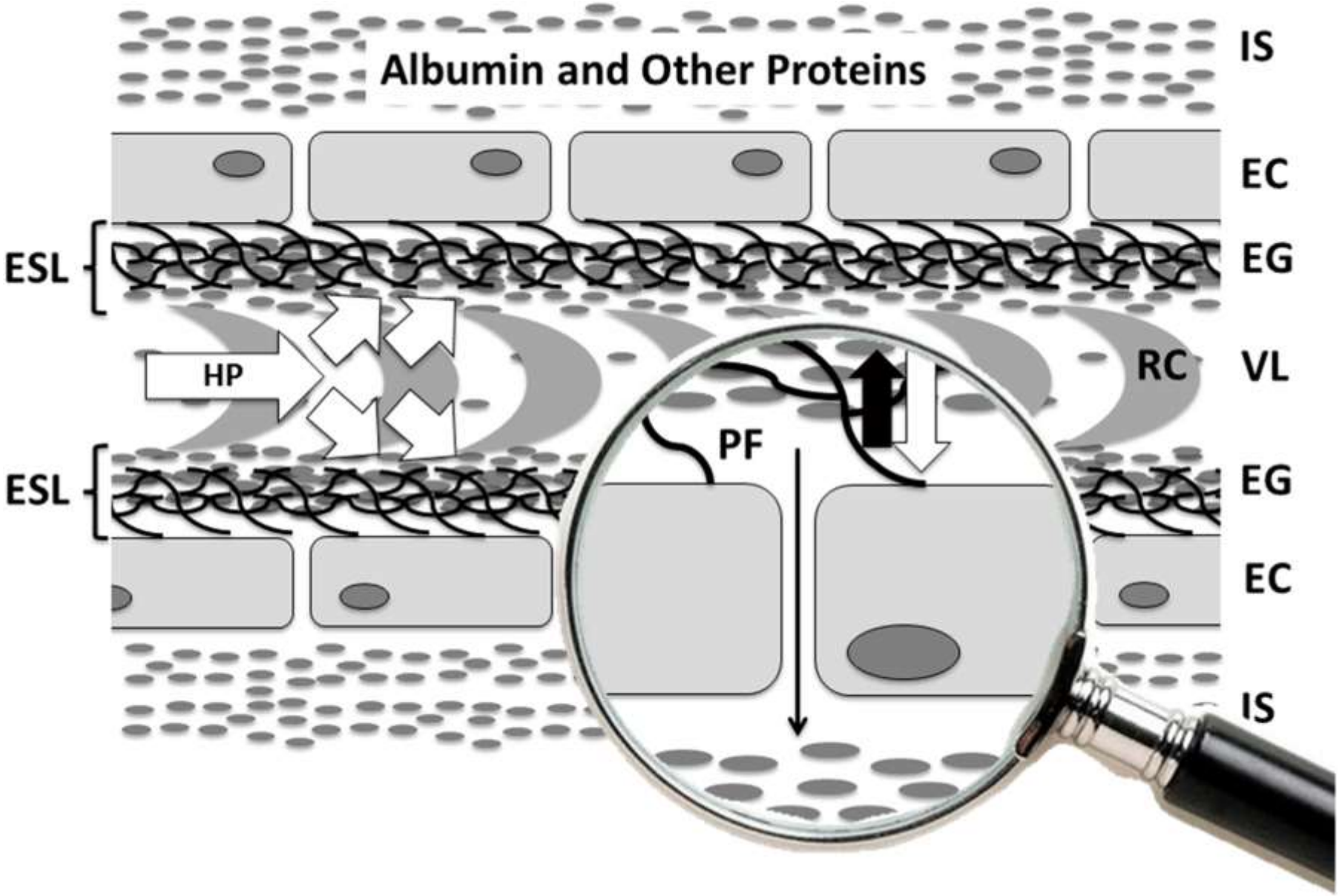

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Clinical conditions associated with increased albumin transvascular escape rate

- Hypertension
- Congestive heart failure
- Exercise
- Catecholamines
- Diabetes mellitus
- Infection, sepsis, and shock
- Hypothyroidism
- Major surgery and trauma
- Fluid loading
- Chemotherapy
- Vasculitis/glomerulonephritis
- Cardiopulmonary bypass
- Ischaemia/reperfusion
- Burns

Boldt J. Br. J. Anaesth. 2010;104:276-284

BJA British Journal of Anaesthesia

Hypoalbuminemia

- serum albumin concentration ≤3.0 g/dl
- very common in critically ill patients:
  - increased albumin losses (bleeding, gastrointestinal tract, renal)
  - increased capillary permeability (redistribution from the intravascular to the interstitial space)
  - dilution due to intravenous fluid administration
  - poor nutritional status
  - altered liver function

Hypoalbuminemia

Associated with:

- increased complications
- reduced short-term and longer-term survival in critically ill patients[1]
- each 1.0 g/dl decrease in serum albumin is associated with a 137% increase in risk of death, an 89% increase in morbidity and a 71% increase in length of hospital stay[2]

[1] Caironi P, Gattinoni L. Blood Transfus 2009, 7:259–267.

[2] Vincent JL, Dubois MJ, et al. Ann Surg 2003, 237:319–334.

Hypoalbuminemia

- There is an association between the severity of the injury and the albumin level[1]
- The effect of hypoalbuminemia on outcome is a cause – effect relationship or hypoalbuminemia is a marker of serious disease [2]

[1] Gibbs J, et al. Arch Surg 1999, 134:36–42

[2] Vincent et al. Critical Care 2014, 18:231.

Albumin story

Vincent *et al. Critical Care* 2014, 18:231
http://ccforum.com/content/18/4/231

CRITICAL CARE

REVIEW

Albumin administration in the acutely ill: what is new and where next?

Jean-Louis Vincent[1*], James A Russell[2], Matthias Jacob[3], Greg Martin[4], Bertrand Guidet[5,6], Jan Wernerman[7], Ricard Ferrer Roca[8], Stuart A McCluskey[9] and Luciano Gattinoni[10]

Key points in the albumin story so far

Year	Event
1941	First clinical use of human albumin solution in a patient with multiple trauma and circulatory shock
1943	One of the first published reports of human albumin use in 200 patients
1975	First randomized controlled trial of human albumin in 16 patients undergoing abdominal aortic surgery
1998	Cochrane meta-analysis including 30 randomized controlled trials and reporting increased mortality rates in critically ill patients who received albumin
1998	US Food and Drug Administration issued a 'Dear Doctor' letter to all healthcare providers expressing serious concern over the safety of albumin administration in the critically ill population, based on the findings of the Cochrane meta-analysis, and urging physicians to exercise discretion in its use

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Woodruff LM, Gibson ST: The clinical evaluation of human albumin. US Naval Med Bull 1943, 40:791–796.

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RCT conducted in just 16 patients, compared the effects of intraoperative use of albumin solution with those of a sodium-rich fluid during surgery and showed that albumin infusion led to less extracellular fluid expansion.

Skillman JJ. Randomized trial of albumin vs. Electrolyte solutions during abdominal aortic operations. Surgery 1975, 78:291–303.

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CONCLUSIONS:

There is no evidence that albumin administration reduces mortality in critically ill patients with hypovolaemia, burns, or hypoalbuminaemia and a strong suggestion that **IT MAY INCREASE MORTALITY.** These data suggest that use of human albumin in critically ill patients should be urgently reviewed and that it should NOT be used outside the context of rigorously conducted, randomised controlled trials.

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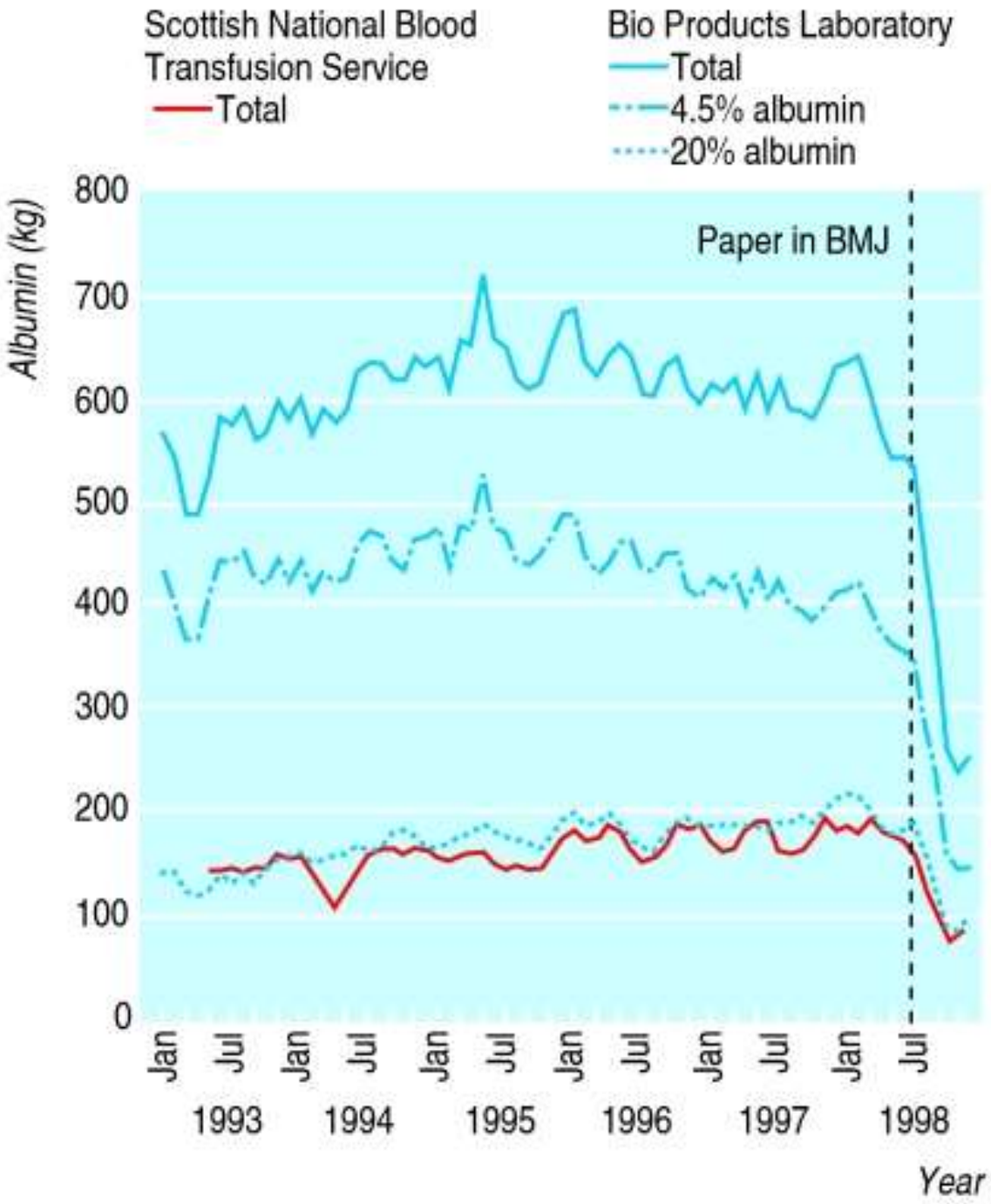
STOP
WRONG WAY
DO NOT ENTER



More on albumin. Use of human albumin in UK fell substantially when systematic review was published.

BMJ. May 1, 1999; 318(7192): 1214.

Cochrane Injuries Group Albumin Reviewers: Human albumin administration in critically ill patients: systematic review of randomised controlled trials. BMJ 1998, 317:235–240.

Limitations:

- Only 32 studies included in this meta-analysis
- Average patient sample was 46 / study
- No large multi-center RCT used

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1999	Study in 126 patients with cirrhosis and spontaneous bacterial peritonitis randomized to treatment with intravenous cefotaxime or cefotaxime and intravenous albumin; hospital and 3-month mortality rates were lower in the patients who received albumin
2001	Wilkes and Navickis' meta-analysis including 55 trials and reporting no overall effect of albumin on mortality
2003	Meta-analysis of 90 cohort studies evaluating hypoalbuminemia as an outcome predictor by multivariate analysis and nine prospective controlled trials evaluating use of albumin to correct hypoalbuminemia; results showed hypoalbuminemia to be a dose-dependent predictor of poor outcome and correction of serum albumin to >30 g/l associated with reduced complications
2004	Large SAFE study randomizing 6,997 patients to 4% albumin or normal saline when fluid challenge needed; results showed no difference in mortality rates among groups, and subgroup analyses suggested benefit in patients with severe sepsis and harm in those with traumatic brain injury
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Wilkes MM, Navickis RJ: Patient survival after human albumin administration. A meta-analysis of randomized, controlled trials. Ann Intern Med 2001, 135:149–164.

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Finfer S. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004, 350:2247–2256.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

The SAFE Study Investigators*

METHODS

We randomly assigned patients who had been admitted to the ICU to receive either 4 percent albumin or normal saline for intravascular-fluid resuscitation during the next 28 days. The primary outcome measure was death from any cause during the 28-day period after randomization.

RESULTS

Of the 6997 patients who underwent randomization, 3497 were assigned to receive albumin and 3500 to receive saline; the two groups had similar baseline characteristics.

CONCLUSIONS

In patients in the ICU, use of either 4 percent albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days.

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2006	Pilot study of 100 patients with serum albumin <30 g/l randomized to receive 200 ml of 20% albumin solution on the first day and then 200 ml/day if their serum albumin concentration remained <31 g/l, or to receive no albumin; organ function was improved in patients treated with albumin
2011	Meta-analysis including 17 studies in patients with sepsis reporting a survival benefit for patients who received albumin
2012	ESICM taskforce Consensus statement suggesting that albumin may be included in the resuscitation of severe sepsis patients (grade 2B)
2013	Surviving Sepsis Campaign guidelines for the first time specifically suggest (grade 2C) use of albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids
2013	EARSS randomized controlled multicenter study comparing 100 ml 20% albumin with normal saline in patients with early severe sepsis, showing no differences in mortality rates between groups
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Vincent JL, et al. Is albumin administration in the acutely ill associated with increased mortality? Results of the SOAP study. Crit Care 2005, 9:R745–R754.

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Dubois MJ, et al. Albumin administration improves organ function in critically ill hypo-albuminemic patients: a prospective, randomized, controlled, pilot study. Crit Care Med 2006, 34:2536–2540.

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Delaney AP, et al. The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. Crit Care Med 2011, 39:386–391.

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Dellinger RP, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013, 41:580–637.

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EARSS Study Group: Efficacy and tolerance of hyperoncotic albumin administration in septic shock patients: the EARSS study [abstract]. Intensive Care Med 2011, 37(Suppl 2):S115–0438.

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Caironi P, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med 2014, 370:1412–1421.

Albumin
indications and contraindications

Volemic resuscitation in patients with traumatic brain injury

- In the SAFE trial, patients with traumatic brain injury treated with albumin had worse outcomes than saline treated patients.
- Probable mechanism for the increased mortality appeared to be albumin-induced increases in intracranial pressure.
- The hypotonic and hypooncotic nature of the 4% albumin solution used may also have played a role.

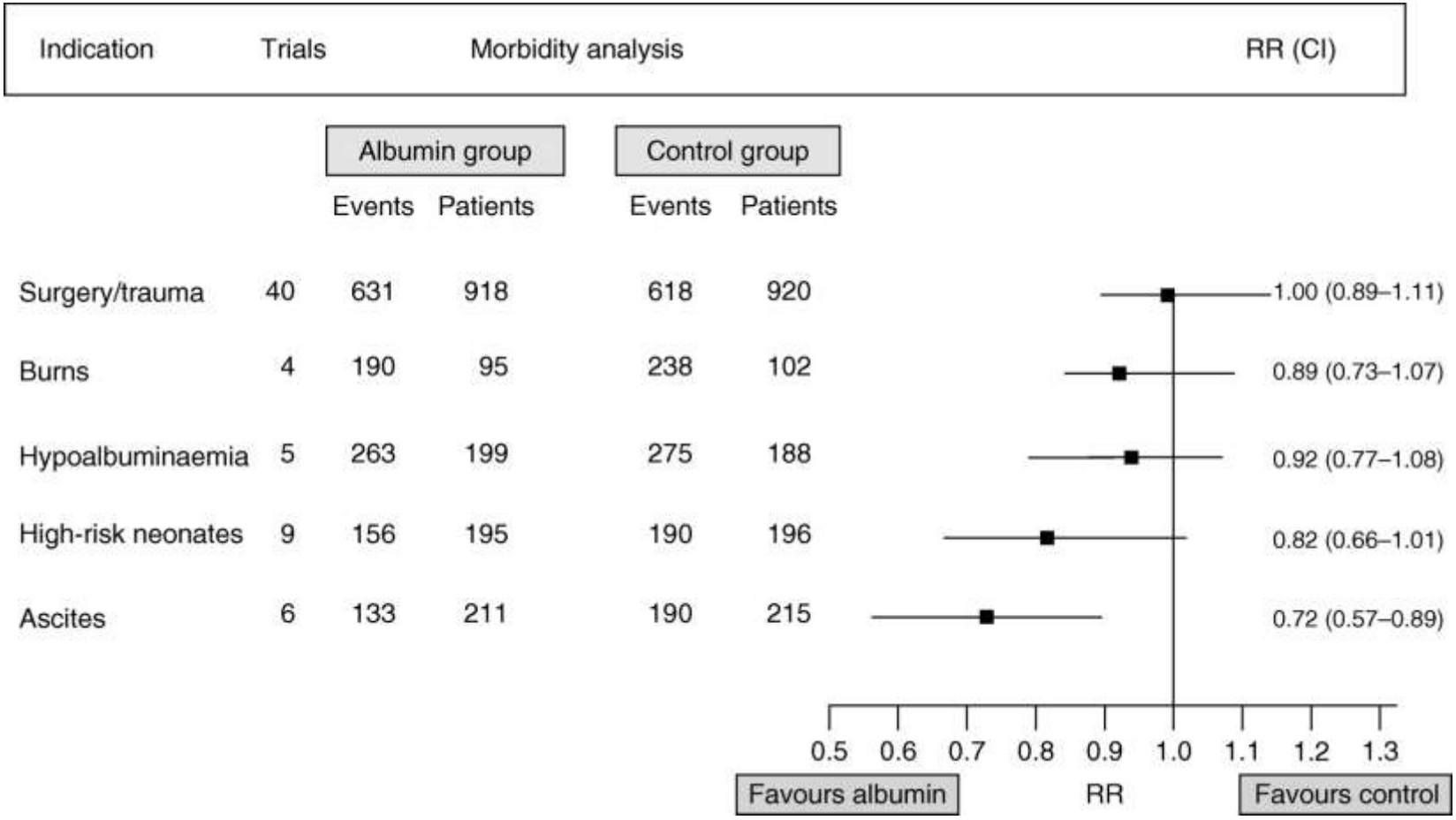
Cooper DJ, et al. Albumin resuscitation for traumatic brain injury: is intracranial hypertension the cause of increased mortality? J Neurotrauma 2013, 30:512–518.

Albumin replacement in patients with hypoalbuminemia

- A meta-analysis of 9 prospective RCT on correcting hypoalbuminemia in acutely ill patients suggested that ***complication rates were reduced in patients who achieved serum albumin concentrations >3 g/dl after albumin administration***.

Vincent JL, et al. Hypoalbuminemia in acute illness: is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials. Ann Surg 2003, 237:319–334.

Effects of use of HA on risk ratio (RR) and confidence interval (CI) for morbidity in different clinical settings (data taken from Vincent and colleagues)



Boldt J Br. J. Anaesth. 2010;104:276-284

BJA British Journal of Anaesthesia

Albumin replacement in patients with hypoalbuminemia

- in a subgroup analysis of the SAFE study in patients with hypoalbuminemia, using a cutoff value of 2,5 g/dl, there were ***no significant differences in outcomes*** in hypoalbuminemic patients and normoalbuminemic patients who received albumin.

Finfer S, et al. Effect of baseline serum albumin concentration on outcome of resuscitation with albumin or saline in patients in intensive care units: analysis of data from the saline versus albumin fluid evaluation (SAFE) study. BMJ 2006,333:1044.

Albumin replacement in patients with hypoalbuminemia

- a RCT of 100 critically ill patients who were randomized either to receive albumin solution targeting seric albumin >3.0 g/dl or to receive no albumin, reported that SOFA score improved more in the albumin-treated patients;
- these patients also had a less positive fluid balance
- beneficial effect on cumulative calorie intake during the first week, suggesting that albumin may have helped decrease intestinal edema.

Dubois MJ, et al. Albumin administration improves organ function in critically ill hypoalbuminemic patients. Crit Care Med 2006, 34:2536–2540.

Recent RCT results

- There are 3 large randomized trials to compare albumin with crystalloids in adult patients with severe sepsis:
  - Saline versus Albumin Fluid Evaluation study (SAFE)-6997 (Australia & NZ)
  - The Albumin Italian Outcome Sepsis study (ALBIOS) – 1818 (Italia)
  - Early Albumin Resuscitation during Septic Shock study (EARSS) – 798 (France)

Recent RCT results

- In the ALBIOS study, 1,818 patients with severe sepsis or septic shock randomized to receive:
  - 300 ml of 20% albumin plus crystalloid

  or
  - crystalloid alone
- to achieve the target resuscitation goals of the early goal-directed therapy protocol (Rivers etal.)

Caironi P, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med 2014, 370:1412–1421.

Recent RCT results

- In the next 28 days:
  - albumin infusions to maintain serum albumin ≥3.0g/dl
  - crystalloid solutions when clinically indicated

  or
  - crystalloid alone

  - No syntethic choloids allowed

Caironi P, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med 2014, 370:1412–1421.

Recent RCT results

- More patients in the albumin group reached the target mean arterial pressure within 6 hours after randomization
- In the first 7 days the mean arterial pressure was higher and the net fluid balance lower in the albumin group, despite similar amounts of fluid being administered to the two groups.

Caironi P, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med 2014, 370:1412–1421.

Recent RCT results

- no overall differences in 28-day mortality rates (32% albumin vs 32% crystalloid)
- no overall differences in 90-day mortality rates (41% albumin vs 44% crystalloid) between the groups.

Caironi P, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med 2014, 370:1412–1421.

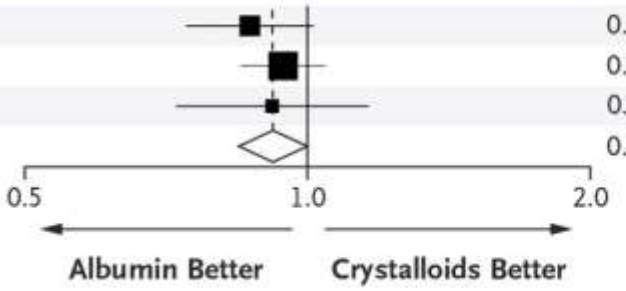
Recent RCT results

- EARSS study in France, 798 patients with septic shock of less than 6 hours duration randomized to receive:
  - 100 ml of 20% albumin or
  - 100 ml of 0.9% saline every 8 hours for 3 days.
- Almost all patients had severe hypoalbuminemia at study inclusion.
- There were no significant differences in mortality rates between the two groups (24.1 vs 26.3%).

EARSS Study Group: Efficacy and tolerance of hyperoncotic albumin administration in septic shock patients: the EARSS study. Intensive Care Med 2011, 37(Suppl 2):S115–0438.

Meta-Analysis of Mortality in Large-Scale Randomized Trials Comparing Albumin with Crystalloids in Adult Patients with Severe Sepsis

Trial	Albumin	Crystalloids	Relative Weight	Relative Risk (95% CI)	P Value
	no. of patients who died/total no.		%		
SAFE[2]	185/603	217/615	30.41	0.87 (0.74–1.02)	
ALBIOS[1]	365/888	389/893	54.90	0.94 (0.85–1.05)	
EARSS[3]	96/399	103/393	14.69	0.92 (0.72–1.17)	
All trials	646/1890	709/1901	100.00	0.92 (0.84–1.00)	0.046



Authors suggest that there is a survival advantage associated with albumin use in patients with severe sepsis.

N Engl J Med 2014;371:83-84.

The NEW ENGLAND JOURNAL of MEDICINE

Should albumin infusions target albumin levels?

Albumin Dose (g) = [desired Alb. concentration (g/dL) – actual Alb. concentration (g/dL)] x 0.8 x kg body weight

Desired albumin concentration ~ 2.5 g/dL

Plasma volume ~ 0.8 x kg body weight (dL)

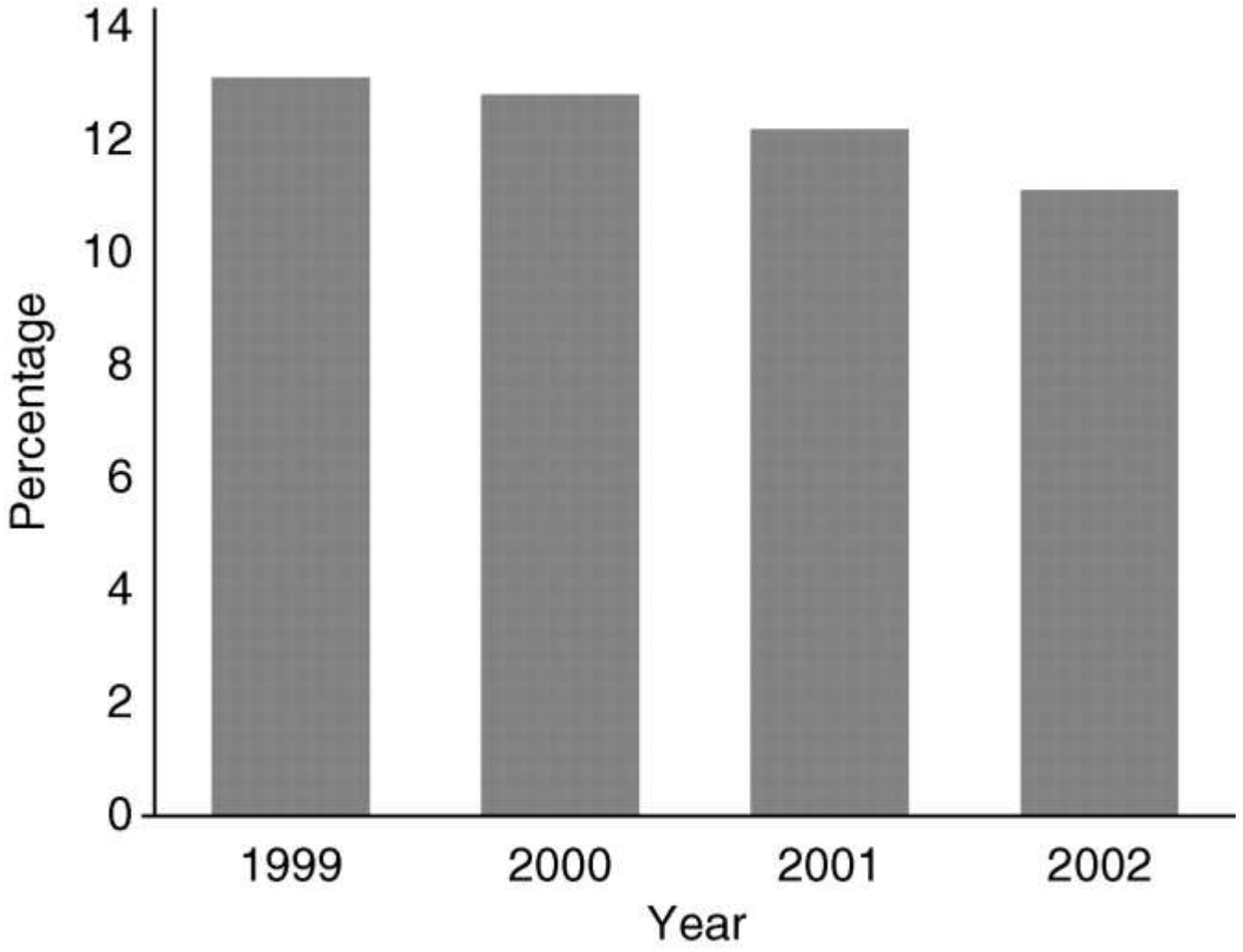
Which concentration of albumin solution?

- Solutions of albumin are prepared from the plasma of healthy donors, pasteurised at 60 °C for 10 hours.
- It can be infused independently of the recipient's blood group.
- Albumin solutions: 5% - isoosmotic, 20% and 25% - hyperosmotic
- All the preparations contain 130–160 mEq of sodium per litre.

Is albumin cost-effective?

- the most expensive non-blood plasma substitute used to treat hypovolaemia
- up to 20x more expensive than colloids

Per cent of ICU costs by fiscal year by albumin use



Boldt J Br. J. Anaesth. 2010;104:276-284

BJA British Journal of Anaesthesia

Recommendations and conclusions

- Albumin administration, although unlikely to cause harm in most patients, is not necessary in all critically ill patients and should be reserved for use in specific groups of patients in whom there is evidence of benefit.

Vincent *et al. Critical Care* 2014, 18:231

Recommendations

- ***Appropriate indications (for which there is widespread consensus)***
  - Paracentesis: 5 g of albumin/L ascitic fluid removed, after paracentesis of volumes > 5 L.
  - Therapeutic plasmapheresis: For exchanges of > 20 mL/kg in one session or > 20 mL/kg/week in more than one session.
  - Spontaneous bacterial peritonitis, in association with antibiotics
  - Ovarian hyperstimulation symdrome according to the severity of hypoalbuminaemia and the total volume of ascitic fluid drained

Recommendations

- A hypotonic albumin solution should be avoided as a resuscitation fluid in patients with traumatic brain injury, based on the results of the SAFE subgroup analysis.

Recommendations

- There is now enough evidence and plausible biological rationale to support use of albumin in patients with septic shock when a colloid is considered.

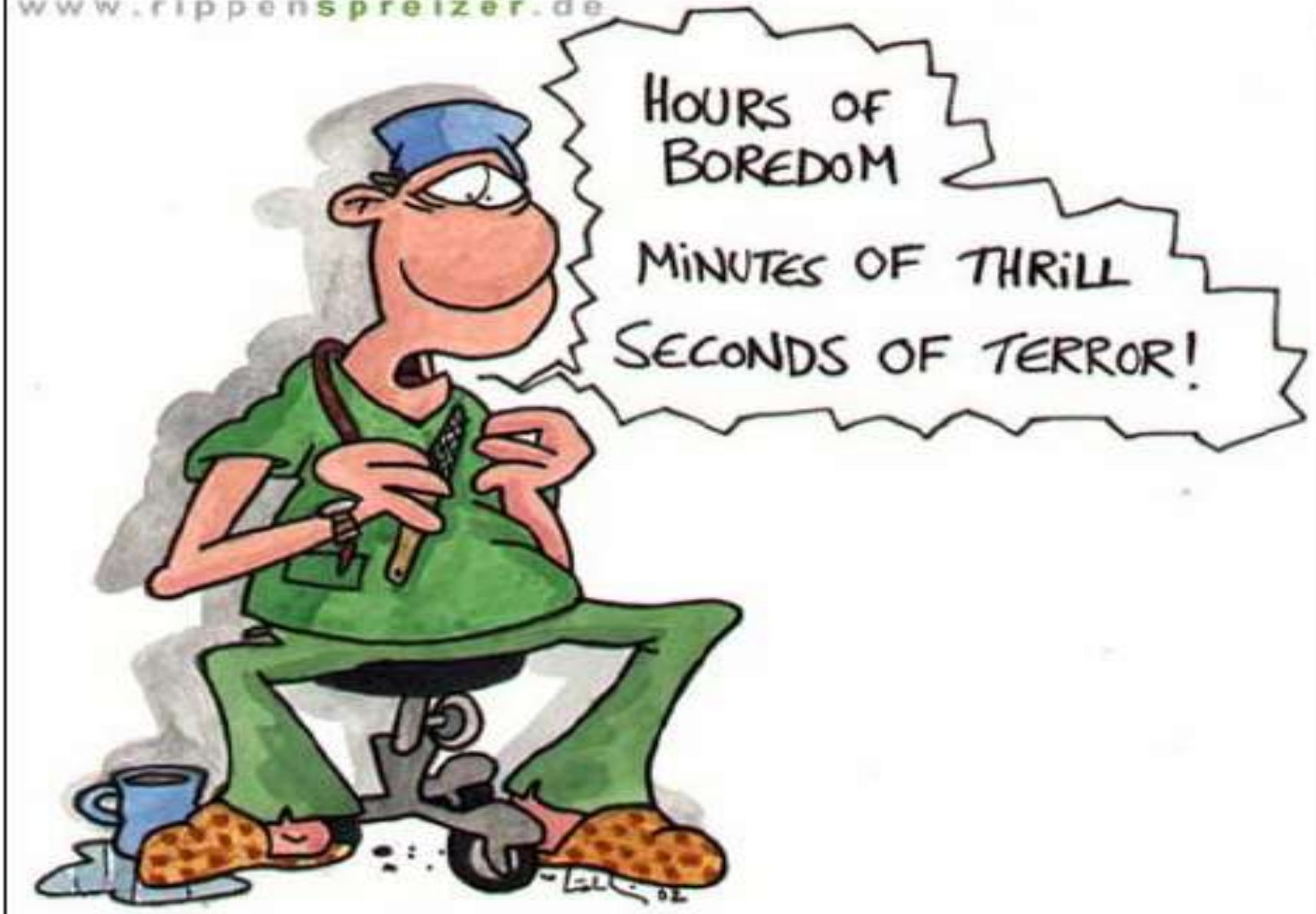
Recommendations

- Albumin administration should be considered in:
  - patients with cirrhosis and spontaneous bacterial peritonitis
  - patients with cirrhosis and other infections
  - in patients with cirrhosis and type 1 hepatorenal syndrome.

Recommendations

- Albumin administration should be considered in:
  - in hypooncotic patients with acute respiratory distress syndrome

Albumin 25% IV bolus every 6 to 12 hours PRN for 24 to 72 hours in combination with furosemide +/- chlorothiazide



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