


Albumin

Understanding the Controversy

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Objectives

- To understand the physiological role of endogenous albumin
- To understand the physiological effects of exogenous albumin
- To clarify the formulations of albumin available in Canada and their differences
- To provide an overview of albumin’s popularity in Canada and motivations for its use
- To review the indications supported by evidence for exogenous albumin administration
- To discuss a real-world case in a patient with severe liver disease and apply our new knowledge

Introduction

What is Albumin?

What is albumin?

- **Most common plasma protein**
  - Water-soluble, globular, negatively charged
  - 40% intravascular, 60% interstital
  - Synthesized in the liver at a rate of 10-15 g / day
  - Catabolized by endothelium with daily turnover 9-12 g
  - Degredation in muscle, skin, liver, other organs
  - Median half life 18 days
  - Approx ½ of total plasma protein content
  - Albumin normal value 40 g/L vs. Total Serum Protein 70 g/L

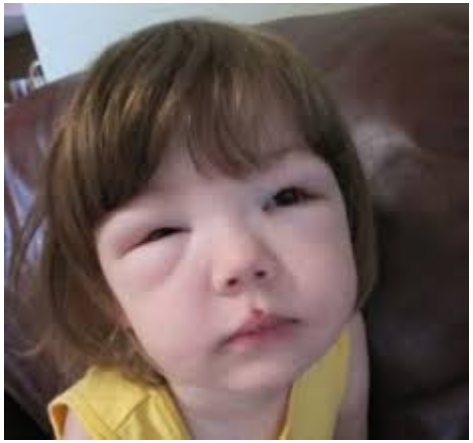
What does albumin do?

- Provides 80% of total plasma oncotic pressure
- Extravascular oncotic pressure
- Carrier
  - Binds endogenous ligands
    - Bilirubin, fatty acids, metals, ions, hormones
  - Binds exogenous substances
    - Drugs

How do we measure albumin levels?

- Green Top (Lithium Heparin tube) preferred
- Alternate tubes: Red, marble, or gold top
  - Draw volume: 0.6 mL blood
  - Processed volume: 0.2 mL serum/plasma post centrifugation
  - Levels are posture dependent - draw while seated (levels may be falsely low if supine draw as plasma volume redistributed)
- Example Assay - **Albumin BCG Assay**

What do albumin levels reflect?



- Liver synthetic function
- Nutritional Status
  - Malabsorpotion, malnutrition
- Losses (burns)
- Renal disease
  - Reduced synthesis, increased degradation, increased losses

Hypoalbuminemia is common with many types of systemic diseases

ENDOgenous vs. EXOgenous Albumin

- **Can be used as an exogenous colloid solution**
- **<u>Blood product for which consent is required</u>**
- Supplied by Canadian Blood Services

- Protein purified from donated human plasma
  - Sterile, latex free, virally inactivated solution, physiological pH (6.4-7.4), Na = 130-160 mmol/L

Due to legislation prohibiting payment and a lack of a fractionation company in Canada, most albumin in Canada from paid U.S. plasma donors

Albumin as a Drug

Formulations, Dosing, and Alternatives

Albumin as a Drug

- 100 ml of 25% (25 g) OR 250 ml of 5% (12.5 g)
  - 25% used for oncotic deficit (hyperoncotic)
  - 5% used for therapeutic plasmapheresis or volume deficit alone (iso-osmotic)

- Widely used largely off-label since the 1940's

- Canadian Brand Names:
  - Alburex-25, Alburex-5
  - Plasbumin-25, Plasbumin-5
  - Albutein
  - Octalbin

Typical Dosage

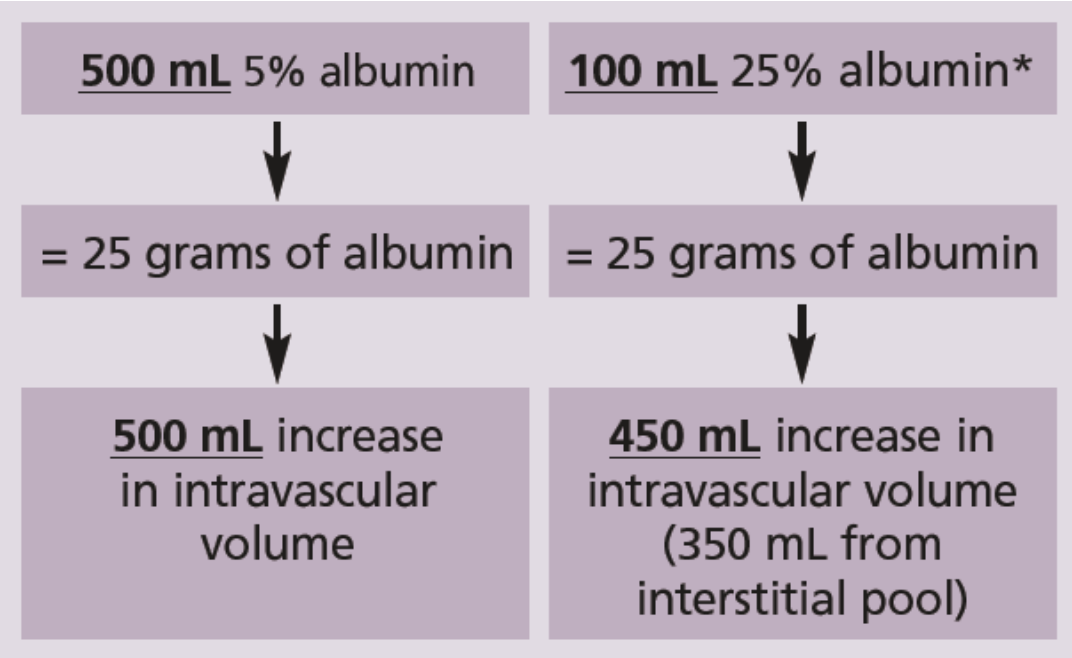
Note difference between 5% and 25% Albumin

- 500 ml of 5% albumin = 25 g of albumin = 500 mL increase in intravascular volume
- 100 ml of 25% albumin = 25 g of albumin = 450 mL increase in intravascular volume (350 mL from interstitial pool)

Adverse reactions:

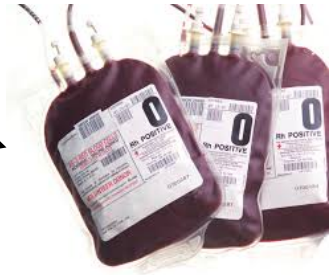
- Rare anaphylaxis
- Circulatory overload - particularly if 25% administered instead of 5%
- Transient hypotension (rare case reports in patients on ACE Inhs)
- No known transmission of viral pathogens (HIV, HCV, etc)

Slide courtesy of Dr. J Callum



What are the alternatives to albumin?

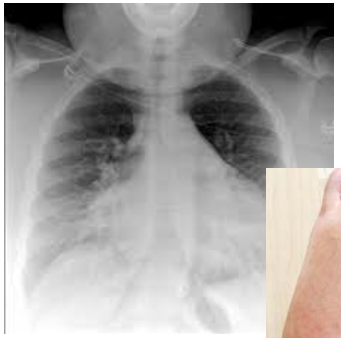
- *Crystalloids*
- *Synthetic Colloids*
- *Other Blood Products*

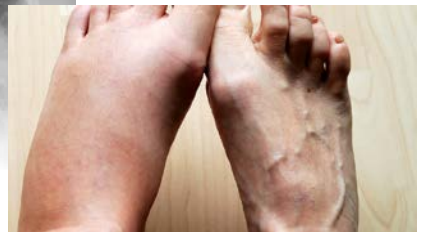


Motivations for Albumin Use

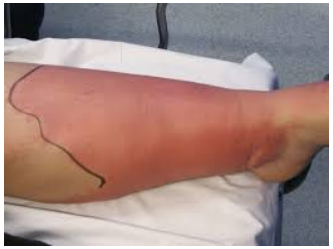
Fluid Balance is tricky and important in very ill patients

Why use albumin to begin with?



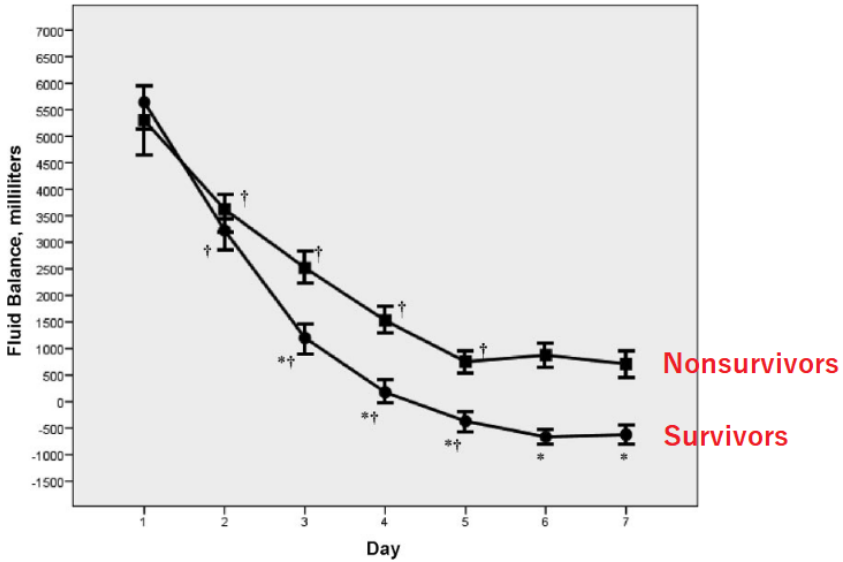


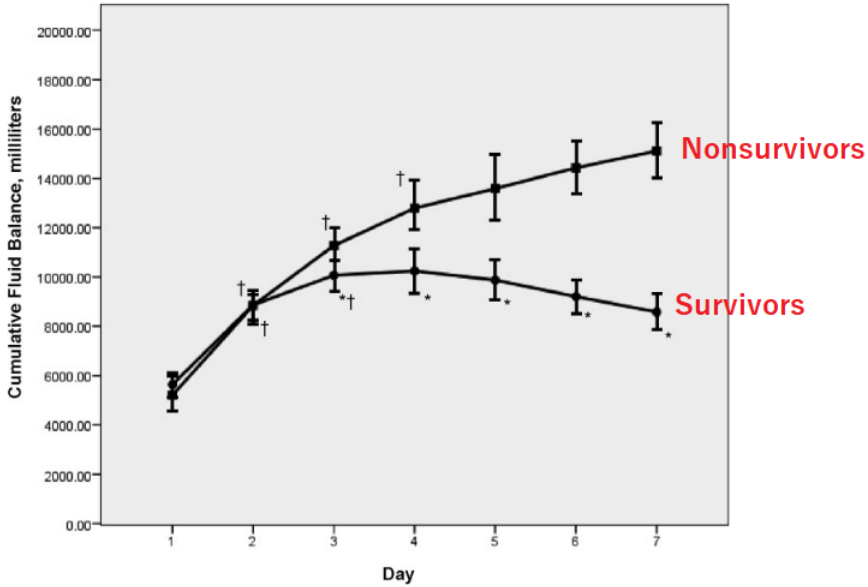
- **Optimal resuscitation is difficult in ill patients**
- **Fluid overload has detrimental effects**
- Venous congestion is associated with organ edema and dysfunction
  - Leads to a higher “afterload” for the kidneys, associated with AKI and RRT
  - Associated with impaired hepatic function, intra-abdominal hypertension



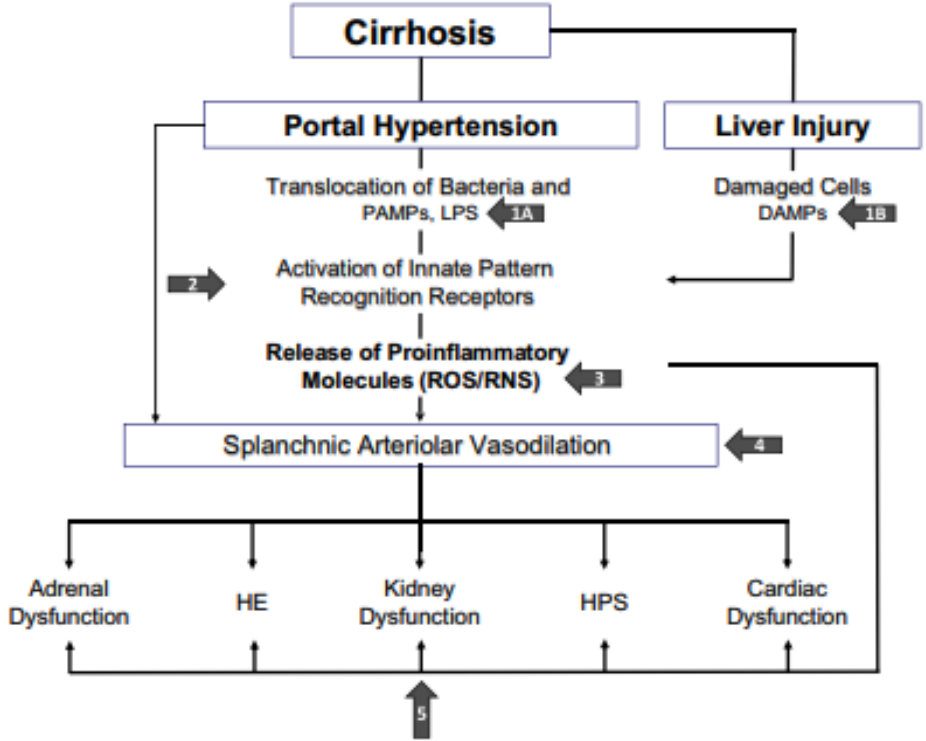
- Associated with skin and soft tissue infection and pressure injuries, longer mechanical ventilation, increased hospital and ICU length of stay
- Associated with higher hospital and ICU mortality

Fluid Balance was (is?) a big colloid vs. crystalloid debate flash point





Are there other effects besides volume?



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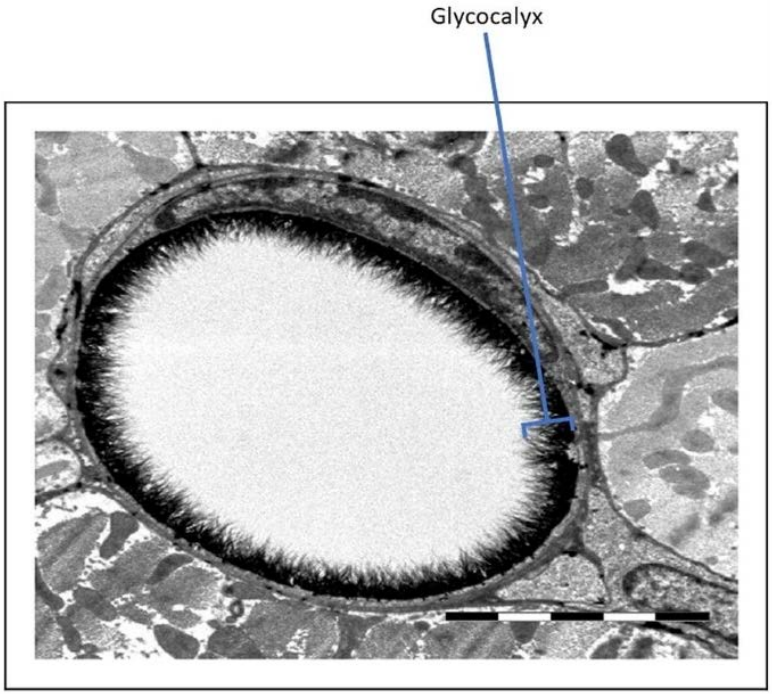
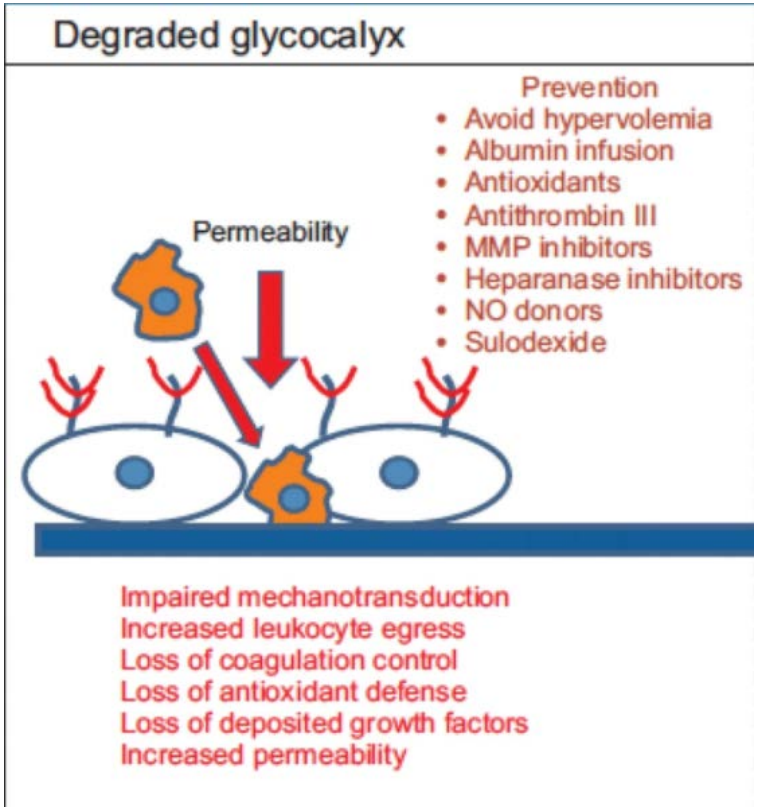


Reproduced with permission from [11]

Electron micrograph of a cross-sectional image of a coronary endothelial glycocalyx (courtesy of B. van den Berg, Maastricht University).



Slide courtesy of Dr. J Callum

Sep 30 year to date actuals F2020/21 Top 10 Receiving Hospitals

Albumin (25 g eqv.)				
Rank	**Province / Territory**	**Hospital Name**	**Total**	**% of Total Hospital Issue**
1	ONTARIO	UHN - TORONTO GENERAL SITE	11,595	7.0%
2	BRITISH COLUMBIA	VANCOUVER GENERAL HOSPITAL	10,333	6.3%
3	ALBERTA	EDMONTON ZONE HOSPITALS	10,192	6.2%
4	ONTARIO	KINGSTON HEALTH SCIENCES CENTRE	4,373	2.7%
5	ALBERTA	FOOTHILLS HOSPITAL	4,255	2.6%
6	BRITISH COLUMBIA	ROYAL COLUMBIAN HOSPITAL	4,009	2.4%
7	SASKATCHEWAN	REGINA GENERAL HOSPITAL	3,764	2.3%
8	ONTARIO	THE OTTAWA HOSPITAL - GENERAL CAMPU	3,628	2.2%
9	ONTARIO	THE OTTAWA HOSPITAL - CIVIC CAMPUS	3,385	2.1%
10	ONTARIO	LONDON HSC - UNIVERSITY HOSPITAL	3,087	1.9%
		Total Issues Of All Hospitals	**164,924**	

The Evidence for Albumin Use

Generally not good quality evidence

Adult Indications with Supporting (Perhaps Low Quality) Evidence

LIVER PATIENTS

- **Spontaneous bacterial peritonitis** - 25% albumin 1.5 g/kg within 6 hours of diagnosis, then 1 g/kg on day 3
- **Large volume paracentesis** - 25% albumin, 6-8 g for every litre removed, administer soon after procedure to avoid procedural complications (hypovolemia, hyponatremia, renal impairment)
- **Acute Onset HRS Type 1** – If eligible for liver transplant, 25% Albumin 1 g/kg on Day 1, 100-200 ml on days 2-14

CRITICAL ILLNESS

- **ARDS** – NOT suggested for volume replacement alone or in combination with diuretics (very low quality evidence)
- **Hypovolemia** – NOT suggested for volume replacement or to increase serum albumin levels (moderate quality evidence)

SPECIAL POPULATIONS

- **OHSS** - 25% albumin, 50-100 g over 4 hours, q4-12 h prn
- **Plasma exchange** - 5 % albumin, titrated to plasma volume removed
- **Burns > 50% TBSA** – low quality evidence, **not recommended**. Historically used when unresponsive to crystalloid, 5% albumin at 0.3-0.5 ml/kg/BSA (50-100 mL/hour)

CBS Recognized Indications

25% Albumin	**5% Albumin**
Liver disease and bacterial peritonitis	Therapeutic plasma exchange
Large Volume (>5 L) paracentesis in Cirrhotic Patients	Thermal Injury Involving > 50% TBSA, if unresponsive to crystalloid
Hepatorenal Syndrome Type 1	

Non-Indications

As per CBS, **NO EVIDENCE** to support albumin use in:

(1) Cardiac Surgery
(2) Volume Resuscitation for hypovolemia
(3) Cerebral Ischemia / hypovolemic brain injury
(4) Hypoalbuminema
(5) Hypotension during dialysis therapy

2004……The Colloid vs. Crystalloid Debate

The NEW ENGLAND JOURNAL of MEDICINE

Is Albumin Safe?

Deborah Cook, M.D.

The Saline versus Albumin Fluid Evaluation (SAFE) Study, reported in this issue of the *Journal*, [1] heralds a new era in critical care marked by the large, simple, randomized trial popularized by cardiologists. In a study of fluid resuscitation involving nearly 7000 critically ill patients, the Australian and New Zealand Intensive Care Society Clinical Trials Group addressed one of the most fundamental and contentious issues in critical care. Questions about the merits and demerits of colloids as opposed to crystalloids in the resuscitation of seriously ill patients have smoldered for decades, sparked by a meta-analysis suggesting that albumin was associated with . . .

Critical Care State of the Evidence: 3 Large RCTs

- **2004 SAFE Trial (Saline versus Albumin Fluid Evaluation)**
  - 6997 Australian ICU patients undergoing fluid resuscitation
  - Randomized to 4% albumin or normal saline for fluid resuscitation during subsequent 28 days
  - Primary outcome death from any cause at 28 days - no difference
  - Secondary outcomes single or multi-organ failure, days in hospitals, days mechanical ventilation, days of RRT at 28 days - no difference

Critical Care State of the Evidence: 3 Large RCTs

- **2013 CRISTAL Trial (Colloids versus Crystalloids for the Resuscitation of the Critically Ill)**
  - 2857 patients across 57 international ICUs stratified by case mix (trauma, sepsis, other hypovolemic shock)
  - Randomized to colloid (gelatins, dextrans, HES, 4% or 20% albumin) or crystalloid
  - Primary outcome death within 28 days - no difference
  - Secondary outcome days not receiving RRT - no difference
  - Secondary outcomes 90-day mortality favoured colloid group (30.7% vs. 34.2%, p=0.03)
  - Secondary outcomes days free of mechanical ventilation or vasopressors at 7 and 28 days favoured colloid group (small absolute mean differences of approx 1 day or less)

Critical Care State of the Evidence: 3 Large RCTs

- **2014 ALBIOS (Albumin Italian Outcome Sepsis)**
  - 1818 patients with severe sepsis in 100 different ICUs
  - Randomized to 20% albumin + crystalloid or crystalloid alone
  - Primary outcome death from any cause at 28 d - no difference
  - Secondary outcomes death at 90 days, degree and incidence or major organ dysfunction, ICU and hospital length of stay - no difference
  - During 1st 7 days patients in albumin group had higher MAP and lower net fluid balance

How much albumin do we use now?

Surviving Sepsis Campaign - Fluid Management

F. FLUID THERAPY

1. We recommend that a fluid challenge technique be applied where fluid administration is continued as long as hemodynamic factors continue to improve (BPS).
2. We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock (strong recommendation, moderate quality of evidence).
3. We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock (weak recommendation, low quality of evidence).
4. We suggest using albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock when patients require substantial amounts of crystalloids (weak recommendation, low quality of evidence).
5. We recommend against using hydroxyethyl starches (HESs) for intravascular volume replacement in patients with sepsis or septic shock (strong recommendation, high quality of evidence).
6. We suggest using crystalloids over gelatins when resuscitating patients with sepsis or septic shock (weak recommendation, low quality of evidence).

De-emphasizing Albumin - Fluid Management

Managing resuscitation:

- Fluids: For patients with sepsis-induced hypoperfusion, provide 30 mL/kg of intravenous crystalloid within 3 hours (strong recommendation; low QOE) with additional fluid based on frequent reassessment (BPS), preferentially using dynamic variables to assess fluid responsiveness (weak recommendation; low QOE).
- Resuscitation targets: For patients with septic shock requiring vasopressors, target a mean arterial pressure (MAP) of 65 mm Hg (strong recommendation; moderate QOE).
- Vasopressors: Use norepinephrine as a first-choice vasopressor (strong recommendation; moderate QOE).

Liver Patients State of the Evidence: Update

March 2021 NEJM – Albumin Infusions for Patients with Decompensated Cirrhosis

- Patients with decopensated cirrhosis are often given elabumin for established indications (HRS Type 1, SBP, large volume paracentesis)
- The benefits of routine infusion are uncertain
    - Preclinical studies support the routine use of albumin for its anti-inflammatory role, among other reasons
    - Albumin < 30 g/L in cirrhosis is predictive of immune dysfunction

Liver Patients State of the Evidence: Update

In hospitalized patients with decompensated cirrhosis, does targeting an albumin level of ≥30 g/L with repeated daily infusions of 20% human albumin solution reduce incidence of infection, kidney dysfunction and death?

Slides courtesy of Dr. Yulia Lin

ATTIRE – Multicenter RCT open

Mostly alcohol-related with mean alb 23+/- 4 g/L
Excluded: advanced HCC, palliatve care
Target albumin > 35 g/L

777 pts hospitalized decompensated cirrhosis + albumin < 30g/L in 1st 72h

Daily 20% albumin to 14d

Standard Care

Composite: new infection, kidney dysfnc or death in 3 to 15 d post initiation	29.7%	30.2%	P=0.87
Albumin infusion (median, IQR)	200 g (140-280)	20 g (0-120)	

China et al. NEJM Mar 2021;384:808-17

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.

Slides courtesy of Dr. Yulia Lin

Table 3. Serious Adverse Events.*

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.

We conclude that targeted albumin therapy had no clinically important effect on preventing infections or reducing the development of kidney dysfunction in hospitalized patients with decompensated cirrhosis. This finding contrasts with those in our laboratory studies,[36] and this difference underscores the importance of appropriately powered confirmatory clinical trials. The infusion of greater quantities of albumin probably would have been unsafe and would have led to more severe or life-threatening serious adverse events in the albumin group.

China et al. NEJM Mar 2021;384:808-17

Slide courtesy of Dr. J Callum

Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial

- n=440
- Patients with cirrhosis on >200 mg spironolactone and 25 mg of furosemide
- RCT: albumin (40g 2x/wk then weekly for 18 months) vs. nothing

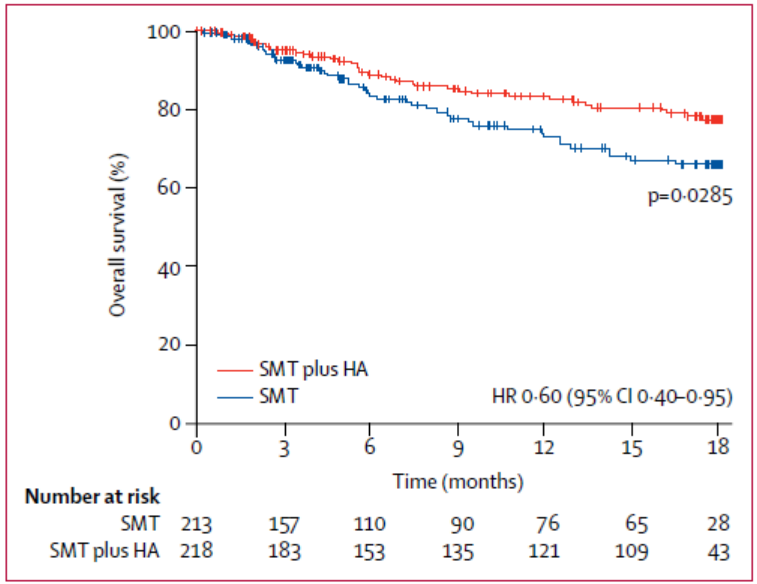


Figure 3: **Overall survival**
Kaplan-Meier estimates for the probability of overall survival in the modified intention-to-treat population of SMT and SMT plus HA groups. The p value was calculated by the log-rank test. HA=human albumin. SMT=standard medical treatment.

Lancet 2018; 391: 2417–29

Case Example

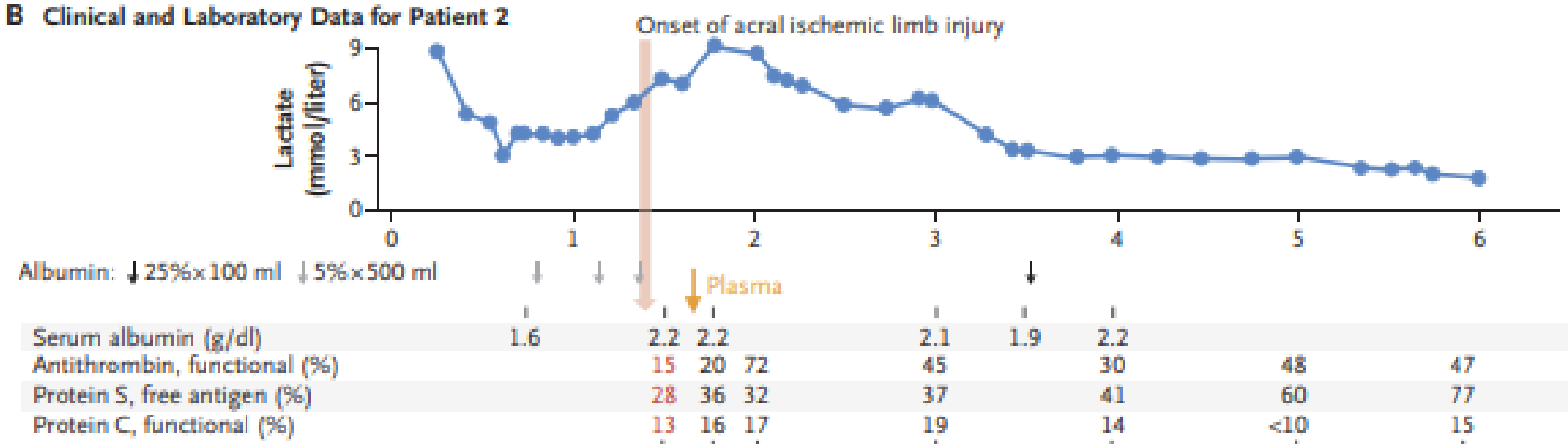
Perioperative Liver Transplant Patient

Case Example - Liver Transplant in the OR

- 68 M with ESLD 2ndry to EtOH cirrhosis, undergoing DCD liver transplantation
- He is known for portal hypertension and tense large volume ascites
- You are in the operating room and the surgeon is about to open the abdomen

What is going to happen next???

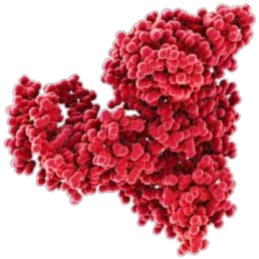
Dilution affects anti-thrombotic factors as well....



Warkentin TE, NEJM 2020

Conclusions

- Albumin has a long history of use in Canada and globally
- It is a blood product derived from human plasma
  - Although generally safe, inherent risks with transfusion
- Albumin use should always be carried out with a specific indication in mind
  - Avoid indiscriminate use in general ICU or medical inpatients
    - No major evidence of benefit over alternatives (balanced crystalloids)
    - Significantly more costly than alternatives (balanced crystalloids)



Thank you!