#FSHP2018

To Give or Not to Give:

The Role of Albumin in the Critically Ill Patient

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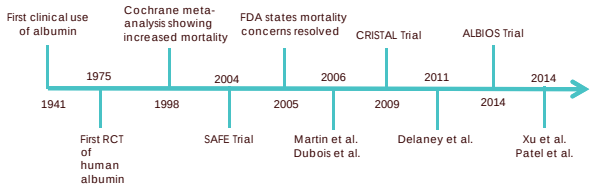
Pharmacy Supervisor
Orlando Health

Objectives

- Discuss the role of albumin as replacement therapy in hypoalbuminemic patients
- Review the evidence surrounding the use of albumin for fluid resuscitation in sepsis
- Outline the literature for the use of albumin in burn patients

Albumin in Clinical Practice



Vincent, J. L. (2014). Critical Care, 18(4), 231.

Established Roles for Albumin

Cirrhosis Complications	Guideline-Recommended Albumin Use
Post-paracentesis circulatory dysfunction (Prevention)	8g/L of ascites fluid removed above 5 L
Spontaneous Bacterial Peritonitis	Day 1: 1.5 g/kg + antibiotics Day3: 1 g/kg + antibiotics
Hepatorenal Syndrome	1 g/kg daily x2 days 25-50 g daily until resolution

Bernardi, M. (2014).*Journal of clinical and experimental hepatology*, *4*(4), 302-311.

Controversial Uses of Albumin

- Supplementation in hypoalbuminemic patients
- Overcoming loop diuretic resistance
- Large volume resuscitation in sepsis
- Fluid resuscitation in burn patients

Physiology of Albumin

Advantages
Maintenance of colloid oncotic pressure
Volume Expansion
Free Radical Scavenger
Acid-Base Equilibrium
Anti-inflammatory

Vincent, J. L. (2014). Critical Care, 18(4), 231.

Albumin Formulations

Characteristic	Albumin 5%	Albumin 25%
Oncotic Effect	Iso-oncotic	Hyper-oncotic
Formulations	250 mL vial 500 mL vial	50 mL vial 100 mL vial

Intravenous Fluid	Cost (250 mL)
Albumin 5%	$83.16
Albumin 25%	$344.40
Normal Saline	$5.75
Lactated Ringer's Solution	$5.27

Break Through Branch Out

Albumin Supplementation in Hypoalbuminemic States

Break Through Branch Out

Hypoalbuminemia

- Defined as serum albumin < 3.0 g/dL
- Very common in critical illness
  - Acute phase negative reactant
  - Dilution from IV fluid administration
  - Redistribution from intravascular to interstitial space
- Associated with worse clinical outcomes
  - Increased morbidity and mortality
  - Every 1 g/dL decrease of albumin increases:
    - ICU & hospital length of stay
    - Mortality

Break Through

Vincent, J. L.(2003). *Annals of surgery*, *237*(3), 319.

Branch Out

Hypoalbuminemia

REVIEW

ANNALS OF SURGERY
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Hypoalbuminemia in Acute Illness: Is There a Rationale for Intervention?

A Meta-Analysis of Cohort Studies and Controlled Trials

Jean-Louis Vincent, MD, PhD, FCCM,* Marc-Jacques Dubois, MD,* Roberta J. Navickis, PhD,† and Mahlon M. Wilkes, PhD†

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Albumin level >3.0 g/dL associated with less complications

Break Through

Vincent, J. L.(2003). *Annals of surgery*, *237*(3), 319.

Branch Out

Albumin Supplementation

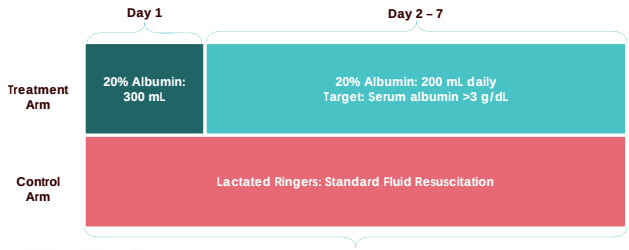
Study	Design	Population	Intervention	Outcomes
Dubois 2006 N=100	Single center RCT Open Label	Critically Ill Albumin: <3 g/dL	Albumin 20% Target: Albumin >3 g/dL	Δ SOFA score (Day 7)
Martin 2006 N=40	Multicenter RCT Double Blind	Mechanical Ventilated ARDS Total protein <6 g/dL	25% Albumin + Furosemide	Δ PaO_2/FiO_2 ratio (24 hours)
ALBIOS 2014 N=1810	Multicenter RCT Open Label	Severe Sepsis	20% Albumin + crystalloid Target: Albumin >3 g/dL	All-cause mortality (Day 28)

Break Through

Dubois, M. J.(2006). Critical care medicine, 34(10), 2536-2540.
Martin, G. S.(2005).Critical care medicine, 33(8), 1681-1687.
Caironi, P. (2014). NEJM 370(15), 1412-1421.

Branch Out

Treatment Plan



Break Through

Dubois, M. J.(2006). Critical care medicine, 34(10), 2536-2540.

Branch Out

Dubois et al.

	Control Group (n=50)	Albumin Group (n=50)
Age	65.2 (13.7)	63 (14.3)
Medical	28 (56%)	29 (58%)
Surgical	22 (44%)	21 (42%)
APACHE II	21.3	22.4
SOFA Score	5.7	6.3
Mechanical Ventilation	78%	80%
Vasopressors	44%	48%
Albumin, g/dL	2.3	2.3

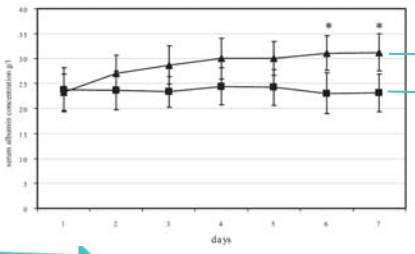
Dubois, M. J.(2006). Critical care medicine, 34(10), 2536-2540.

Sequential Organ Failure Assessment

SOFA Score	0	1	2	3	4
Respiration PaO_2/FiO_2 ratio mmHg	>400	≤ 400	≤ 300	≤ 200	≤ 100
Coagulation Platelets	>150	≤ 150	≤ 100	≤ 50	≤ 20
Liver Bilirubin, mg/dL	<1.2	1.2 – 1.9	2.0 – 5.9	6.0 – 11.9	>12
Cardiovascular Hypotension	None	MAP <70	DA ≤ 5	DA >5 EPN ≤ 0.1 NE ≤ 0.1	DA >15 EPN >0.1 NE >0.1
CNS Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal Serum Creatinine or Urine output	<1.2	1.2 – 1.9	2.0 – 3.4	3.5 – 4.9 or <500 mL/day	>5 or <200 mL/day

Dubois, M. J.(2006). Critical care medicine, 34(10), 2536-2540.

Serum Albumin



Albumin: 3.1 g/dL

Control: 2.4 g/dL

p<0.01

Dubois, M. J.(2006). Critical care medicine, 34(10), 2536-2540.

Dubois et al.

Outcome	Control (n=50)	Albumin (n=50)	P value
Δ SOFA	1.4 +/- 1.1	3.1 +/- 1.0	0.03
Last SOFA	4.6 +/- 1.2	4.1 +/- 1.1	0.65
PaO_2/FiO_2 ratio (Baseline vs Day 7)	238 mmHg vs 248 mmHg	215 mmHg vs 257 mmHg	0.006
Deaths	15 (30%)	12 (24%)	0.65
Length of Stay	7 +/- 2	8 +/- 2	0.13
Mean Daily Caloric Intake	760	1122	0.05

Dubois, M. J.(2006). Critical care medicine, 34(10), 2536-2540.

Albumin Supplementation

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Martin 2006 N=40	Multicenter RCT Double Blind	Mechanical Ventilated ARDS Total protein <6 g/dL Hemodynamically Stable	25% Albumin + Furosemide	Δ PaO_2/FiO_2 ratio (24 hours)
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Dubois, M. J.(2006). Critical care medicine, 34(10), 2536-2540.
Martin, G. S.(2005).Critical care medicine, 33(8), 1681-1687.
Caironi, P. (2014). NEJM 370(15), 1412-1421.

Treatment Plan

Treatment Arm

Furosemide
Loading Dose: 20 mg x1
Continuous infusion: 10 mg/hr x 3 days

+

Albumin 25%
25g every 8 hours x 3 days

Control Arm

Furosemide
Loading Dose: 20 mg x1
Continuous infusion: 10 mg/hr x 3 days

Martin, G. S.(2005).Critical care medicine, 33(8), 1681-1687.

Martin et al.

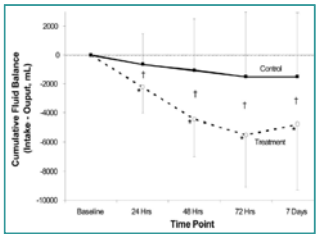
Variable	Control Group (n=20)	Albumin Group (n=20)
Age	46.4	48.9
Hospital Service	Medical: 70%	Medical: 60%
Lung injury etiology	Sepsis: 40% Trauma: 20% Pneumonia: 25%	Sepsis: 35% Trauma: 30% Pneumonia: 15%
APACHE II Score	14.0	13.4
PaO_2/FiO_2 ratio	182 mmHg	162 mmHg
Serum albumin	1.6 g/dL	1.7 g/dL
Tidal volume	8.8 mL/kg	9.1 mL/kg

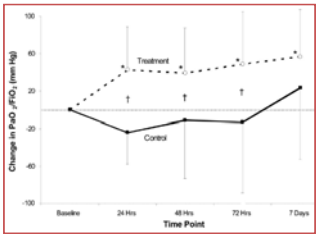
Break Through

Martin, G. S.(2005).Critical care medicine, 33(8), 1681-1687.

Branch Out

Martin et al. – Results





Break Through

Martin, G. S.(2005).Critical care medicine, 33(8), 1681-1687.

Branch Out

Martin et al.

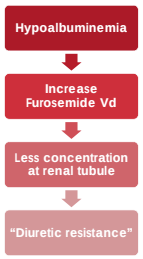
- Cost:
  - Furosemide arm: $10 total
  - Furosemide + albumin arm: $1250 total
- Hypoproteinemic patients with positive fluid balance despite diuresis benefit from albumin supplementation

Break Through

Branch Out

Diuretic Resistance

- Furosemide– 95% protein bound
- Furosemide – Albumin complex transported to renal tubules
- Common practice to combine albumin with furosemide
- Clinical efficacy of albumin-furosemide combination inconclusive



Break Through

Kitsios, G. D. (2014) Journal of critical care, 29(2), 253-259.

Branch Out

Kitsios et al.

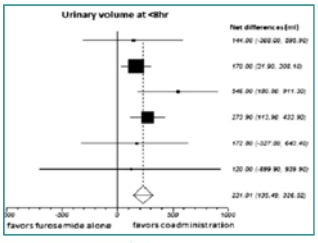
- Meta-analysis
  - Furosemide + albumin to overcome diuretic resistance in hypoalbuminemic patients
- 10 studies (n=343)
  - Administration of loop diuretics with albumin vs without albumin
- Outcomes
  - Urine output at 8 hours and 24 hours
  - Sodium excretion at 8 hours and 24 hours

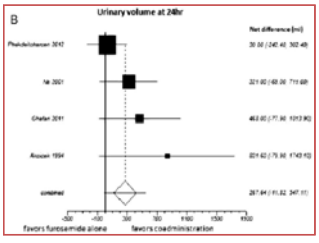
Break Through

Kitsios, G. D. (2014) Journal of critical care, 29(2), 253-259.

Branch Out

Kitsios et al. – Results





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Branch Out

Albumin Supplementation

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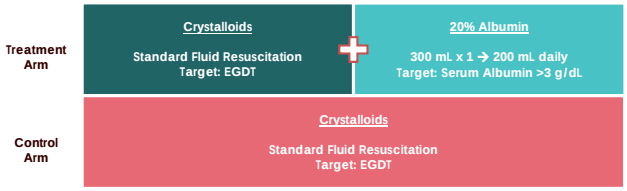
Caironi, P. (2014). NEJM 370(15), 1412-1421.

Treatment Plan



EGTD: Early Goal Directed Therapy

Caironi, P. (2014). NEJM 370(15), 1412-1421.

ALBIOS Trial

Variable	Control Group (n=907)	Albumin Group (n=903)
Intervention (28 days or ICU discharge)	Crystalloids Target: EGDT	20% Albumin: 300 mL x1 → 200 mL daily Target: albumin >3 g/dL + Crystalloids
Age	70	69
Reason for ICU admission	Medical: 57% Surgery: 43%	Medical: 57% Surgery: 43%
SOFA score	8	8
Shock	63%	63%
Mechanical Ventilation	81%	79%
Serum albumin	2.4 g/dL	2.4 g/dL

Caironi, P. (2014). NEJM 370(15), 1412-1421.

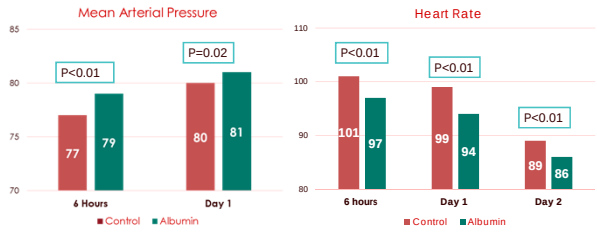
ALBIOS Trial – Results

Outcome	Control (n=907)	Albumin (n=903)	P value
All-cause mortality (28 days)	32%	31.8%	0.94
All-cause mortality (90 days)	43.6%	41.1%	0.29
New organ failure	54.4%	55.6%	0.99
Vasopressor Duration	4 days	3 days	0.007
Mechanical ventilation Duration	6 days	6 days	0.5
Serum Albumin	Day 1: 2.4 g/dL Day 7: 2.3 g/dL	Day 1: 2.4 g/dL Day 7: 2.9 g/dL	<0.001

Caironi, P. (2014). NEJM 370(15), 1412-1421.

ALBIOS Trial

Total Cost
Control: $370
Albumin Arm: $1850



Caironi, P. (2014). NEJM 370(15), 1412-1421.

Role of Albumin

- ✗ • Routine supplementation in hypoalbuminemic patients
- ✗ • Overcome "diuretic resistance"
- ✓ • Hypervolemic, hypoproteinemic, diuresis refractory patients with ARDS
  - 25% Albumin 25g every 8 hours + diuresis for 3 days
  - Improves oxygenation, but not mortality
- ✓ • Significant increase in cost, no increase in harm

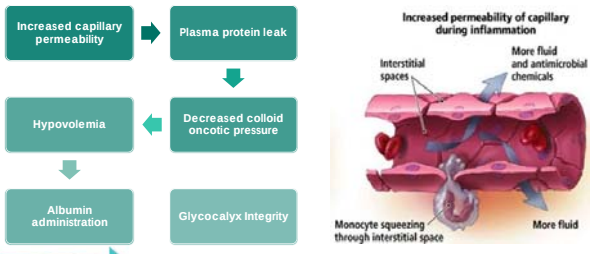
Fluid Resuscitation in Hypovolemic Patients

Surviving Sepsis – Fluid Choice

2004	2012	2016
- "Fluid resuscitation may consist of natural or artificial **colloids or crystalloids**." - "No evidence to support benefit in clinical outcomes between types of fluids" - Grade C	- "**Crystalloids** are initial fluid of choice" (Grade 1B) - "**Albumin** may be used in severe sepsis and septic shock when **substantial crystalloids are required**" (Grade 2C)	- "**Crystalloids** are initial fluid of choice" (strong recommendation, moderate evidence) - "**Albumin in addition to crystalloids** in sepsis and septic shock where **substantial crystalloids are required**" (weak recommendation, low quality of evidence)

Rhodes, A., (2017). *Intensive care medicine*, *43*(3), 304-377.

Role of Albumin



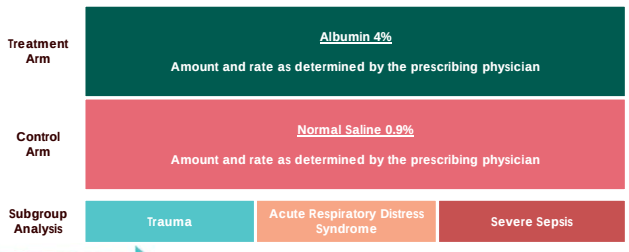
Vincent, J. L. (2014). Critical Care, 18(4), 231.

Fluid Resuscitation

Study	Design	Population	Intervention	Outcomes
SAFE Trial 2004 N=6997	Multicenter RCT Double Blind	Hypovolemic critically ill patients	4% albumin	All-cause mortality 28 days
CRISTAL 2009 N=2857	Multicenter RCT Open Label	Hypovolemic critically ill patients	Colloids (gelatins, dextrans, HES, 4% or 20% albumin)	All-cause mortality 28 days
ALBIOS 2014 N=1810	Multicenter RCT Open Label	Severe Sepsis	20% Albumin + crystalloid Target: Albumin >3 g/dL	All-cause mortality (Day 28)

Finfer, S. (2004). N Engl j Med, 350(22), 2247-2256..
Annane, D.,(2013). Jama, 310(17), 1809-1817.
Caironi, P. (2014). NEJM 370(15), 1412-1421

Treatment Plan



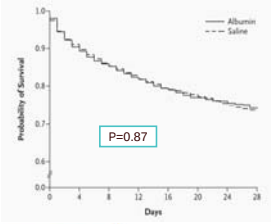
Finfer, S. (2004). N Engl j Med, 350(22), 2247-2256

SAFE Trial – Population

Variable	Saline Group (n=3338)	Albumin Group (n=3339)
Age	58.5	58.6
APACHE II Score	19.0	18.7
Mechanical ventilation	64.8%	63.8%
Serum albumin	2.7 g/dL	2.7 g/dL
Trauma	597 (17.4%)	590 (17.2%)
Severe Sepsis	603 (18.1%)	615 (18.4%)
Acute Respiratory Distress Syndrome	61 (1.8%)	66 (1.9%)

Finfer, S. (2004). N Engl j Med, 350(22), 2247-2256

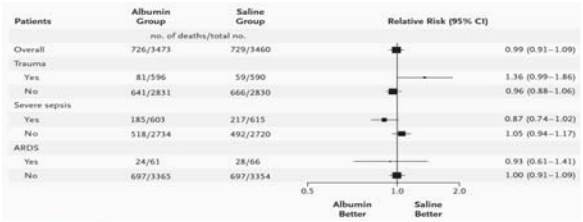
SAFE Trial – Mortality Results



- No difference in:
  - Mechanical ventilation duration
  - New organ failure
  - Renal replacement duration
  - ICU or hospital length of stay
- Serum Albumin
  - Albumin group: 2.9 g/dL
  - Saline group: 2.3 g/dL

Finfer, S. (2004). N Engl j Med, 350(22), 2247-2256

SAFE Trial – Subgroup Analysis



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Annane, D..(2013). Jama, 310(17), 1809-1817.
Caironi, P. (2014). NEJM 370(15), 1412-1421

Treatment Plan

Treatment Arm	Colloids Gelatins, hydroxyethyl starches (HES), albumin 4% or 20-25%, dextrans Amount and rate as determined by the prescribing physician
Control Arm	Crystalloids Isotonic saline, hypertonic saline, Lactated Ringer's Solution Amount and rate as determined by the prescribing physician
Subgroup Analysis	Sepsis / Trauma / Hypovolemic Shock (without sepsis or trauma)

Annane, D. (2013). Jama, 310(17), 1809-1817.

CRISTAL Trial

Variable	Crystalloids (n=1443)	Colloids (n=1414)
Age	63	63
SOFA	8	8
Mechanical Ventilation	73.5%	71.2%
Renal Replacement	5.1%	4.7%
Sepsis	779 (54%)	774 (54.7%)
Trauma	92 (6.4%)	85 (6%)
Hypovolemic Shock (without sepsis or trauma)	572 (39.6%)	555 (39.3%)

Annane, D. (2013). Jama, 310(17), 1809-1817.

CRISTAL Trial

Outcome	Crystalloids (n=1443)	Colloids (n=1414)	P value
All-cause mortality (28 days)	27%	25.4%	0.26
All-cause mortality (90 days)	34.2%	30.7%	0.03
Days without mechanical ventilation (Day 7	1.8	2.1	0.01
Days without renal replacement therapy (Day 7)	4.6	4.8	0.99
Days without vasopressor therapy (Day)	4.7	5	0.04
Days without organ failure (Day 7)	6.1	6.2	0.31
Days not in ICU (Day 28)	8.1	8.3	0.69
Days not in hospital (Day 28)	11.6	11.9	0.37

Annane, D. (2013). Jama, 310(17), 1809-1817.

Fluids Administered

Fluid Type	Colloid (n=1414)	Crystalloid (n=1443)
Isotonic Saline	17.8%	85.7%
Ringers Lactate	6.2%	17.7%
Hypertonic Saline	1.3%	4.2%
Gelatins	34.9%	1.66%
Hydroxyethyl Starch	68.8%	4.78%
Albumin 4%	6.2%	4.2%
Albumin 20%	14.2%	12.3%
Dextrans	0.4%	0%

Annane, D.,(2013). Jama, 310(17), 1809-1817.

Subgroup Analysis

Single Fluid

Subgroup	Albumin (n=80)	NS (n=1035)	Hazard Ratio
28 day mortality	30%	27%	1.10 (0.72 – 1.68)
90 day mortality	35%	33%	1.02 (0.69 – 1.50)

Sepsis

Subgroup	Albumin (n=59)	NS (n=557)	Hazard Ratio
28 day mortality	32%	28%	1.16 (0.72 – 1.87)
90 day mortality	37%	35%	1.07 (0.69 – 1.67)

Annane, D.,(2013). Jama, 310(17), 1809-1817.

Meta-Analysis

	Delaney (2011)	Patel (2014)	Xu (2014)
Studies	17 RCT n=1977	18 Prospective RCT n=4190	5 Prospective RCT n=3658
Population	Sepsis	Sepsis Critically Ill	Severe Sepsis Septic Shock
Primary Outcome	All-cause mortality	All-cause mortality	All-cause mortality

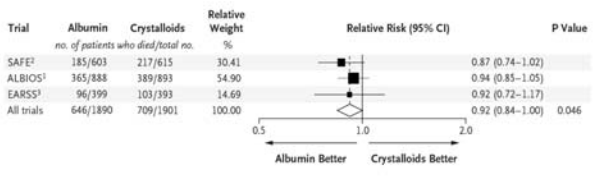
Delaney, A. P. (2011). Critical care medicine, 39(2), 386-391.
Patel, A. (2014). Bmj, 349, g4561.
Xu, J. Y.(2014).Critical Care, 18(6), 702.

Summary of Meta-analysis

		All-Cause Mortality
Delaney et al. 2011	Albumin and crystalloids have similar effect on all-cause mortality	OR: 0.82 (0.67 – 1.0) P=0.47
Patel et al. 2014	Albumin and crystalloids have similar effect on all-cause mortality No difference in severe sepsis subgroup	RR: 0.94 (0.87 – 1.01) P=0.11
Xu et al. 2014	Albumin and crystalloids have similar effect on all-cause mortality Septic shock: 90-day mortality significantly lower in albumin group	Septic Shock OR: 0.88 (0.67 – 0.97)

Delaney, A. P. (2011). Critical care medicine, 39(2), 386-391.
Patel, A. (2014). Bmj, 349, g4561.
Xu, J. Y.(2014).Critical Care, 18(6), 702.

Pooled Mortality



N Engl J Med 2014; 371:83-84

Cost Comparison (100 kg patient)

Strategy	Cost Per Patient	Cost Per Month[b]	Cost Per Year[c]
Albumin 5% (30 mL/kg/day)	$4989.60[a]	$24948.00	$299,376.00
Isotonic Saline (30 mL/kg/day)	$345.00[a]	$1725.00	$20,700.00
Albumin (ALBIOS)	$1838.00	$9190.00	$110,280.00
Isotonic Saline (ALBIOS)	$371.00	$1855.00	$22,260.00

a. 5 days of treatment
b. 5 patients per month
c. 60 patient per year

Role of Albumin

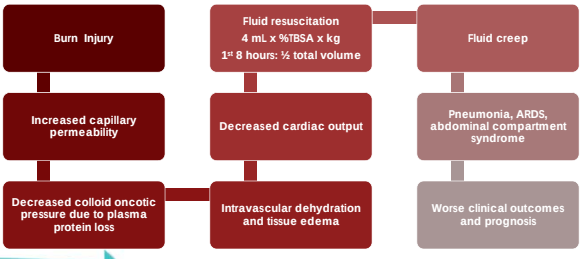
- ✗ • Beneficial effect on mortality compared to crystalloids?
- ✗ • Evidence of increased harm?
- ✗ • Consistent dosing schemes?
- ✓ • Surviving Sepsis Campaign 2016
  - Crystalloids – fluid of choice for intravascular fluid replacement
  - Albumin – add to crystalloids in severe sepsis and septic shock

Break Through Branch Out

Fluid Resuscitation: Burn Patients

Break Through Branch Out

Physiologic Role of Albumin



Cartotto, R.,(2012). Journal of Burn Care & Research, 33(6), 702-717.

Break Through Branch Out

Navickis et al. (2016)

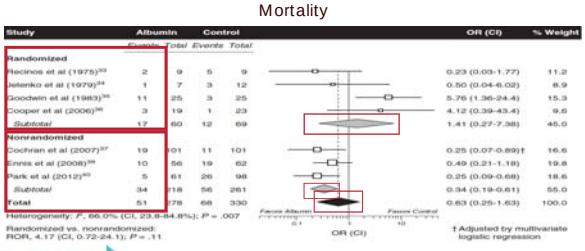
Design	Study	Mean TBSA (%)	Patients
Randomized	Recinos et al. (1975)	57%	18
	Jelenko et al. (1979)	47%	19
	Goodwin et al. (1983)	51%	50
	Cooper et al. (2006)	36%	42
Non-Randomized	Cochran et al. 2007	41%	202
	Dulhunty et al. 2008	43%	80
	Ennis et al. 2008	51%	118
	Park et al. 2012	39%	159
			Total: 869

Navickis, R. J. (2016). Journal of Burn Care & Research, 37(3), e268.

Break Through Branch Out

Navickis et al. (2016)

Mortality

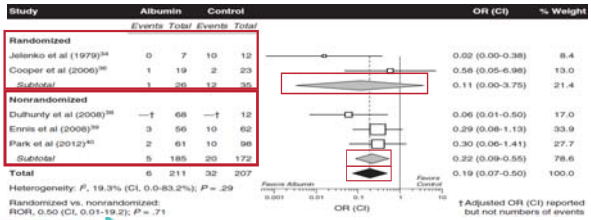


Navickis, R. J. (2016). Journal of Burn Care & Research, 37(3), e268.

Break Through Branch Out

Navickis et al. (2016)

Compartment Syndrome



Navickis, R. J. (2016). Journal of Burn Care & Research, 37(3), e268.

Break Through Branch Out

Eljaiek et al. (2017)

Design	Study	Mean TBSA (%)	Patients
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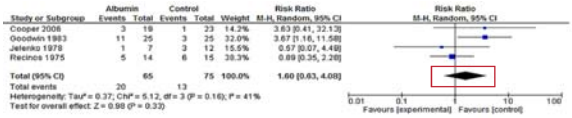
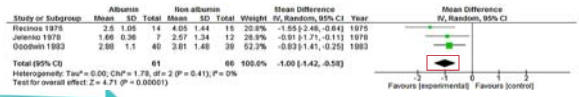
Eljaiek, R. (2017). Burns, 43(1), 17-24.

Eljaiek et al. (2017)

Effect on Mortality



Effect on Total Volume



Eljaiek, R. (2017). Burns, 43(1), 17-24.

Role of Albumin

- Fluid requirements in excess of 6 mL x %TBSA x kg
  - Full thickness burns
  - Inhalation injury
  - Delay in resuscitation
- Dosing of albumin (Orlando Health)
  - 5%: albumin (1/3 Parkland rate) + Lactated Ringer's (2/3 Parkland rate)
  - 25%: albumin (1/15 Parkland rate) +Lactated Ringer's (2/3 Parkland rate)

Pham, T. N. (2008). Journal of Burn Care & Research, 29(1), 257-266.

Summary

- No clear benefit of supplementing hypoalbuminemic patients
- No clear harm nor benefit on mortality as large volume resuscitation
- Benefit in burn patients as part of colloid rescue
- Higher cost relegates albumin to alternative agent in most cases

#FSHP2018

To Give or Not to Give:

The Role of Albumin in the Critically Ill Patient

Dominick Curry, PharmD
Pharmacy Supervisor
Orlando Health