Fluid Resuscitation in Sepsis

A Literature Review

"On the floor lay a girl of slender make and juvenile height, but with the face of a superannuated hag... The colour of her countenance was that of lead - a silver blue, ghastly tint; her eyes were sunk deep into sockets, as though they had been driven an inch behind their natural position; her mouth was squared; her features flattened; her eyelids black; her fingers shrunk, bent, and inky in their hue…

NOTICE.

PREVENTIVES OF

CHOLERA!

Published by order of the Sanatory Committee, under the sanction of the Medical Counsel.

BE TEMPERATE IN EATING & DRINKING!

Avoid Raw Vegetables and Unripe Fruit !.

Abstain from COLD WATER, when heated, and above all from *Ardent Spirits*, and if habit have rendered them indispensable, take much less than usual.

SLEEP AND CLOTHE WARM !

DO NOT SLEEP OR SIT IN A DRAUGHT OF AIR.

Avoid getting Wet !

Attend immediately to all disorders of the Bowels.

TAKE NO MEDICINE WITHOUT ADVICE.

Medicine and Medical Advice can be had by the poor, at all hours of the day and night, by applying at the Station House in each Ward.

CALEB S. WOODHULL, *Mayor.*

JAMES KELLY, *Chairman of Sanatory Committee.*

The Pioneers

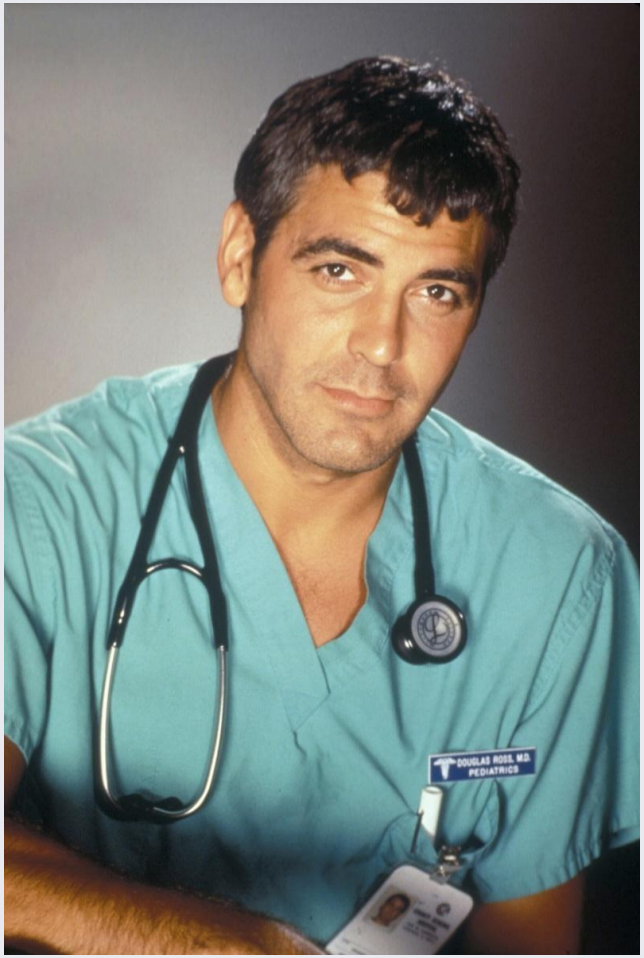
Dr Latta's Saline Solution

Two to three drachms of muriate of soda (NaCl), two scruples of the bicarbonate of soda in six pints of water and injected it at temperature 112 Fah

(approximately 58mmol/l Na^+, 49mmol/l Cl^-, 9mmol/l HCO_3^-)

Ten of the first fifteen patients died

180 years on…..



Current controversies in fluid therapy in septic patients

When to give fluid

How much fluid to give

Which fluid to use

Definitions

- SIRS: widespread inflammatory response that may or may not be associated with infection: 2 or more of
  - Temperature, tachycardia, tachypnoea and WCC

- Sepsis: SIRS in the presence of or as a result of suspected or proven infection

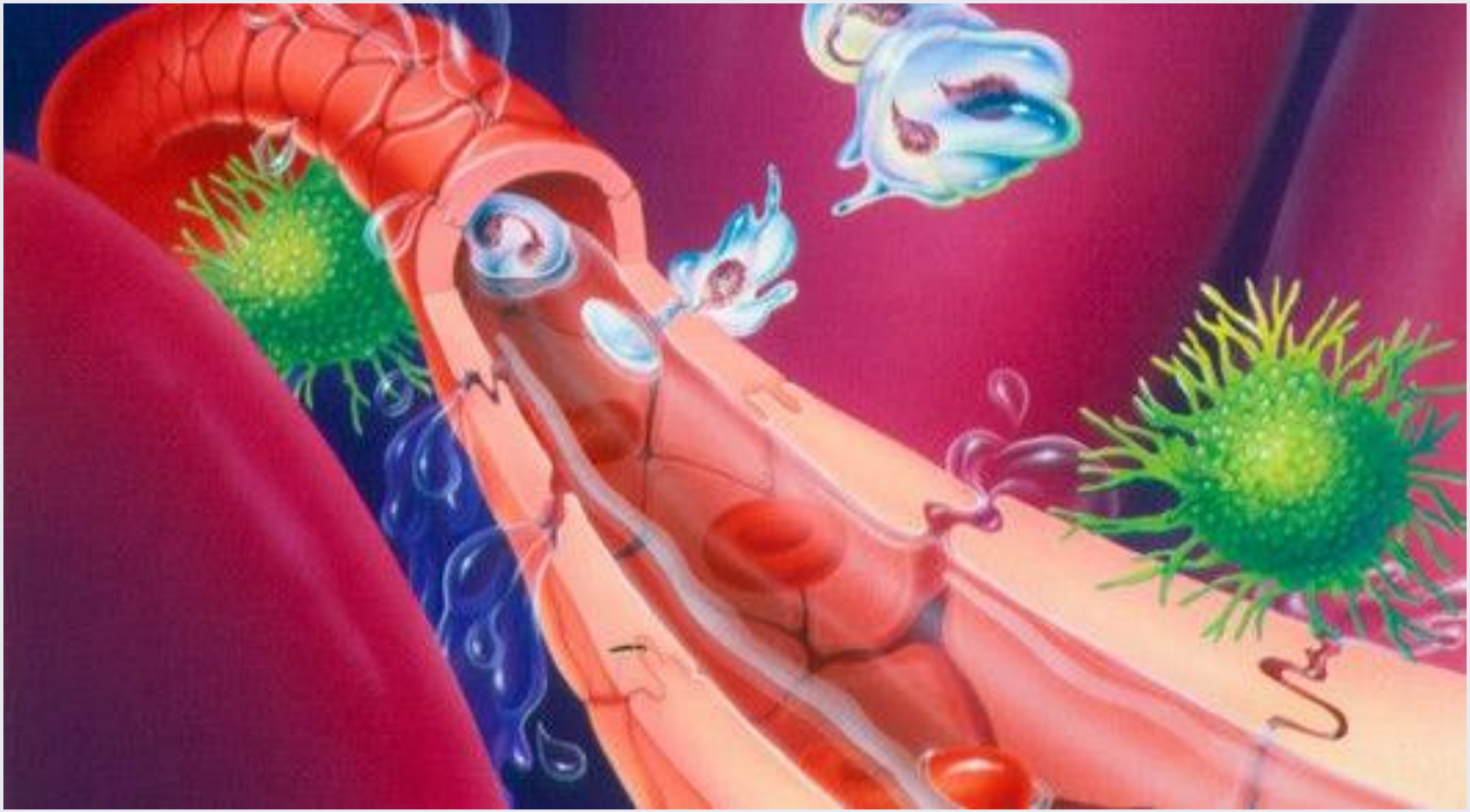
- Septic shock: Sepsis with cardiovascular dysfunction despite the administration of >40ml/kg isotonic fluid in one hour

Epidemiology

- Angus et al. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome and associated costs of care. Critical Care Med 2001; 29: 1303-1310
  - Estimated 750,000 cases of severe sepsis annually in US
  - Mortality of 28.6%
  - $22,100 per case

- Starship Hospital
  - 2010-2012
  - 90 cases of sepsis/septic shock

Pathophysiology



The Evidence

When to give fluid

How much fluid should we give

Early Paediatric Practices

- Early 1980's
  - Slow cautious fluid bolus: 10-20ml/kg over 20-30 minutes
    - Era of limited paediatric ventilators/PICU
    - Awareness of SIADH in patients with sepsis and meningitis

- 1988
  - The AHA's Textbook of PALS
  - Rapid 20ml/kg fluid boluses to a total of 60ml/kg or more in the first hour of resuscitation

Carcillo et al. Role of Early Fluid Resuscitation in Pediatric Septic Shock. JAMA 1991; 266 (9): 1242-1245.

- Children's Hospital National Medical Centre
  - 1982-1989
- All patients with septic shock with a PAC at 6 hours
  - Group 1: up to 20ml/kg
  - Group 2: 20-40ml/kg and
  - Group 3: >40ml/kg in first hour
- End points: survival, ARDS, hypovolaemia at 6 hours

- 34 patients
  - Median age 13.5 months
  - Pre-existing chronic disease in 31%
  - 82% required ventilation
  - 100% required inotropic support
- Fluid resuscitation
  - Crystalloids (0.9% or lactated Ringer's)
  - Colloids: 5% albumin or blood products (RBC, FFP, cryoprecipitate)

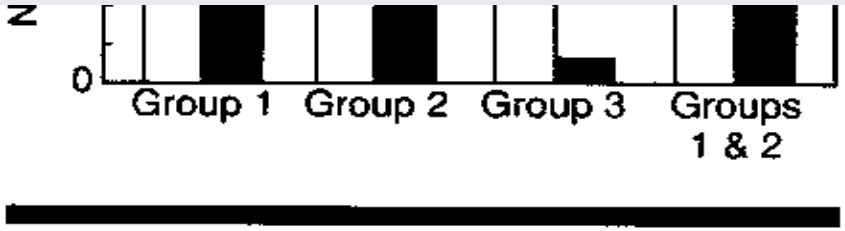


Fig 1.—The distribution of survivors and nonsurvivors within fluid resuscitation groups (see text for definition of groups). The asterisk indicates a significant difference in survival between group 3 and groups 1 and 2 individually and combined.

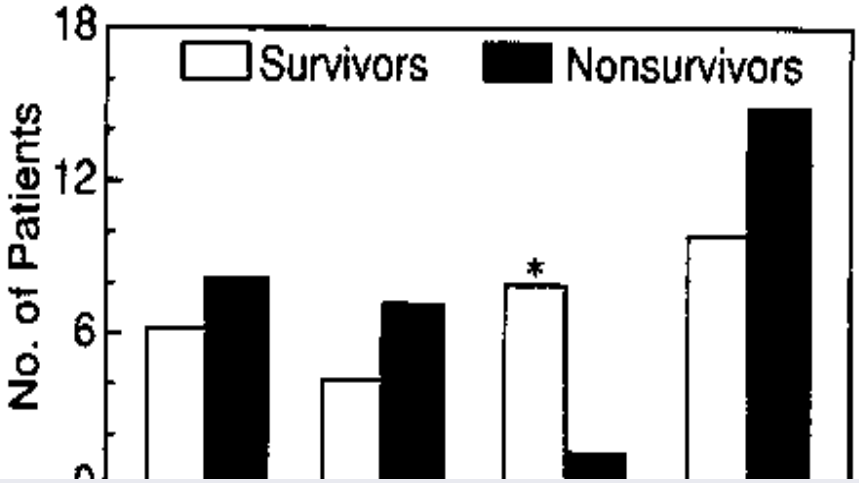
loid fluids in the form of normal saline or lactated Ringer's solution. Colloid preparations consisted of 5% albumin or blood products including packed red blood cells, fresh frozen plasma, or cryoprecipitate. The average volume of fluid administered in the first hour was 33 mL/kg, of which 9 mL/kg was colloid

Survivors (n = 18)	42 ± 28‡	97 ± 49
Nonsurvivors (n = 16)	23 ± 18	94 ± 37

*$P < .05$, comparing the mean volume administered at 1 hour in each group to the other groups.

†$P < .05$, comparing the mean volume administered at 6 hours in group 1 to group 2 or group 3.

‡$P < .05$, mean volume administered in first hour in survivors compared with nonsurvivors.



3 mm Hg, and 8 mm Hg, but did not have urine outputs of less than 1 mL/kg per hour and experienced no persistent episodes of hypotension after initial therapy. No patient who received more than 40 mL/kg of fluid in the first hour was hypovolemic at 6 hours (Fisher's Exact Test, $P = .003$), and only one of nine patients in group 3 had a PCWP of less than 9 mm Hg; this patient survived.

The presence of ARDS was associated with an increased risk of death (Fisher's Exact Test, $P = .029$; Fig 2). The presence of preexisting chronic disease appeared to affect survival, but this association was not statistically significant (Fisher's Exact Test, $P = .066$). There was no association between mortality and development of CPE. Indeed,

tions do not prove cause and effect. However, the study does suggest that following current pediatric advanced life support guidelines for fluid resuscitation[1] may improve survival without any increase in morbidity in children with septic shock.

Until recently, the therapy for pediatric shock called for a fluid bolus of 10 to 20 mL/kg over 20 to 30 minutes with careful monitoring of the central venous pressure.[5,6] We believe that relatively slow fluid resuscitation was founded in an era when pediatric ventilators and positive-end expiratory pressure measurements were not readily available to treat the child with ARDS or CPE. If central venous pressures and PCWPs were not measured, the presence of pul-

Carcillo et al. Role of Early Fluid Resuscitation in Pediatric Septic Shock. JAMA 1991; 266 (9): 1242-1245.

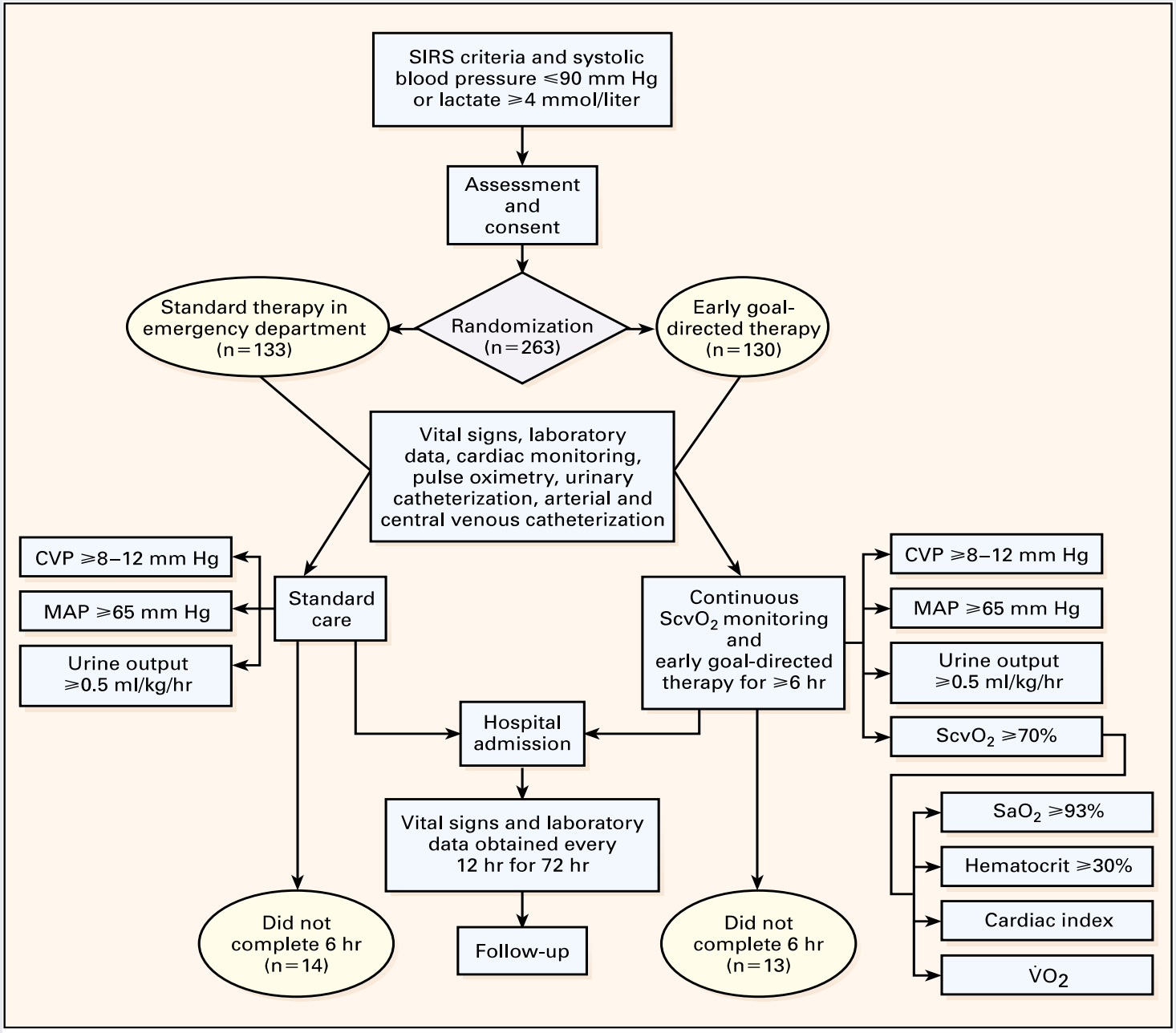
- Criticisms
  - Treatment groups assigned non-randomly
  - Treatment based on clinical criteria
  - Criteria determined by different individuals

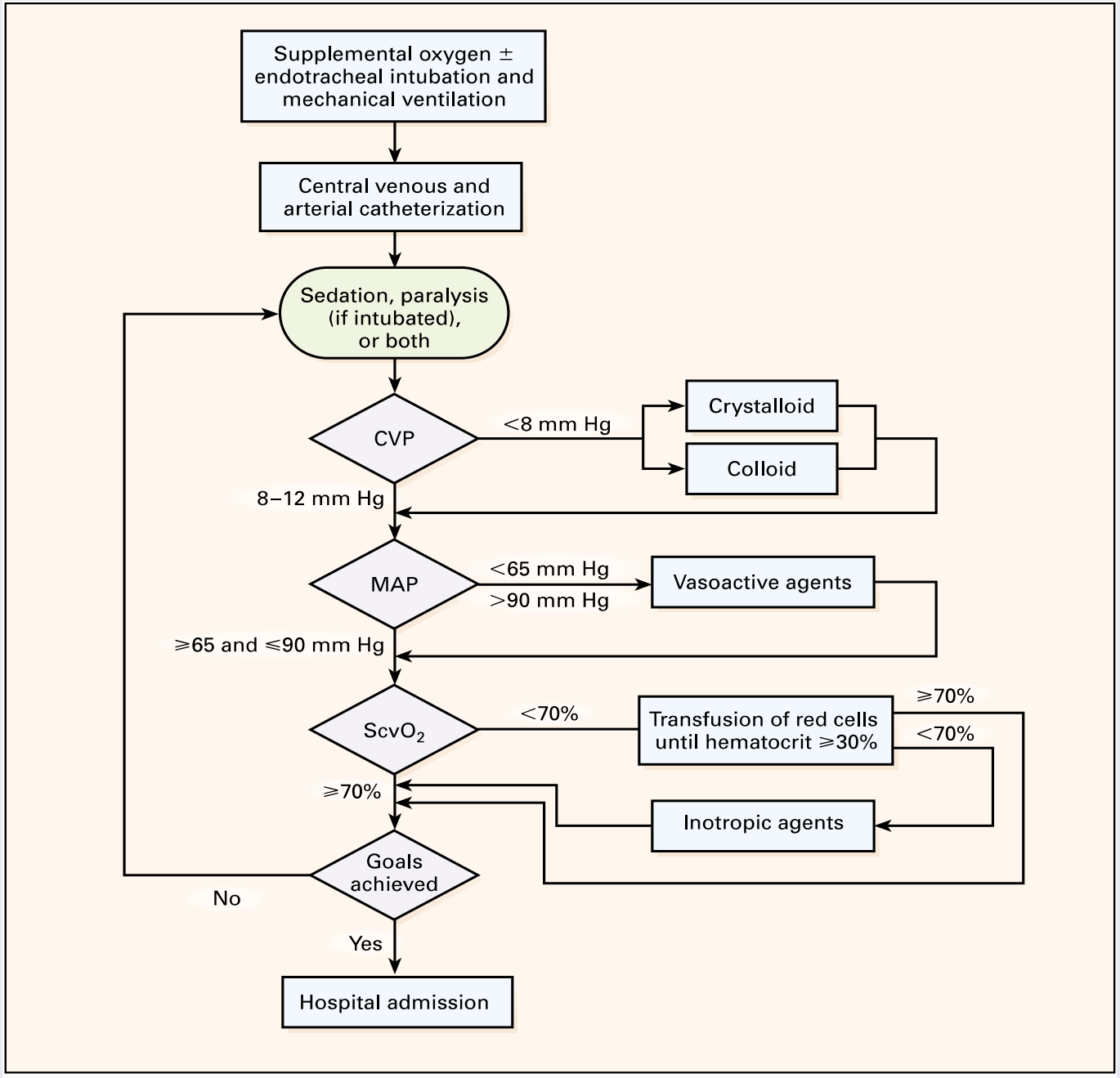
- But….findings suggested current PALS guidelines may improve survival in children with septic shock

Rivers et al. Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock. NEJM 2001; 345: 1368-77

- To evaluate the efficacy of EGDT before admission to ICU
  - Single center: Detroit Hospital
  - Emergency Department

- 263 patients: severe sepsis or septic shock
  - Randomly assigned
  - 6 hours of standard versus EGT
  - End points: MOF, mortality,


SIRS criteria and systolic blood pressure ≤90 mm Hg or lactate ≥4 mmol/liter
Assessment and consent
Randomization (n=263)
Standard therapy in emergency department (n=133)
Early goal-directed therapy (n=130)
Vital signs, laboratory data, cardiac monitoring, pulse oximetry, urinary catheterization, arterial and central venous catheterization
CVP ≥8–12 mm Hg
MAP ≥65 mm Hg
Urine output ≥0.5 ml/kg/hr
Standard care
Continuous $ScvO_2$ monitoring and early goal-directed therapy for ≥6 hr
CVP ≥8–12 mm Hg
MAP ≥65 mm Hg
Urine output ≥0.5 ml/kg/hr
$ScvO_2$ ≥70%
SaO_2 ≥93%
Hematocrit ≥30%
Cardiac index
$\dot{V}O_2$
Hospital admission
Vital signs and laboratory data obtained every 12 hr for 72 hr
Follow-up
Did not complete 6 hr (n=14)
Did not complete 6 hr (n=13)


Supplemental oxygen ± endotracheal intubation and mechanical ventilation
Central venous and arterial catheterization
Sedation, paralysis (if intubated), or both
CVP
<8 mm Hg
Crystalloid
Colloid
8–12 mm Hg
MAP
<65 mm Hg
>90 mm Hg
Vasoactive agents
≥65 and ≤90 mm Hg
ScvO2
<70%
Transfusion of red cells until hematocrit ≥30%
≥70%
<70%
≥70%
Inotropic agents
Goals achieved
No
Yes
Hospital admission

Rivers et al. Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock. NEJM 2001; 345: 1368-77

- Results
  - 263 patients
    - 8.7% excluded or did not consent
    - Similar baseline characteristics including adequacy and duration of antibiotic therapy
  - Standard patients in ED 6.3 hours v 8 hours ($p<0.001$)
    - No difference in HR or CVP
    - MAP's significantly lower

TABLE 3. KAPLAN–MEIER ESTIMATES OF MORTALITY AND CAUSES OF IN-HOSPITAL DEATH.*

VARIABLE	STANDARD THERAPY (N=133)	EARLY GOAL-DIRECTED THERAPY (N=130)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
In-hospital mortality†				
All patients	59 (46.5)	38 (30.5)	0.58 (0.38–0.87)	0.009
Patients with severe sepsis	19 (30.0)	9 (14.9)	0.46 (0.21–1.03)	0.06
Patients with septic shock	40 (56.8)	29 (42.3)	0.60 (0.36–0.98)	0.04
Patients with sepsis syndrome	44 (45.4)	35 (35.1)	0.66 (0.42–1.04)	0.07
28-Day mortality†	61 (49.2)	40 (33.3)	0.58 (0.39–0.87)	0.01
60-Day mortality†	70 (56.9)	50 (44.3)	0.67 (0.46–0.96)	0.03
Causes of in-hospital death‡				
Sudden cardiovascular collapse	25/119 (21.0)	12/117 (10.3)	—	0.02
Multiorgan failure	26/119 (21.8)	19/117 (16.2)	—	0.27

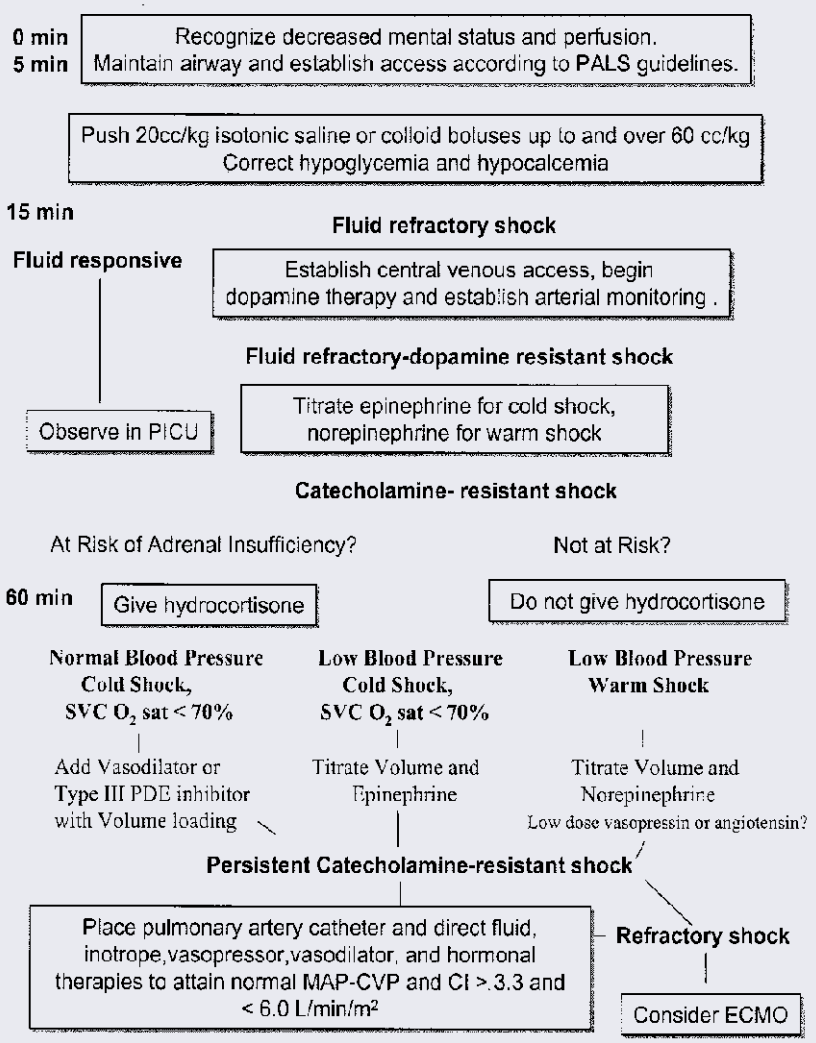
Table 4. Treatments Administered.*

Treatment	Hours after the Start of Therapy		
	0–6	7–72	0–72
Total fluids (ml)			
Standard therapy	3499±2438	10,602±6,216	13,358±7,729
EGDT	4981±2984	8,625±5,162	13,443±6,390
P value	<0.001	0.01	0.73
Red-cell transfusion (%)			
Standard therapy	18.5	32.8	44.5
EGDT	64.1	11.1	68.4
P value	<0.001	<0.001	<0.001
Any vasopressor (%)†			
Standard therapy	30.3	42.9	51.3
EGDT	27.4	29.1	36.8
P value	0.62	0.03	0.02
Inotropic agent (dobutamine) (%)			
Standard therapy	0.8	8.4	9.2
EGDT	13.7	14.5	15.4
P value	<0.001	0.14	0.15
Mechanical ventilation (%)			
Standard therapy	53.8	16.8	70.6
EGDT	53.0	2.6	55.6
P value	0.90	<0.001	0.02
Pulmonary-artery catheterization (%)‡			
Standard therapy	3.4	28.6	31.9
EGDT	0	18.0	18.0
P value	0.12	0.04	0.01

Rivers et al. Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock. NEJM 2001; 345: 1368-77

- Criticisms
  - Single center
  - Single physician
  - Treatment group mortality similar across centers

Carcillo et al. Clinical practice parameters for haemodynamic support of paediatric and neonatal patients in septic shock. Critical Care Med 2002; 30:1365-1378.



St. Mary's Hospital, London

- Specialist Tertiary Referral Centre, 2002
  - High rates of meningococcal disease
  - Consultant led retrieval service
  - Telephone advice throughout the south of England
  - Centralization of meningococcal disease care

- Early aggressive fluid resuscitation
  - 4% Albumin

deOliveira et al. ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcomes comparison with and without monitoring central venous saturation. Intensive Care Medicine 2008; 34: 1065-1075.

- 102 children with severe sepsis or fluid refractory septic shock
  - Randomly assigned to ACCM/PALS with or without ScvO2 goal-directed resuscitation for 72 hours

- Control group
  - ACCM/PALS therapies without continuous ScvO2
  - Fluid resuscitation (crystalloid or colloid), RBC or CVS drugs
  - Maintain normal perfusion pressure for age, UO >1ml/kg/hour, CRT of 2 seconds and normal pulses

- Intervention group
  - Endpoint of ScvO2 >70% using continuous monitoring
  - If <70% then more fluid, RBC (if Hb<10g/l) or inotropes were given

- Other supportive therapies: CMV, nutrition, antibiotics and RRT decided by medical team

deOliveira et al. ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcomes comparison with and without monitoring central venous saturation. Intensive Care Medicine 2008; 34: 1065-1075.

- Intervention Group
  - 28 day mortality (11.8% v 39.2%)
  - More crystalloid (28 v 5mls/kg)
  - RBC transfusion (45.1% v 15.7%)
  - More inotropic support (29.4% v 7.8%)
  - Fewer new organ dysfunctions

- Support of the current ACCM/PALS guidelines
  - Goal-directed therapy using the endpoint of ScvO2 $\geq$70% provided a significant impact on the outcome of children

Guideline Update

- Brierly et al. Clinical practice parameters for haemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine CCM 2009;37:666-88

- Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock. Critical Care Med 2008. 36(1):296-327

Improved outcomes in paediatric septic shock

- Han et al. Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. Pediatrics 2003; 112:793-9

- Inwald et al. Emergency management of children with severe sepsis in the UK: the results of the Paediatric Intensive Care Society sepsis audit. Arch Disease in Childhood 2009;94:348-53

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Mortality after Fluid Bolus in African Children with Severe Infection

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Background

- Early aggressive fluid resuscitation in patients with shock

- sub-Saharan Africa
  - Malaria, sepsis and other infectious disease
  - High early mortality
  - Fluid resuscitation not practiced unless severe anaemia

- WHO recommends fluid resuscitation in advanced shock only
  - CRT > 3 seconds
  - Weak and fast pulse
  - Cold extremities

Aims

- FEAST trial designed to investigate the practice of:
  - Early resuscitation with a saline bolus as compared with no bolus (control)
  - With an albumin bolus as compared with a saline bolus

Study Design

- 2 stratum, multi-center, open, randomised controlled study
  - January 2009-2011
  - Age between 60 days and 12 years
  - 6 clinical centers: 1 Kenya; 1 Tanzania; 4 Uganda

- Stratum A
  - Children without severe hypotension

- Stratum B
  - Children with severe hypotension
    - SBP <50mmHg if <12 months; <60mmHg if 1-5 years; < 70mmHg >5 years

Study Design

Stratum A	Stratum B
Randomly assigned 1:1:1	Randomly assigned 1:1
Rapid volume expansion over 1 hour	Rapid volume expansion over 1 hour
20mls/kg (40ml/kg June 2010)	40ml/kg (60ml/kg June 2010)
1. 0.9% NaCl (saline-bolus group) 2. 5% HAS (albumin-bolus group) 3. none (control group)	1. 0.9% or (saline-bolus) 2. 5% HAS (albumin-bolus)
Additional 20ml/kg bolus at 1 hour if impaired perfusion (not in control group)	Additional 20ml/kg bolus at 1 hour if impaired perfusion
Severe hypotension: 40ml/kg of study fluid (saline in control group)	Severe hypotension: 40ml/kg of study fluid

Study Population

Inclusions	Exclusions
Age 60 days to 12 years Severe febrile illness complicated by Impaired consciousness Respiratory distress Impaired perfusion 1. CRT >3 seconds 2. Lower limb temperature gradient 3. Weak radial-pulse volume 4. Severe tachycardia	Severe malnutrition Gastroenteritis Non-infectious causes of shock 1. Trauma 2. Surgery 3. Burns Conditions for which volume expansion is contraindicated

End Points

- Primary End Point
  - Mortality at 48 hours

- Secondary End Points
  - Mortality at 4 weeks
  - Neurologic sequelae at 4 & 24 weeks
  - Episodes of hypotensive shock within 48 hours after randomisation
  - Adverse events potentially related to fluid resuscitation
    - Pulmonary oedema
    - Increased ICP
    - Severe allergic reaction

Study Procedures

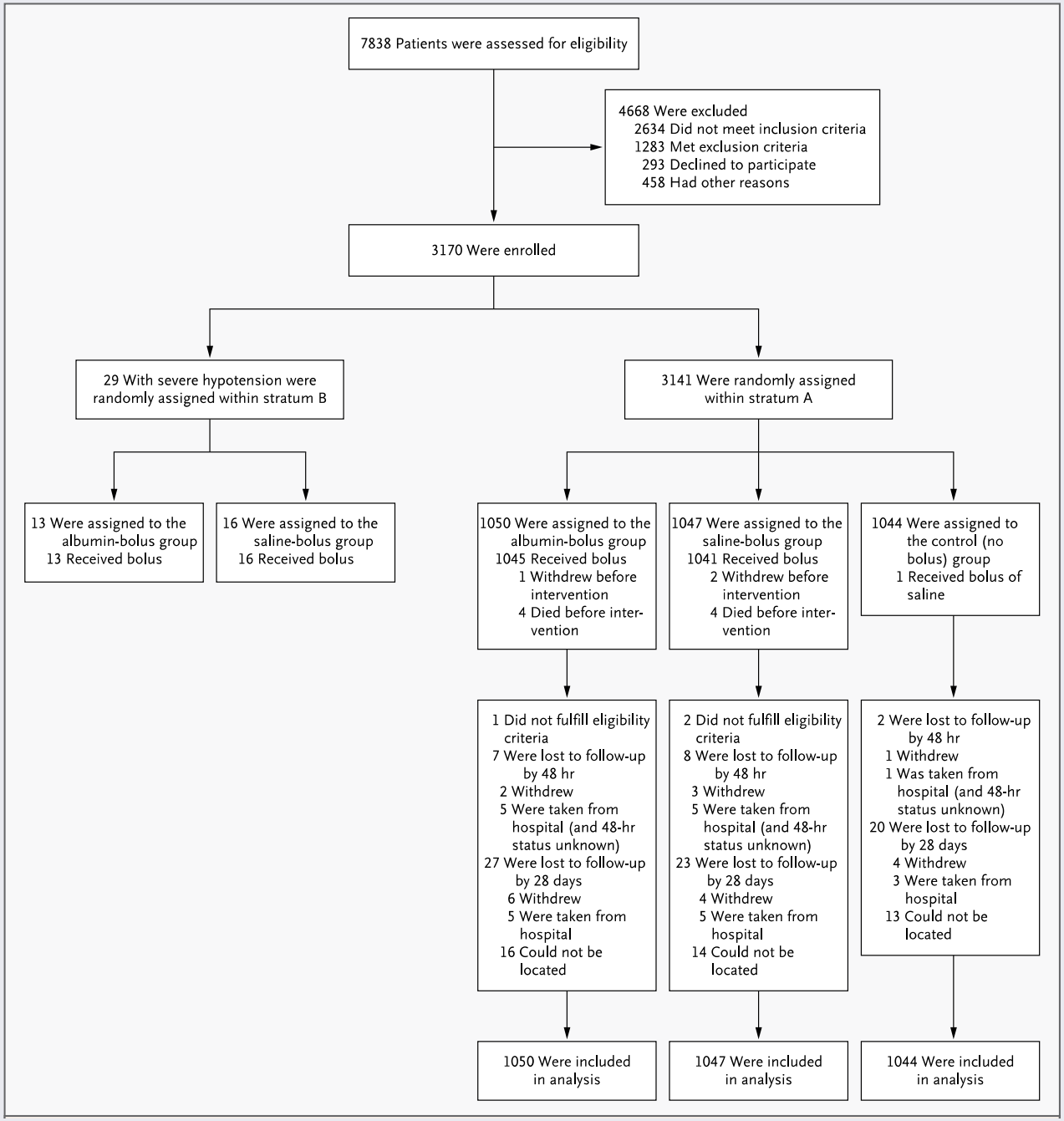
- Treated on general paediatric ward
  - Assisted ventilation bag-mask only
  - Provided with monitors for saturations and blood pressure
  - Training in triage & emergency paediatric life support

- Supportive management
  - IV maintenance fluids (2.5 – 4ml/kg/hour)
  - Antibiotics, anti-malarials, anti-pyretics, anticonvulsant drugs
  - Treated for hypoglycaemia (<2.5mmol/L)
  - RBC transfusion at 20ml/kg over 4 hours if Hb <5g/dl

Study Procedures

- Clinical case-report form completed at 1,4, 8, 24 and 48 hours
  - Hypovolaemia, neurologic and cardiorespiratory status
  - Adverse events were reported

- Neurological assessment at 4 weeks
  - Reviewed by independent clinician
  - Reassessed at 24 weeks if neurological sequelae present


7838 Patients were assessed for eligibility
4668 Were excluded
2634 Did not meet inclusion criteria
1283 Met exclusion criteria
293 Declined to participate
458 Had other reasons
3170 Were enrolled
29 With severe hypotension were randomly assigned within stratum B
3141 Were randomly assigned within stratum A
13 Were assigned to the albumin-bolus group
13 Received bolus
16 Were assigned to the saline-bolus group
16 Received bolus
1050 Were assigned to the albumin-bolus group
1045 Received bolus
1 Withdrew before intervention
4 Died before intervention
1047 Were assigned to the saline-bolus group
1041 Received bolus
2 Withdrew before intervention
4 Died before intervention
1044 Were assigned to the control (no bolus) group
1 Received bolus of saline
1 Did not fulfill eligibility criteria
7 Were lost to follow-up by 48 hr
2 Withdrew
5 Were taken from hospital (and 48-hr status unknown)
27 Were lost to follow-up by 28 days
6 Withdrew
5 Were taken from hospital
16 Could not be located
2 Did not fulfill eligibility criteria
8 Were lost to follow-up by 48 hr
3 Withdrew
5 Were taken from hospital (and 48-hr status unknown)
23 Were lost to follow-up by 28 days
4 Withdrew
5 Were taken from hospital
14 Could not be located
2 Were lost to follow-up by 48 hr
1 Withdrew
1 Was taken from hospital (and 48-hr status unknown)
20 Were lost to follow-up by 28 days
4 Withdrew
3 Were taken from hospital
13 Could not be located
1050 Were included in analysis
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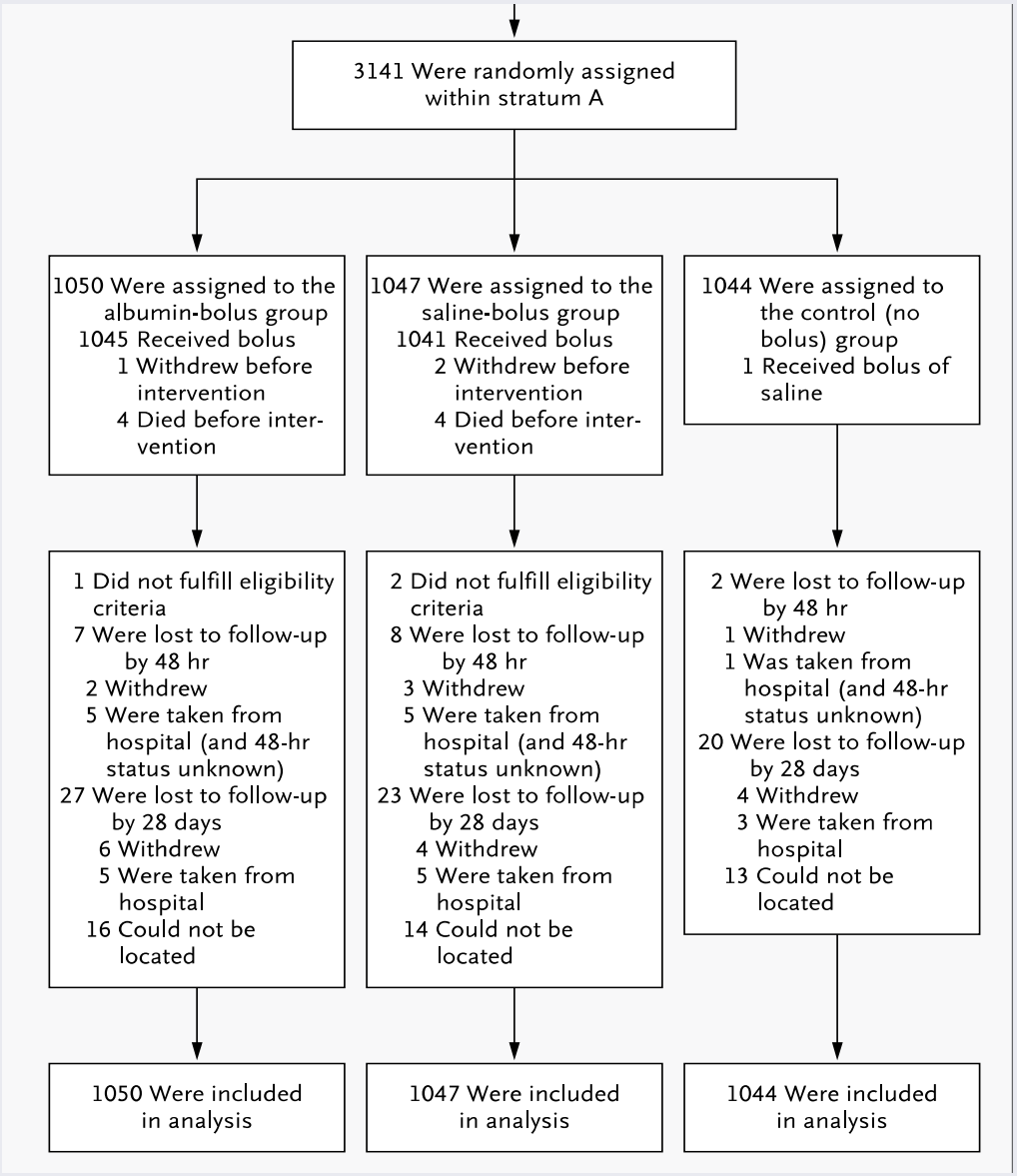
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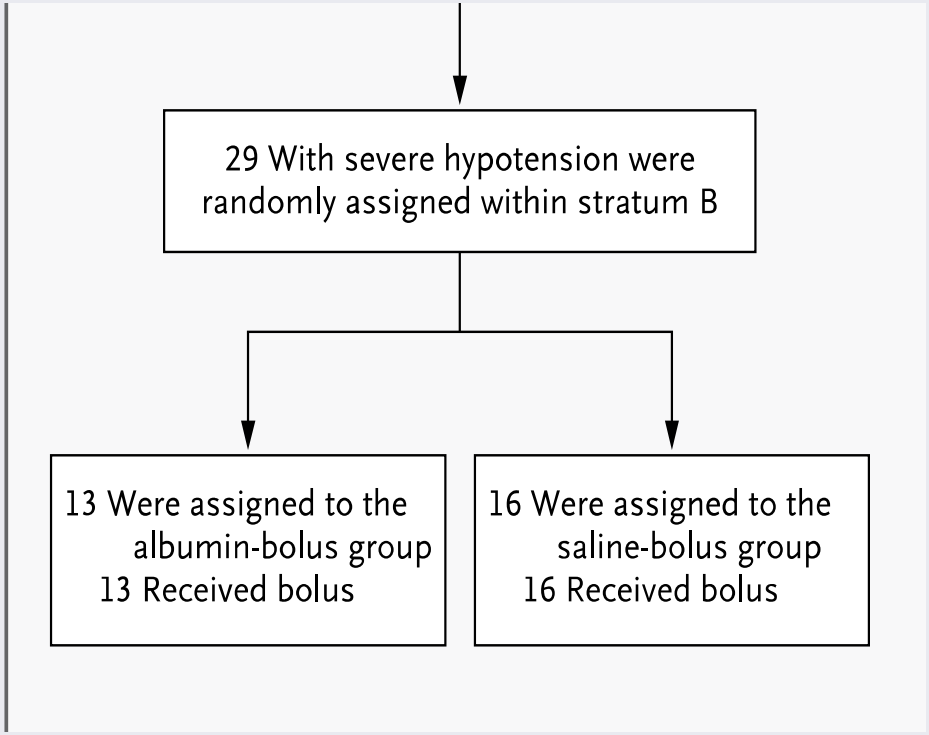
29 With severe hypotension were randomly assigned within stratum B
13 Were assigned to the albumin-bolus group
13 Received bolus
16 Were assigned to the saline-bolus group
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Table 1. Baseline Characteristics of the Children.*

Variable	Albumin Bolus (N=1050)	Saline Bolus (N=1047)	No Bolus (N=1044)	Total (N=3141)
Demographic and anthropometric characteristics				
Age — mo				
Median	23	23	25	24
Interquartile range	14–37	13–37	14–40	13–38
Female sex — no. (%)	474 (45)	480 (46)	498 (48)	1452 (46)
Mid-upper-arm circumference ≤11.5 cm — no./total no. (%)	21/982 (2)	24/974 (2)	25/1003 (2)	70/2959 (2)
Findings at presentation				
Axillary temperature >39°C — no. (%)	243 (23)	236 (23)	264 (25)	743 (24)
Hypothermia (temperature <36°C) — no. (%)	59 (6)	64 (6)	66 (6)	189 (6)
Respiratory distress — no./total no. (%)	874/1048 (83)	854/1045 (82)	857/1037 (83)	2585/3130 (83)
Respiratory rate — breaths/min	58±15	58±15	57±15	58±15
Oxygen saturation <90% — no. (%)†	249/1015 (25)	253/1008 (25)	257/1015 (25)	759/3038 (25)
Bradycardia (<80 beats/min) — no. (%)	13 (1)	7 (1)	10 (1)	30 (1)
Severe tachycardia — no. (%)	736 (70)	721 (69)	738 (71)	2195 (70)
Weak radial pulse — no. (%)	210 (20)	238 (23)	206 (20)	654 (21)
Capillary refill time — no. (%)				
≥2 sec	712 (68)	720 (69)	673 (64)	2105 (67)
≥3 sec	263 (25)	299 (29)	257 (25)	819 (26)
Positive temperature gradient — no. (%)‡	620 (59)	629 (60)	610 (58)	1859 (59)
Systolic blood pressure — mm Hg				
Median	92	93	92	93
Interquartile range	85–101	85–101	86–101	85–101
Moderate hypotension — no./total no. (%)§	66/1030 (6)	69/1036 (7)	57/1034 (6)	192/3100 (6)
Dehydration — no. (%)¶	78 (7)	95 (9)	58 (6)	231 (7)
Severe pallor manifested in lips, gums, or inner eyelids — no. (%)	523 (50)	546 (52)	520 (50)	1589 (51)
Prostration — no./total no. (%)‖	655/1048 (62)	667/1046 (64)	619/1044 (59)	1941/3138 (62)
Coma — no. (%)**	156 (15)	161 (15)	140 (13)	457 (15)
Convulsions during this illness — no./total no. (%)	414/1047 (40)	387/1045 (37)	371/1039 (36)	1172/3131 (37)
Hemoglobinuria (dark urine) — no. (%)	122 (12)	123 (12)	144 (14)	389 (12)
Jaundice visible to clinician — no. (%)	336 (32)	336 (32)	330 (32)	1002 (32)

Table 1. (Continued.)

Variable	Albumin Bolus (N = 1050)	Saline Bolus (N = 1047)	No Bolus (N = 1044)	Total (N = 3141)
Laboratory assessments†††				
Positive for malaria parasitemia — no./total no. (%)‡‡	590/1044 (57)	612/1042 (59)	591/1037 (57)	1793/3123 (57)
Hemoglobin — no./total no. (%)				
<5 g/dl	323/1024 (32)	332/1015 (33)	332/1015 (33)	987/3054 (32)
>10 g/dl	231/1024 (23)	230/1015 (23)	244/1015 (24)	705/3054 (23)
Glucose — no./total no. (%)				
<2.5 mmol/liter (45 mg/dl)	43/990 (4)	46/991 (5)	42/989 (4)	131/2970 (4)
<3.0 mmol/liter (54 mg/dl)	67/990 (7)	61/991 (6)	59/989 (6)	187/2970 (6)
Lactate ≥5 mmol/liter — no./total no. (%)	357/1000 (36)	407/989 (41)	395/992 (40)	1159/2981(39)
Base deficit ≥8 mmol/liter — no./total no. (%)	380/710 (54)	360/689 (52)	330/680 (49)	1070/2079 (51)
Severe acidemia (pH <7.2) — no./total no. (%)	71/712 (10)	73/694 (11)	65/685 (9)	209/2091 (10)
Hyperkalemia (potassium >6.5 mmol/liter) — no./total no. (%)	67/686 (10)	68/687 (10)	65/670 (10)	200/2043 (10)
Positive for HIV antibody — no./total no. (%)	37/817 (5)	28/827 (3)	41/839 (5)	106/2483 (4)
Positive blood culture — no. of positive cultures/total no. of cultures (%)	38/347 (11)	52/360 (14)	36/363 (10)	126/1070 (12)
Positive cerebrospinal fluid culture — no. of positive cultures/total no. of cultures (%)	2/94 (2)	4/102 (4)	4/96 (4)	10/292 (3)

Administered Fluids

- Adherence to protocol
  - 99.5% in albumin group
  - 99.4% in saline group
  - 99.9% in control group

- Median volume of all fluids (including blood):
  - Albumin Bolus Group: First hour: 20ml/kg; Second hour: 4.5ml/kg
  - Saline Bolus Group: First hour: 20ml/kg; Second hour: 5ml/kg
  - Control Group: First hour: 1.2ml/kg; Second hour: 2.9ml/kg

Fluid Administered

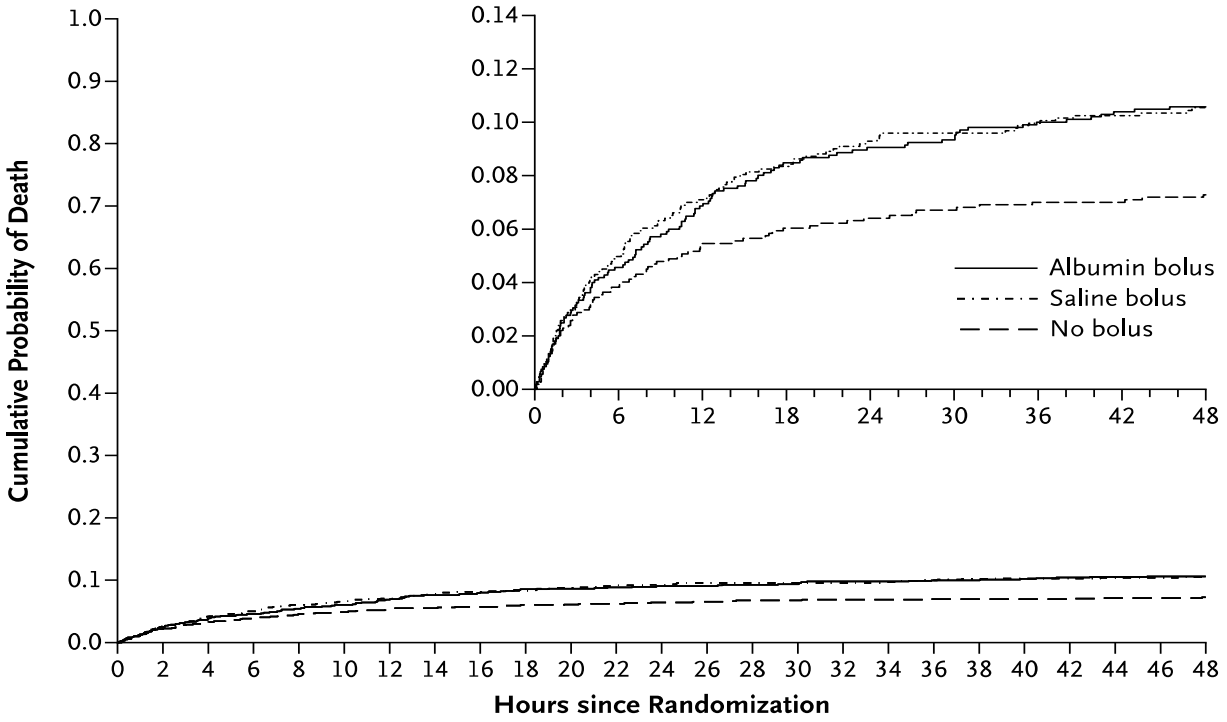
- Over course of 8 hours
  - Median cumulative volume of fluid
    - Albumin-bolus group: 40ml/kg (30-50)
    - Saline-bolus group: 40ml/kg (30.4-50)
    - Control: 10.1 ml/kg (10-25.9)

- RBC transfusion in 1408 children
  - 45% in albumin; 47% in saline; 43% in control
  - Initiated earlier in control group but proportions and volumes similar across all groups

Table 2. Death and Other Adverse Event End Points at 48 Hours and 4 Weeks.

End Point	Albumin Bolus (N=1050)	Saline Bolus (N=1047)	No Bolus (N=1044)	Saline Bolus vs. No Bolus		Albumin Bolus vs. No Bolus		Albumin Bolus vs. Saline Bolus		Albumin and Saline Boluses vs. No Bolus	
				Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
		no. (%)									
48 Hours											
Death — no. (%)	111 (10.6)	110 (10.5)	76 (7.3)	1.44 (1.09–1.90)	0.01	1.45 (1.10–1.92)	0.008	1.00 (0.78–1.29)	0.96	1.45 (1.13–1.86)	0.003
Pulmonary edema — no. (%)	14 (1.3)	6 (0.6)	6 (0.6)								
Increased intracranial pressure — no. (%)	16 (1.5)	18 (1.7)	11 (1.1)								
Severe hypotension — no. (%)*	1 (0.1)	2 (0.2)	3 (0.3)								
Allergic reaction — no. (%)	3 (0.3)	4 (0.4)	2 (0.2)								
Pulmonary edema, increased intracranial pressure, or both — no. (%)†	27 (2.6)	23 (2.2)	17 (1.6)	1.34 (0.72–2.51)	0.34	1.57 (0.87–2.88)	0.10	1.17 (0.68–2.03)	0.49	1.46 (0.85–2.53)	0.17
4 Weeks											
Death — no. (%)	128 (12.2)	126 (12.0)	91 (8.7)	1.38 (1.07–1.78)	0.01	1.40 (1.08–1.80)	0.01	1.01 (0.80–1.28)	0.91	1.39 (1.11–1.74)	0.004
Neurologic sequelae — no./total no. (%)‡	22/990 (2.2)	19/996 (1.9)	20/997 (2.0)	0.95 (0.51–1.77)	0.87	1.10 (0.61–2.01)	0.74	1.16 (0.63–2.14)	0.62	1.03 (0.61–1.75)	0.92
Neurologic sequelae or death — no./total no. (%)‡	150/990 (15.2)	145/996 (14.6)	111/997 (11.1)	1.31 (1.04–1.65)	0.02	1.36 (1.08–1.71)	0.008	1.04 (0.84–1.28)	0.71	1.33 (1.09–1.64)	0.005

A **Mortality at 48 Hours**



	Hr 1			Hr 2			Hr 3			Hr 4			Hr 5–8			Hr 9–24			Hr 24–48		
	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus	Albumin bolus	Saline bolus	No bolus
No. at Risk	1050	1047	1044	1037	1033	1030	1024	1018	1021	1016	1010	1015	1010	1001	1011	992	980	996	954	945	975
Died	13	12	14	13	15	9	8	7	6	6	9	4	17	20	14	38	34	20	16	13	9
%	1.2	1.1	1.3	1.3	1.5	0.9	0.8	0.7	0.6	0.6	0.9	0.4	1.7	2.0	1.4	3.8	3.5	2.0	1.7	1.4	0.9

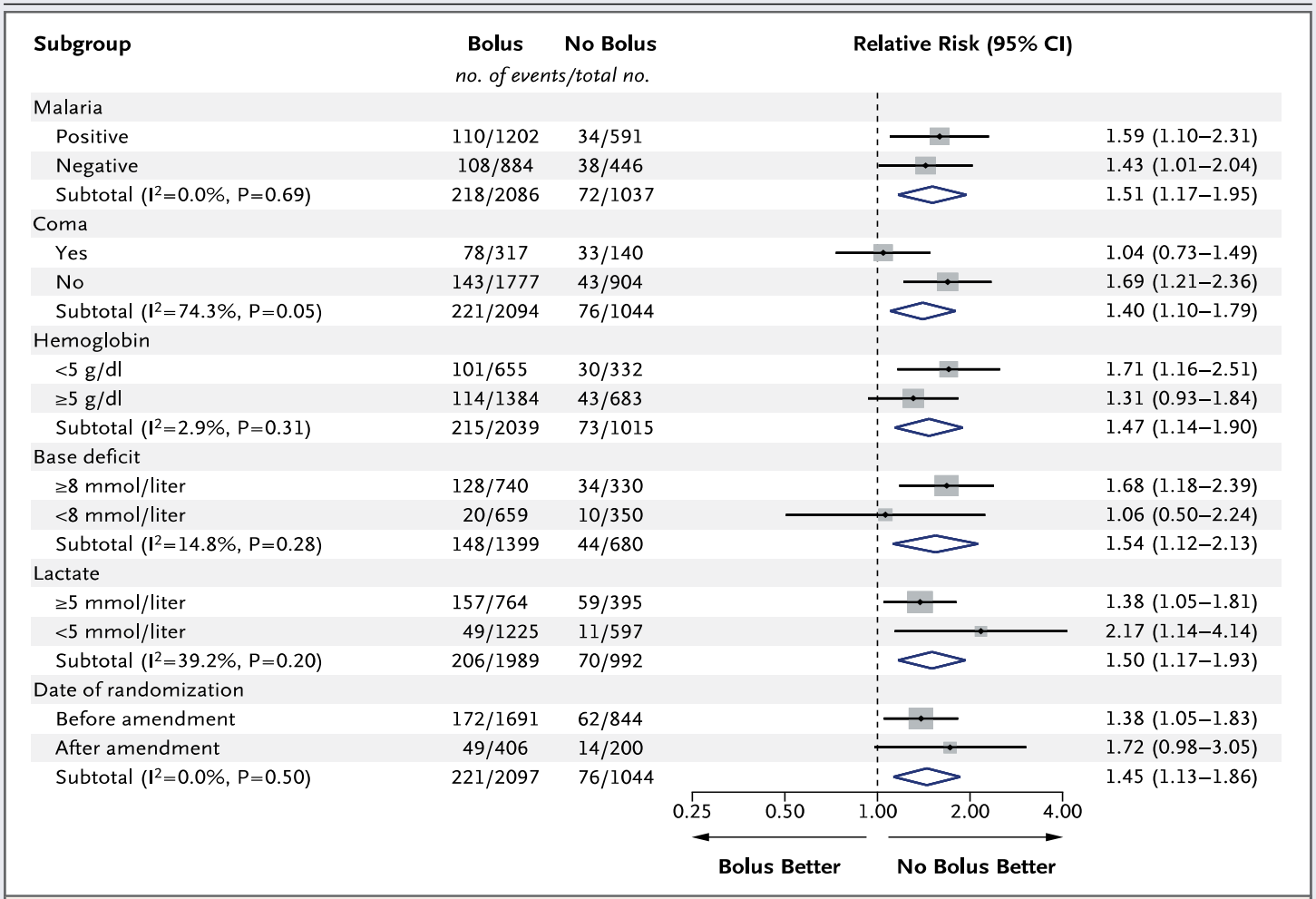


Figure 3. Mortality at 48 hours in Prespecified Subgroups.

The sizes of the boxes are proportional to the Mantel–Haenszel weights. The I^2 statistic indicates the percentage of total variation that was due to heterogeneity.

Good Points

- Large numbers of children enrolled
- Multinational nature of sample
- Small numbers lost to follow up
- Blinding of treatment assignments
- High rate of adherence to assigned treatment
- Confirmed what we know about saline versus albumin

Limitations

- Setting
- Limited access to diagnostics
- Different pattern of disease e.g. cerebral malaria
- Exclusions: gastroenteritis, severe malnutrition or non-infectious causes of shock
- Few children recruited to stratum B
- Definitions of ‘shock’

Restricted Fluid Strategy

- Adult Literature
  - ARDS
  - Colorectal Surgery
  - Penetrating Trauma

What type of fluid?

Types of IV Fluids

Crystalloids	Colloids
<u>Isotonic</u> 0.9% Saline Plasma-Lyte Hartman's solution Lactated Ringer's Solution <u>Hypertonic</u> 3% Saline	<u>Natural</u> 4% Albumin (iso-oncotic) 20% Albumn (hyper-oncotic) <u>Synthetic Colloids</u> Dextrans: 6% dextran 70; 10% dextran 40 Gelatins: Gelofusin, Haemaccel, gelofundiol HES preparations: Tetrastarch, Pentastarch, Voluven

Crystalloid versus Colloid

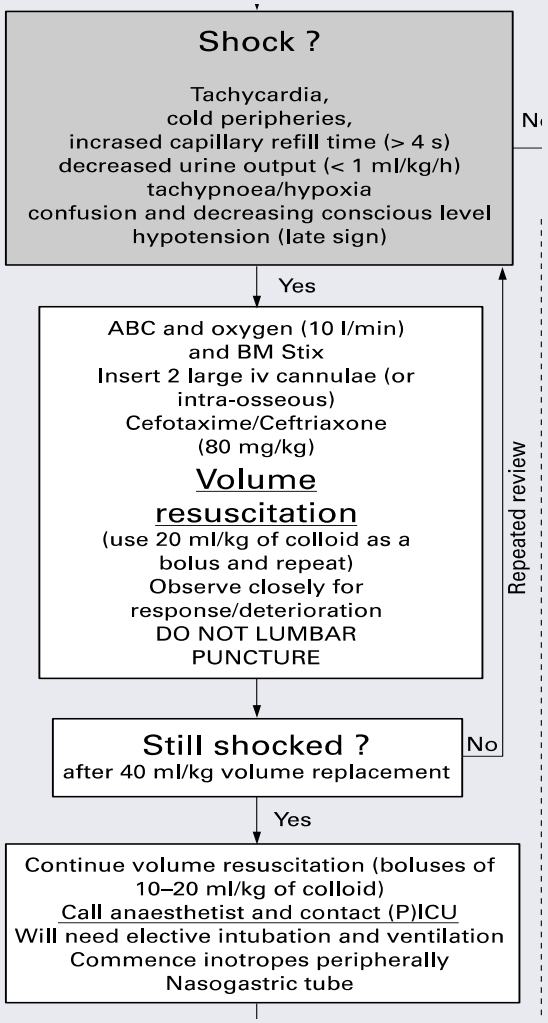
Crystalloids	**Colloids**
Cheap	Expensive
Readily available	Anaphylaxis
Hyperchloraemia	Coagulopathy
	Exposure to blood products
	Pruritis

Albumin

- Human albumin
  - Natural colloid, MW 69kDa
  - Accounts for 80% plasma oncotic pressure
  - Drug & hormone transport
  - Anti-oxidant and anti-inflammatory properties
  - Hypoalbuminaemic critically ill patients have a worse prognosis

- Albumin solutions
  - Safe, natural, well tolerated
  - Iso-oncotic (4% or 5%) or hyper-oncotic (20-25%)

Levin et al. Improved survival in children admitted to intensive care with meningococcal disease. 2nd Annual Spring Meeting of the RCPCH. University of York. 1998



The Colloid versus Crystalloid Debate

- Cochrane Injuries Group Albumin Reviewers

  - Human albumin administration in critically ill patients: Systematic review of randomised controlled trials. BMJ 1998; 317: 235-240

  - 30 RCT including 1419 randomised patients
    - Burns, hypoalbuminaemia or hypovolaemia
    - 6% increased risk of death with albumin

Booy et al. Reduction in case fatality rate from meningococcal disease associated with improved healthcare delivery. Arch Dis Child 2001; 85:386-390.

- 331 children with MD admitted to PICU
  - 1992-1997
  - Case fatality rate 23% (1992/93) to 2% (1997)

- A significant improvement in outcome for children admitted with MD to a PICU as a result of improvements in the use of their algorithm:
  - 4% albumin boluses
  - Initial management at referring hospitals
  - Use of a mobile intensive care service
  - Centralization of care in a specialist unit

Finfer et al. A Comparison of Albumin and Saline for Fluid Resuscitation in the ICU NEJM 2004; 350:2247-56
The SAFE Study

- 2001-2003
  - Multicenter, randomised, double-blind trial
  - Primary outcome: death from any cause/28 days

- Eligible patients
  - Anyone for whom fluid resuscitation required
  - Exclusions: cardiac surgery, liver transplant, burns
  - 4% albumin versus 0.9% saline

The SAFE Study

- 6997 patients
  - Similar baseline characteristics
- Fluids Administered
  - Albumin group: significantly less study fluid
  - Saline: Albumin of 1: 1.4
- Haemodynamics
  - No differences in MAP
  - Albumin group: lower HR & higher CVP

Total Fluids Administered

Variable	Albumin Group		Saline Group		P Value†
	No. of Patients	Value	No. of Patients	Value	
Study fluid (ml)					
Day 1	3410	1183.9±973.6	3418	1565.3±1536.1	<0.001
Day 2	3059	602.7±892.7	3068	954.0±1484.4	<0.001
Day 3	2210	268.0±554.5	2202	348.3±753.5	0.03
Day 4	1686	192.3±427.0	1664	228.6±642.6	0.57
Nonstudy fluid (ml)					
Day 1	3392	1459.4±1183.2	3405	1505.6±1254.3	0.30
Day 2	3051	2615.9±1372.5	3057	2707.3±1435.7	0.009
Day 3	2199	2618.5±1346.5	2191	2660.9±1319.3	0.15
Day 4	1680	2691.5±1228.7	1656	2707.7±1255.4	0.36
Day 2	3044	1015.3±1826.9	3032	1505.1±2215.9	<0.001
Day 3	2190	422.1±1633.3	2182	553.0±1732.3	0.007
Day 4	1671	137.2±1491.0	1649	155.7±1650.6	0.70
Mean arterial pressure (mm Hg)					
Day 1	3406	81.4±14.4	3408	80.9±14.5	0.14
Day 2	3068	84.4±15.1	3075	84.2±15.7	0.49
Day 3	2215	87.2±15.3	2209	86.9±16.1	0.62
Day 4	1688	88.3±15.9	1666	88.4±16.3	0.87
Heart rate (beats/min)					
Day 1	3398	88.0±20.2	3406	89.7±20.8	<0.001
Day 3	3071	88.5±19.5	3075	89.5±19.2	0.06
Day 3	2216	88.8±19.1	2213	89.7±18.8	0.10
Day 4	1691	89.5±18.9	1668	89.9±18.5	0.52
Central venous pressure (mm Hg)					
Day 1	2204	11.2±4.8	2270	10.0±4.5	<0.001
Day 2	2095	11.6±4.9	2135	10.4±4.3	<0.001
Day 3	1531	11.4±4.8	1589	10.7±4.4	<0.001
Day 4	1221	11.1±4.8	1230	10.5±4.4	<0.001
Serum albumin (g/liter)					
Day 1	2081	28.7±7.0	2061	24.7±6.5	<0.001
Day 2	2708	30.8±6.4	2703	24.5±5.9	<0.001
Day 3	1921	30.0±6.4	1905	23.6±5.6	<0.001
Day 4	1498	29.0±6.2	1478	23.1±5.5	<0.001

Albumin	Saline	Ratio
2247ml	3096ml	1:1.4

The SAFE Study

- 28 day mortality
  - 726 deaths (20.9%; albumin) v 729 deaths (21.1% saline)

- Single organ and multiple-organ failure similar
  - No differences in ICU days, hospital days, days of mechanical ventilation, days of RRT

The SAFE Study

- Sub–group analysis in severe sepsis
  - Improved outcomes with albumin
    - Saline group 35.3% died
    - Albumin group 30.7% died
  - RR of death 0.87 amongst those in the albumin group
    - RR of death 1.05 without severe sepsis

Paediatric Albumin Trials

- Maitland et al. Randomized trial of volume expansion with albumin or saline in children with severe malaria: preliminary evidence of albumin benefit. Clin Infect Dis 2005; 40(4):538-45

- Maitland et al. Mortality after fluid bolus in African children. NEJM Jun 30;364(26):2483-95

Current Trials

- The PRECISE Trial
  - Evolution of an Early Septic Shock Fluid Resuscitation Trial
  - Canadian Critical Care Trials Group.
  - 5% albumin versus 0.9% NaCl on 90 day mortality

- ALBIOS Trial
  - The Volume Replacement with Albumin in Severe Sepsis
  - 1350 Italian ICU patients
  - 28- and 90-day mortality; organ dysfunction (secondary end-point)
  - Albumin plus crystalloid versus crystalloid only

Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock. Critical Care Med 2008. 36(1):296-327

- Dellinger et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med 2008; 34:17-60

- Recommends the use of either crystalloid or colloid for the early resuscitation of patients with sepsis

Gelatins

- Synthetic colloid
  - Hydrosylates of connective tissue of animal origin
  - MW limited to 30-35 kDA
    - Tendency to gel at higher molecular weights
    - Much lower than albumin
    - Limited oncotic effects; intravascular persistence 2-3 hours

Gelatins

- Upadhyay et al. Randomized evaluation of fluid resuscitation with crystalloid (saline) and colloid (polymer from degraded gelatin in saline) in pediatric septic shock. Indian Pediatr 2005; 42(3):223-31
  - 60 children with septic shock
  - 20ml/kg boluses of saline or gelatin
  - Equally effective as a resuscitation fluid

Gelatin

- Acute Kidney Injury
  - Schabinski et al. Effects of a predominantly HES based and a predominantly non HES based fluid therapy on renal function in surgical ICU patients. Intensive Care Medicine 2009; 35:1539-1547
    - 6% HES 130/0.4 versus gelatin
    - Gelatin exposure independent RF for ARF (OR 1.99)

- Anaphylactoid reactions reported

Hydroxyethyl Starch

- Commonest colloid used in European ICU's
  - HES 58%; gelatin 35%; albumin 5%
  - Synthesised by partial hydrolysis of maize or potato starch, amylopectin

- 4 Elements
  - Concentration: 6% or 10%
  - Molecular weight: 70-670kDa
  - Degree of substitution: 0.4 (tetrastarch), 0.7 (hetastarch)
  - C2/C6 ratio

- 3 Generations

HES & Bleeding

- Cardiac surgery RCT's
  - HES 120/0.7, 130/0.4, 200/0.5, 450/0.7 impaired TEG assessed clotting compared with albumin
  - Blood loss increased with HES 130/0.4 and 450/0.7 (greater blood transfusion) compared with albumin

- General paediatric surgery patients
  - HES 130/0.4 caused deterioration in TEG parameters in a RCT compared with albumin

Acute Kidney Injury

- Schortgen et al. Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomised study. Lancet 2001;357:911-916
  - 129 French patients with severe sepsis
  - 6% HES 200/0.6 increased risk of RF by 2.57 compared with gelatin

- Brunkhorst et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. NEJM 2008:358:125-39
  - 10% HES, 200kDa versus Ringer's lactate
  - Higher incidence of renal failure and RRT

Acute Kidney Injury

Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. Intensive Care Medicine 2012; 38(3):368

- Recommend against using HES>200kDa and/or degree of substitution of 0.4 in patients with severe sepsis or risk of AKI

- Suggest not using 6% HES 130/0.4 in these populations

Anaphylactoid Reaction

- Wills et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. NEJM 2005:353:877-889.
  - RCT of 383 children
  - Severe allergic reactions more frequent after
  - Dextran 70>HES 200/0.5>Ringer's lactate

- Case reports described in patients exposed to gelatins, HES and albumin

Pruritis

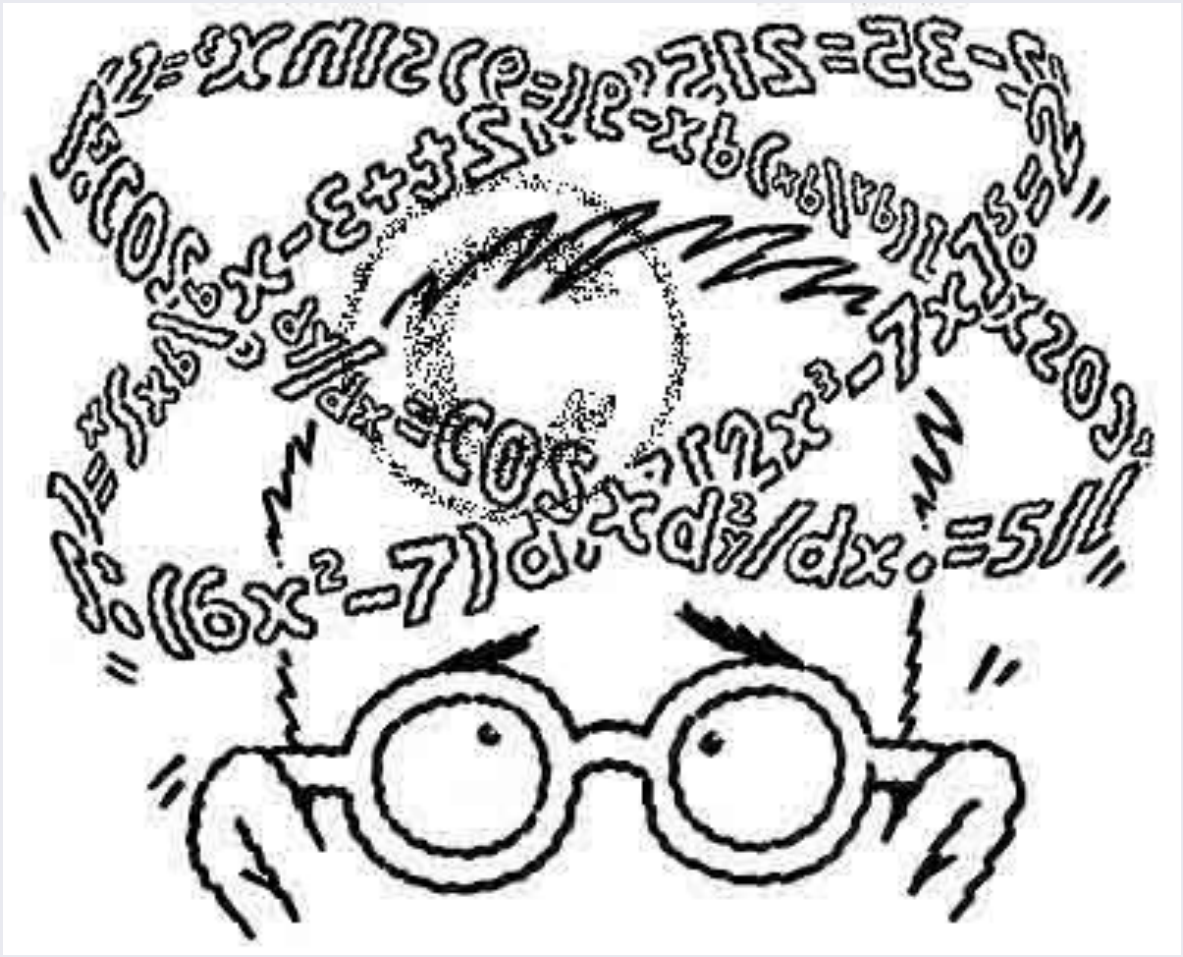
- Bork et al. Pruritus precipitated by hydroxyethyl starch: a review. Br J Dematol. 2005; 152:3-12
  - Systematic review of 18 clinical studies; 3239 patients
  - All HES solutions of all molecular weights, substitutions and C2/C6 ratios
  - Incidence
    - 13-34% in ICU
    - 22% in cardiac surgery
    - 3-54% in stroke

Current Trials

- The CHEST Trial
  - Crystalloid Versus Hydroxyethyl Starch Trial
  - 7000 ANZ ICU patients
  - HES 130/0.4 versus saline
  - 90 day mortality; need for RRT (secondary end-point)

- The Scandinavian Starch for Severe Sepsis/Septic Shock Trial
  - 800 ICU patients
  - HES 130/0.4 or Ringer's acetate
  - Mortality or dialysis dependence at 90 days after infusion

Time to put it all together



Summary

- When should fluid be given:
  - Fluid should be given in a time-sensitive manner
- How much fluid to give
  - Directed toward the goal of improved stroke volume as evidenced by return of HR to normal, CRT <2 second, peripheral pulses and BP as well as correction of Hb and ScvO2$\geq$70%
- Crystalloid or albumin?
  - Probably doesn't matter
  - No place for HES, gelatins or dextrans in paediatric septic shock