ARDS and Fluid

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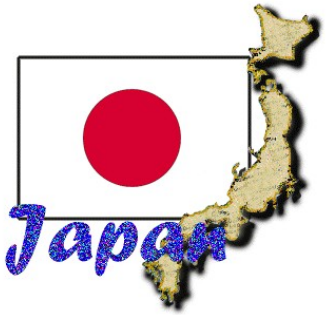
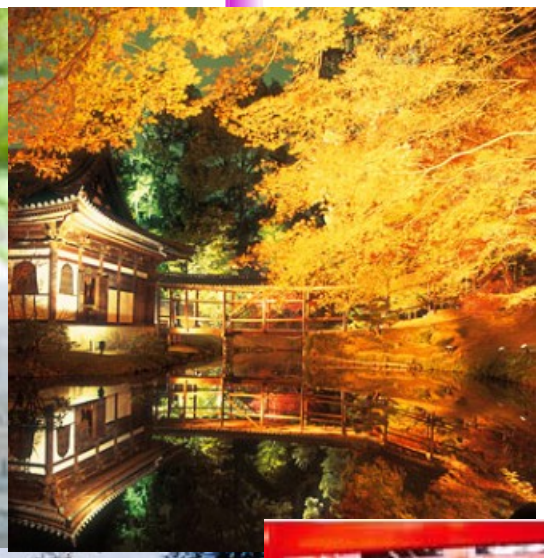
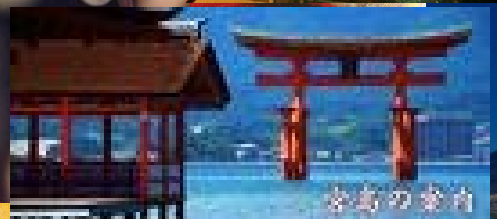
JAPAN







Self-Introduction

Tokai University, School of Medicine

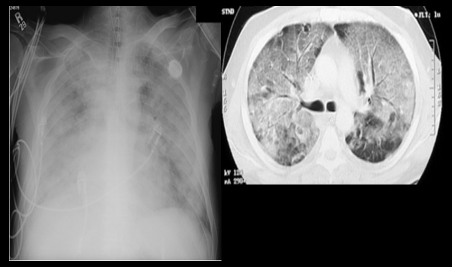
Dr. Helicopter

2000 M.D.
2008 Ph.D.
2008-2010 Post Doc.
Washington University in St. Louis (USA)
2010 Assistant Professor

Agenda

Why “Fluid”?

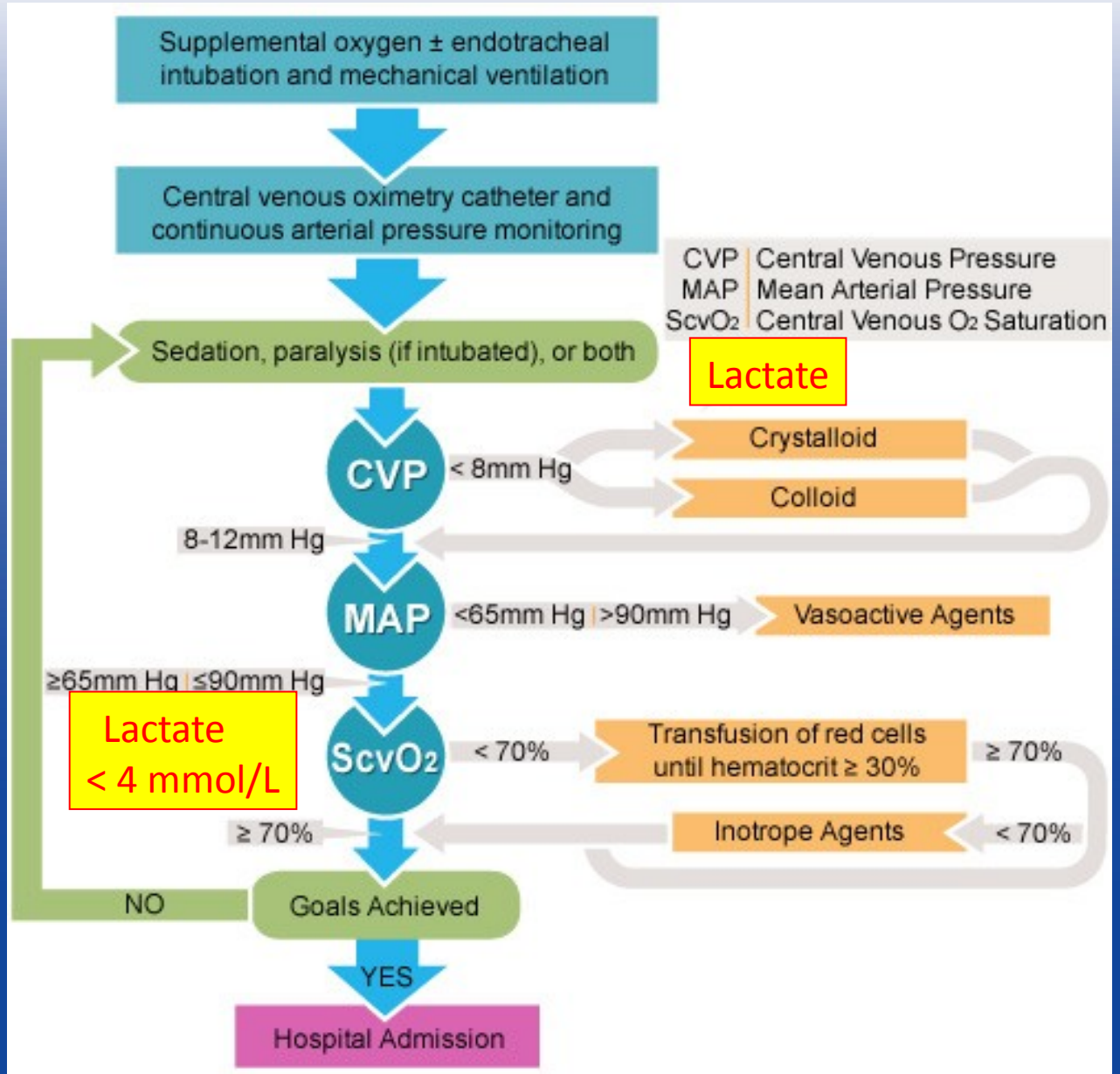
Sepsis and Fluid



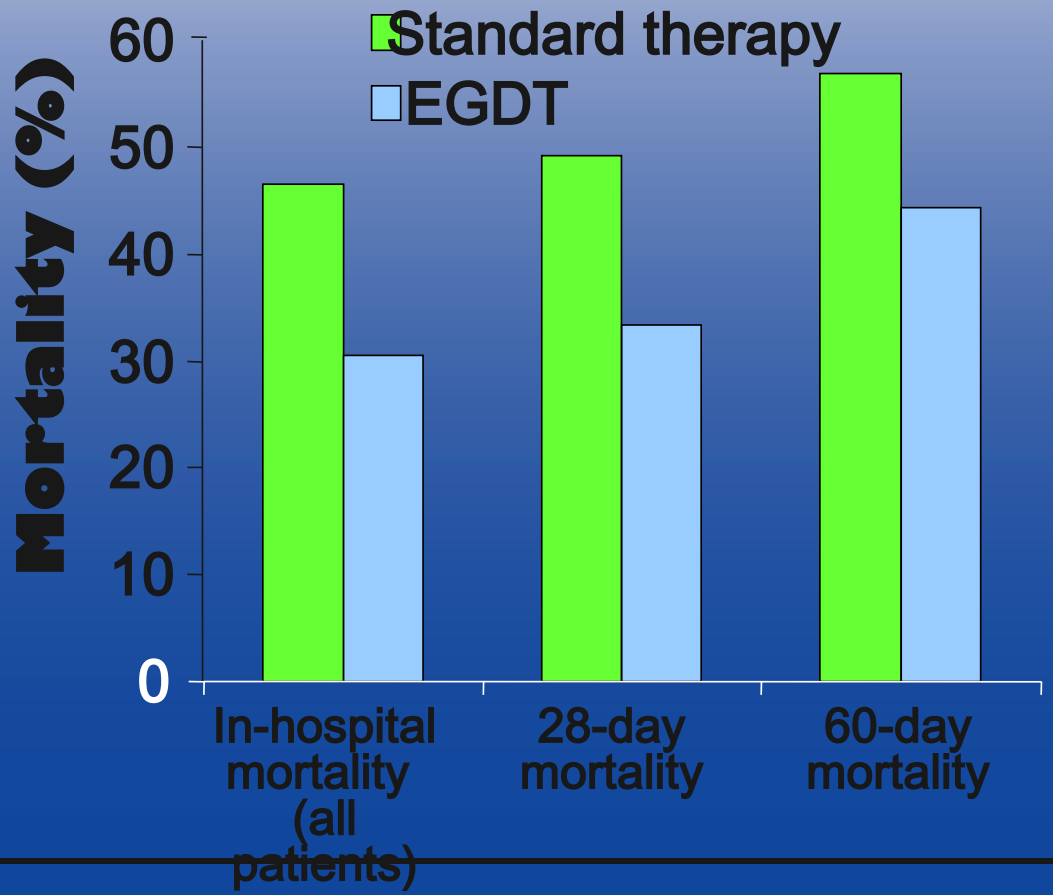
ARDS and Fluid

Early Goal Directed Therapy (EGDT)

Surviving Sepsis Campaign



EGDT improves survival after sepsis



Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368-1377

Early goal directed therapy

Surviving Sepsis Campaign

Goal for the first 6hrs after septic shock (1 C)

Directed Goal

CVP 8-12mmHg
MAP ≧65mmHg
Urine ≧0.5ml/kg/h
$S_{cv}O_2$≧70%

How to improve hypoxia in the peripheral tissue?

Purpose	O2 delivery↑	O2 consumption↓
Treatment	Fluid therapy	Hypothermia ?

River in the body

$DO_2 = CaO_2$ (ship) × CO (river)

Ship factor

CaO_2(ml/L) $= 1.34 \times Hb \times SaO_2 + 0.0031 \times PaO_2$

River factor

CO = HR×SV

- Preload （water volume, depth）
- Afterload （bund, wall）

CVP
SVRI
CI

Goals during the first 6 hrs of resuscitation:

- a) Central venous pressure 8–12 mm Hg
- b) Mean arterial pressure (MAP) ≥ 65 mm Hg
- c) Urine output ≥ 0.5 mL/kg/hr
- d) Central venous (superior vena cava) or ScvO270% or 65%, respectively (grade 1 C).

- 2. In patients with elevated lactate levels targeting resuscitation to normalize lactate (grade 2 C).


Special Articles

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign

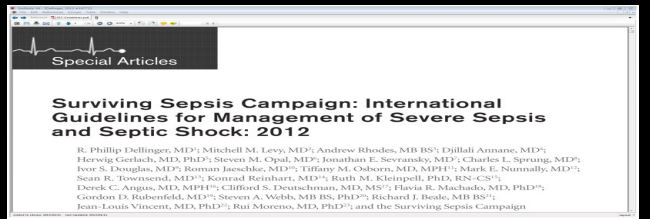
Summary so far

* Is the patient “SHOCK”?
  (lactate acidosis hypothermia)
* Early Goal Directed Therapy
* Goal
* Monitor CVP MAP urine volume
  $ScvO_2$ (Lactate clearance)

Crystalloid or Colloid?

- 1. We recommend crystalloids be used as the i nitial fluid of choice in the resuscitation of s evere sepsis and septic shock (grade 1B).

- 3. We suggest the use of albumin in the fluid r esuscitation of severe sepsis and septic sho ck when patients require substantial amounts of crystalloids (grade 2C).


Special Articles

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

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Is HES harmful?

- 2. We recommend against the use of hydroxyethyl starches (HES) for fluid resuscitation of severe sepsis and septic shock (grade 1B).
- (This recommendation is based on the results of the VISEP [128], CRYSTMAS [122], 6S [123], and CHEST [124] trials. The results of the recently completed CRYSTAL trial were not considered.)


Special Articles

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

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Research

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock

The CRISTAL Randomized Trial

Djillali Annane, MD, PhD; Shidasp Siami, MD; Samir Jaber, MD, PhD; Claude Martin, MD, PhD; Souheil Elatrous, MD; Adrien Descorps Declère, MD; Jean Charles Preiser, MD; Hervé Outin, MD; Gilles Troché, MD; Claire Charpentier, MD; Jean Louis Trouillet, MD; Antoine Kimmoun, MD; Xavier Forceville, MD, PhD; Michael Darmon, MD; Olivier Lesur, MD, PhD; Jean Régnier, MD; Fékri Abroug, MD; Philippe Berger, MD; Christophe Clech, MD; Joël Cousson, MD; Laure Thibault, MD; Sylvie Chevret, MD, PhD; for the CRISTAL Investigators

IMPORTANCE Evidence supporting the choice of intravenous colloid vs crystalloid solutions for management of hypovolemic shock remains unclear.

OBJECTIVE To test whether use of colloids compared with crystalloids for fluid resuscitation alters mortality in patients admitted to the intensive care unit (ICU) with hypovolemic shock.

DESIGN, SETTING, AND PARTICIPANTS A multicenter, randomized clinical trial stratified by case mix (sepsis, trauma, or hypovolemic shock without sepsis or trauma). Therapy in the Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial was open label but outcome assessment was blinded to treatment assignment. Recruitment began in February 2003 and ended in August 2012 of 2857 sequential ICU patients treated at 57 ICUs in France, Belgium, North Africa, and Canada; follow-up ended in November 2012.

Editorial

Supplemental content at jama.com

JAMA. October 09, 2013. doi:10.1001/jama.2013.280502

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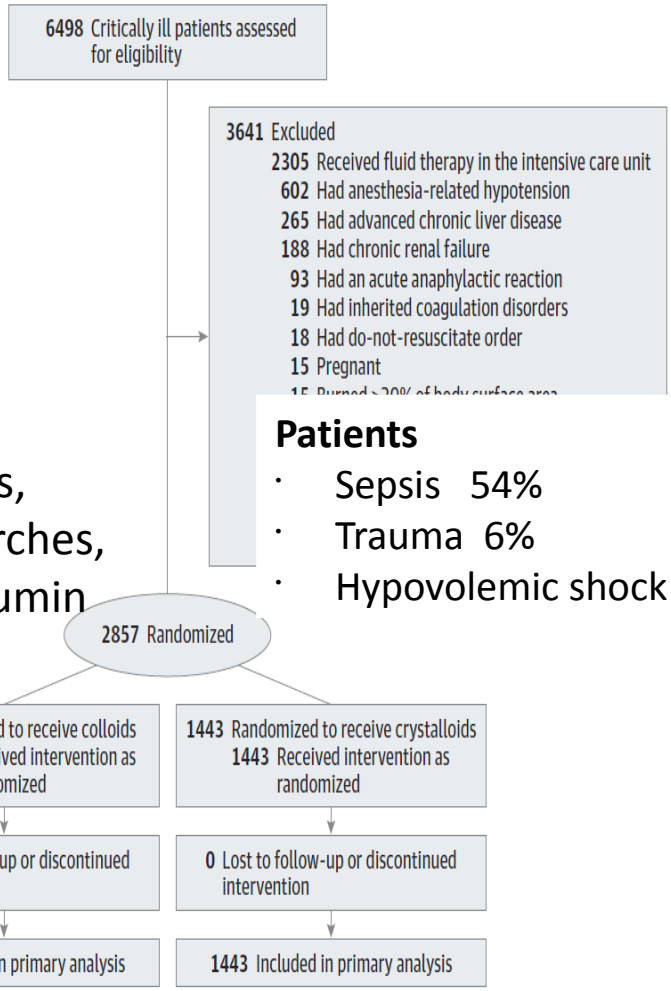
Figure 1. Patient Enrollment in the Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) Trial



Colloids group

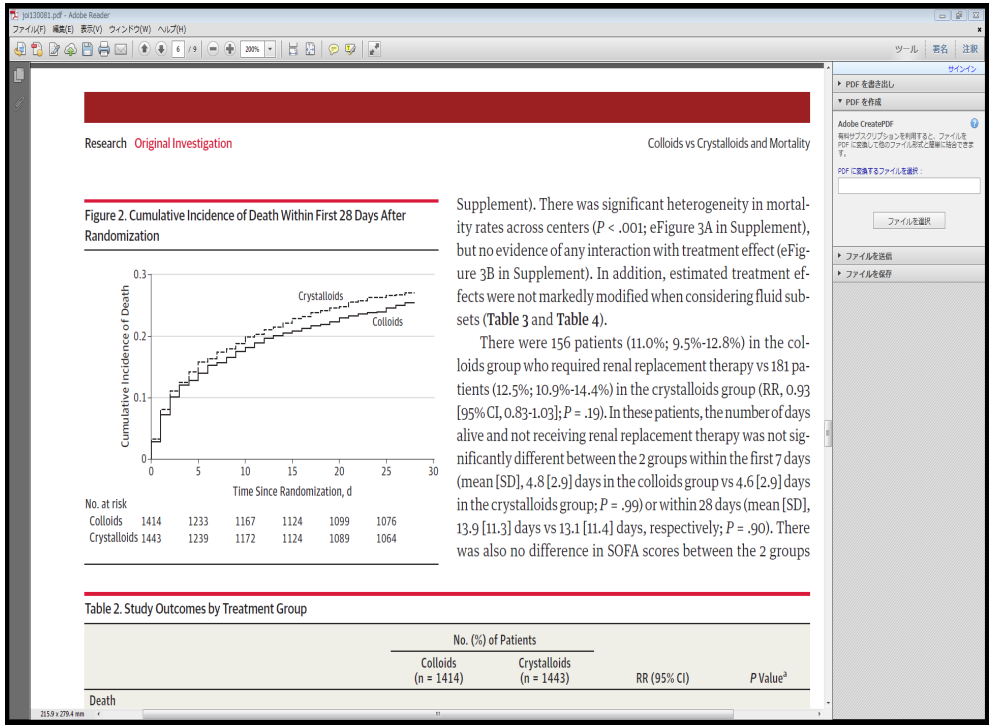
- gelatins, dextrans,
- hydroxyethyl starches,
- 4%or 20% of albumin

Patients

- Sepsis 54%
- Trauma 6%
- Hypovolemic shock (without sepsis and trauma) 40%

Crystalloids group

isotonic or hypertonic saline
Ringer lactate solution



Research Original Investigation

Colloids vs Crystalloids and Mortality

Figure 2. Cumulative Incidence of Death Within First 28 Days After Randomization

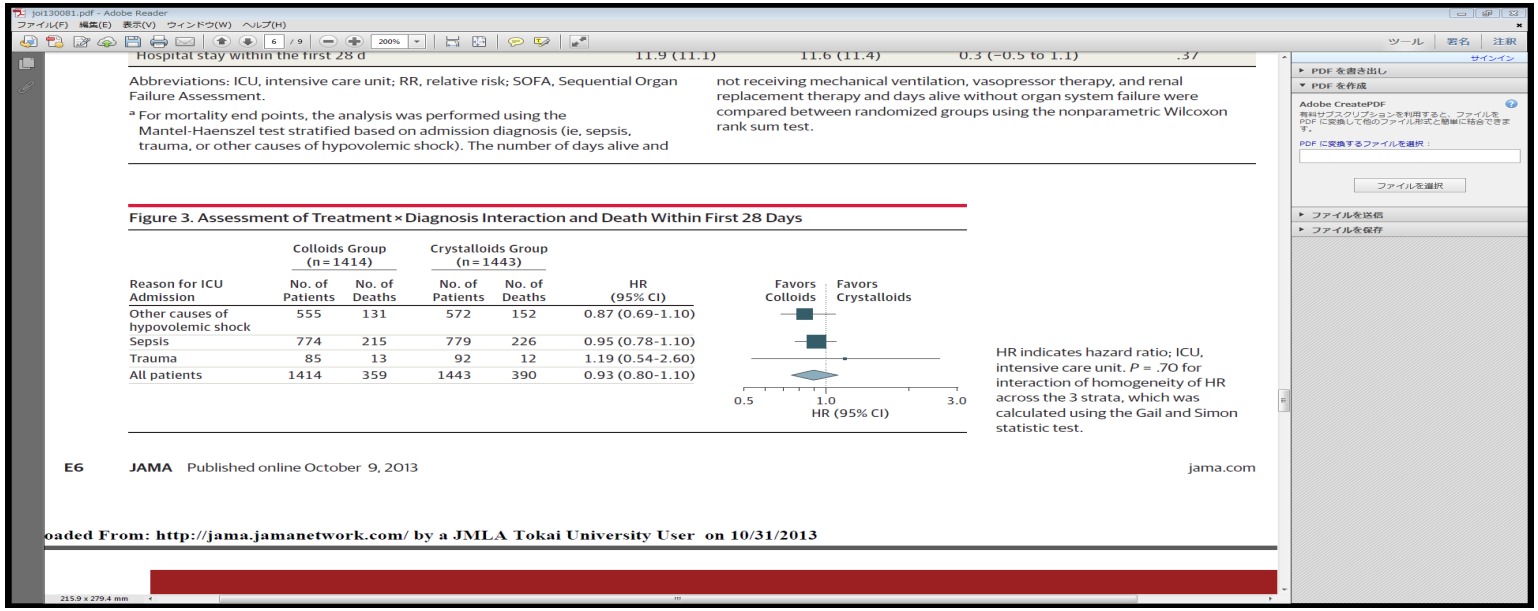
Supplement). There was significant heterogeneity in mortality rates across centers ($P < .001$; eFigure 3A in Supplement), but no evidence of any interaction with treatment effect (eFigure 3B in Supplement). In addition, estimated treatment effects were not markedly modified when considering fluid subsets (**Table 3** and **Table 4**).

There were 156 patients (11.0%; 9.5%-12.8%) in the colloids group who required renal replacement therapy vs 181 patients (12.5%; 10.9%-14.4%) in the crystalloids group (RR, 0.93 [95% CI, 0.83-1.03]; $P = .19$). In these patients, the number of days alive and not receiving renal replacement therapy was not significantly different between the 2 groups within the first 7 days (mean [SD], 4.8 [2.9] days in the colloids group vs 4.6 [2.9] days in the crystalloids group; $P = .99$) or within 28 days (mean [SD], 13.9 [11.3] days vs 13.1 [11.4] days, respectively; $P = .90$). There was also no difference in SOFA scores between the 2 groups

Table 2. Study Outcomes by Treatment Group

	No. (%) of Patients			
	Colloids (n = 1414)	Crystalloids (n = 1443)	RR (95% CI)	*P* Value[a]
Death				

Among ICU patients with hypovolemia, the use of colloids vs crystalloids did not result in a significant difference in 28-day mortality.



Hospital stay within the first 28 d 11.9 (11.1) 11.6 (11.4) 0.3 (−0.5 to 1.1) .37

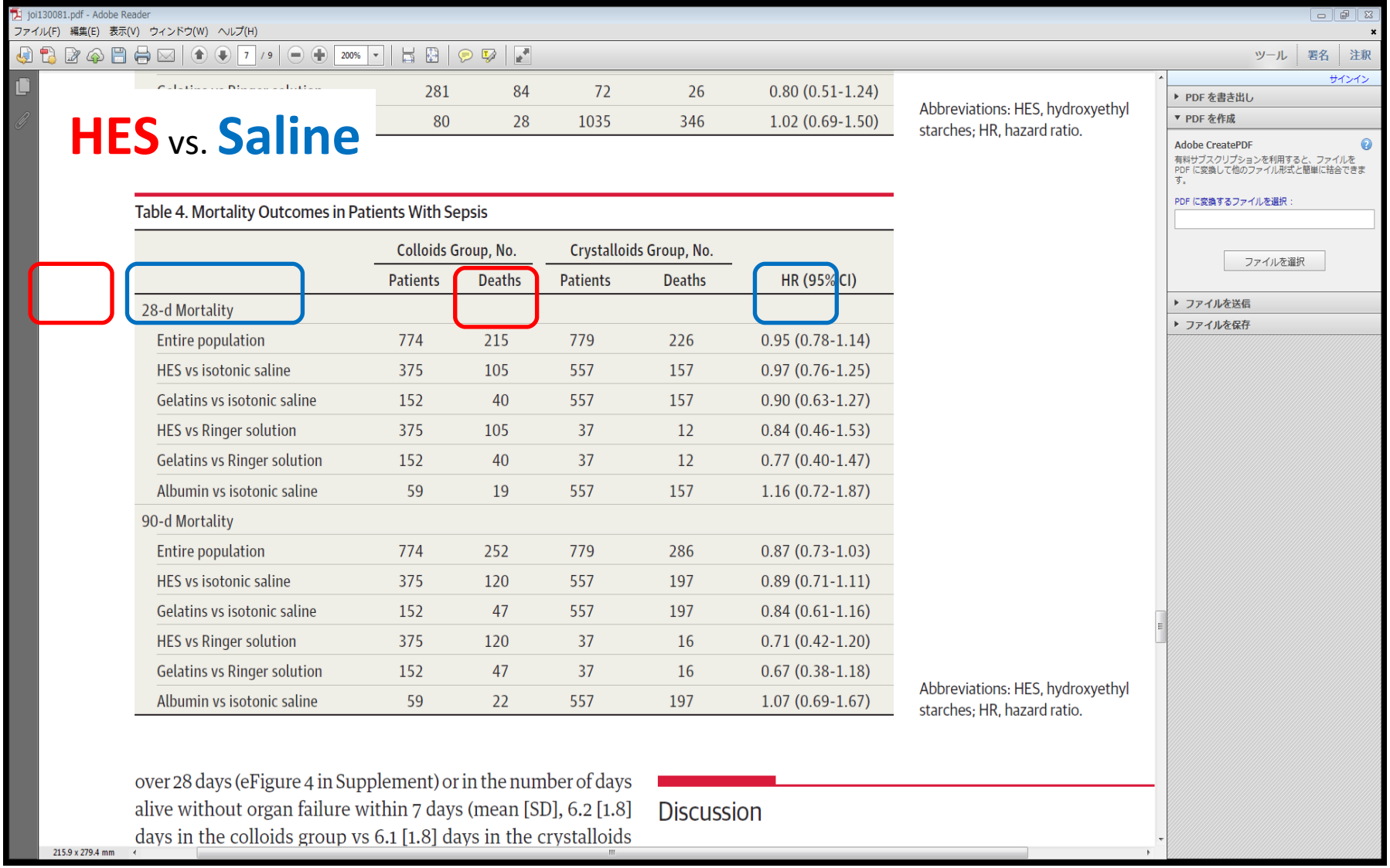
Abbreviations: ICU, intensive care unit; RR, relative risk; SOFA, Sequential Organ Failure Assessment.

[a] For mortality end points, the analysis was performed using the Mantel-Haenszel test stratified based on admission diagnosis (ie, sepsis, trauma, or other causes of hypovolemic shock). The number of days alive and not receiving mechanical ventilation, vasopressor therapy, and renal replacement therapy and days alive without organ system failure were compared between randomized groups using the nonparametric Wilcoxon rank sum test.

Figure 3. Assessment of Treatment × Diagnosis Interaction and Death Within First 28 Days

Reason for ICU Admission	Colloids Group (n = 1414) No. of Patients	Colloids Group (n = 1414) No. of Deaths	Crystalloids Group (n = 1443) No. of Patients	Crystalloids Group (n = 1443) No. of Deaths	HR (95% CI)
Other causes of hypovolemic shock	555	131	572	152	0.87 (0.69-1.10)
Sepsis	774	215	779	226	0.95 (0.78-1.10)
Trauma	85	13	92	12	1.19 (0.54-2.60)
All patients	1414	359	1443	390	0.93 (0.80-1.10)

HR indicates hazard ratio; ICU, intensive care unit. $P = .70$ for interaction of homogeneity of HR across the 3 strata, which was calculated using the Gail and Simon statistic test.



HES vs. Saline

	281	84	72	26	0.80 (0.51-1.24)
	80	28	1035	346	1.02 (0.69-1.50)

Abbreviations: HES, hydroxyethyl starches; HR, hazard ratio.

Table 4. Mortality Outcomes in Patients With Sepsis

	Colloids Group, No.		Crystalloids Group, No.		
	Patients	Deaths	Patients	Deaths	HR (95% CI)
28-d Mortality					
Entire population	774	215	779	226	0.95 (0.78-1.14)
HES vs isotonic saline	375	105	557	157	0.97 (0.76-1.25)
Gelatins vs isotonic saline	152	40	557	157	0.90 (0.63-1.27)
HES vs Ringer solution	375	105	37	12	0.84 (0.46-1.53)
Gelatins vs Ringer solution	152	40	37	12	0.77 (0.40-1.47)
Albumin vs isotonic saline	59	19	557	157	1.16 (0.72-1.87)
90-d Mortality					
Entire population	774	252	779	286	0.87 (0.73-1.03)
HES vs isotonic saline	375	120	557	197	0.89 (0.71-1.11)
Gelatins vs isotonic saline	152	47	557	197	0.84 (0.61-1.16)
HES vs Ringer solution	375	120	37	16	0.71 (0.42-1.20)
Gelatins vs Ringer solution	152	47	37	16	0.67 (0.38-1.18)
Albumin vs isotonic saline	59	22	557	197	1.07 (0.69-1.67)

Abbreviations: HES, hydroxyethyl starches; HR, hazard ratio.

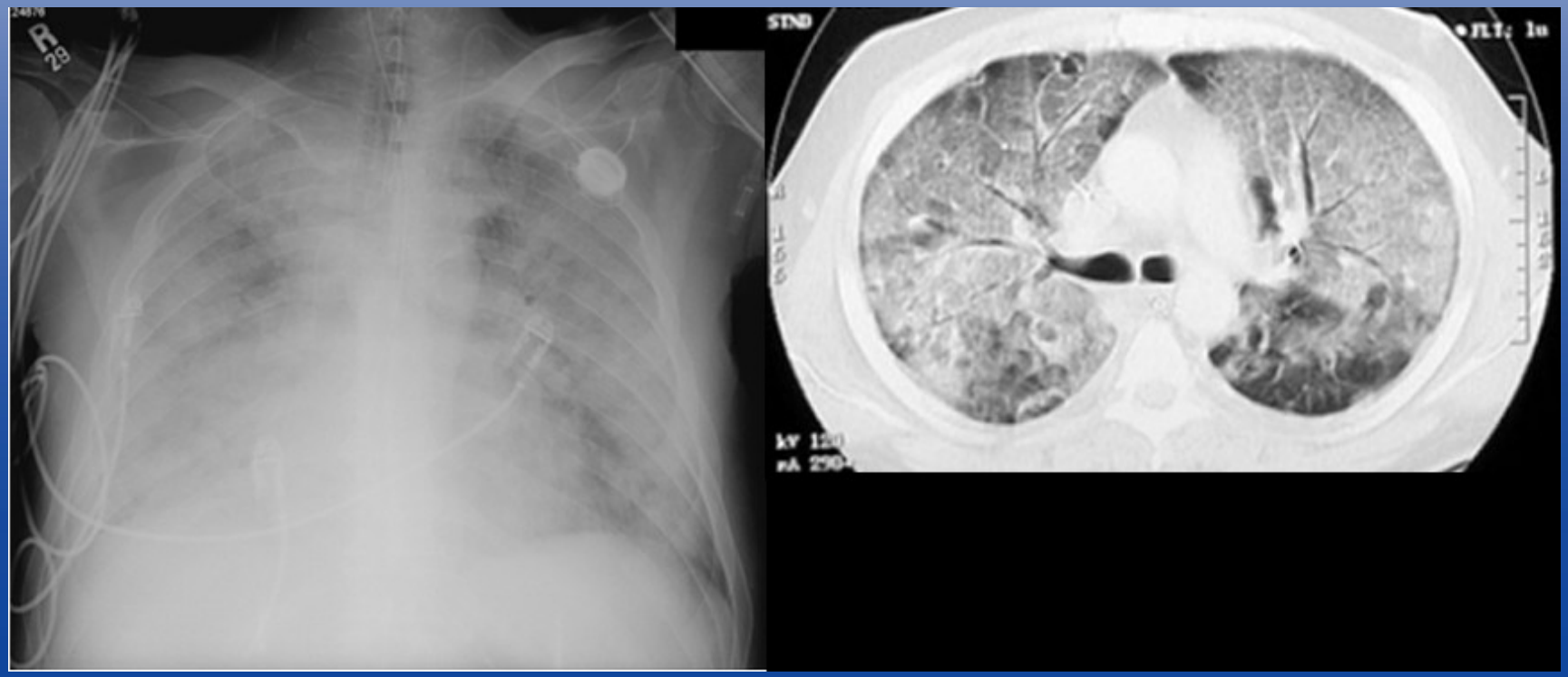
over 28 days (eFigure 4 in Supplement) or in the number of days alive without organ failure within 7 days (mean [SD], 6.2 [1.8] days in the colloids group vs 6.1 [1.8] days in the crystalloids

Discussion

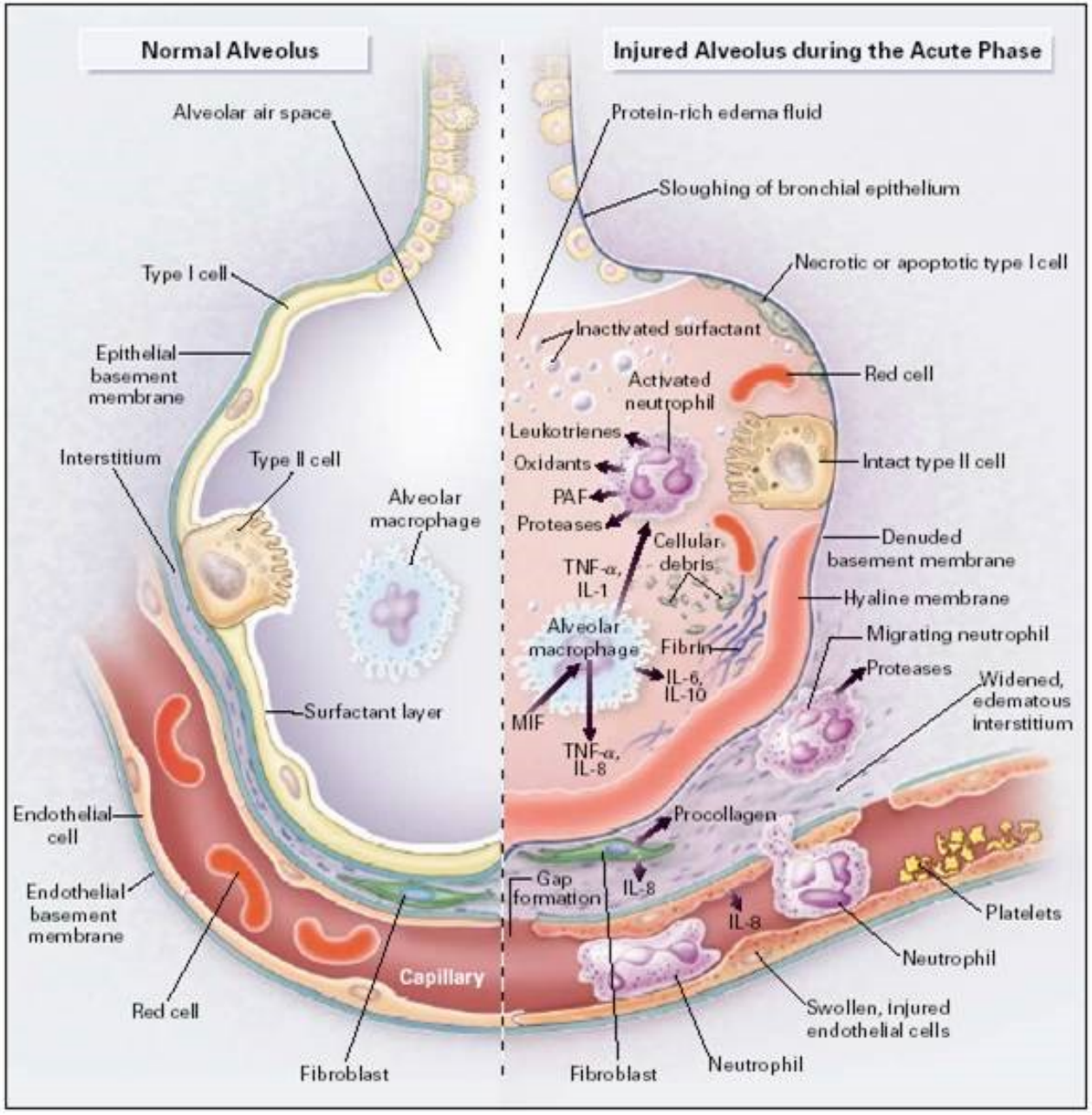
Although 90-day mortality was lower among patients receiving colloids, this finding should be considered exploratory and requires further study before reaching conclusions about efficacy.

Surviving Sepsis Campaign

ARDS

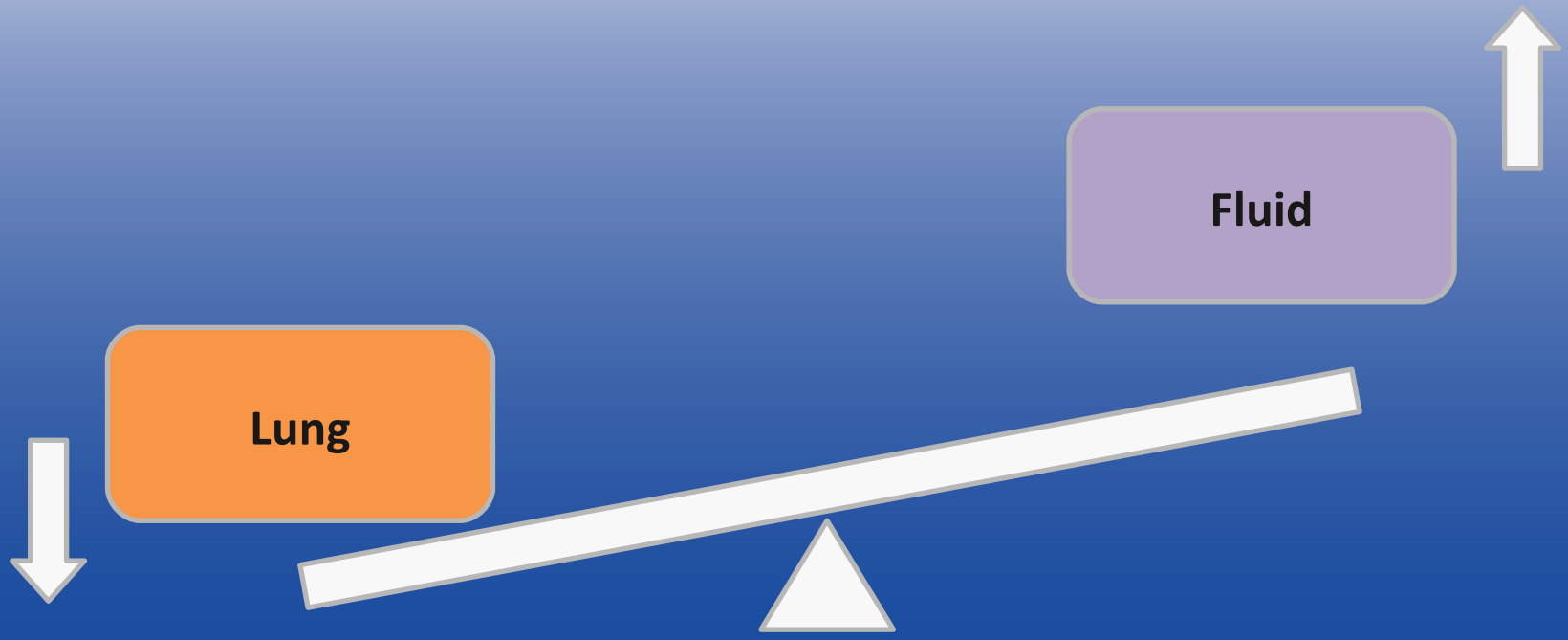


Surviving Sepsis Campaign

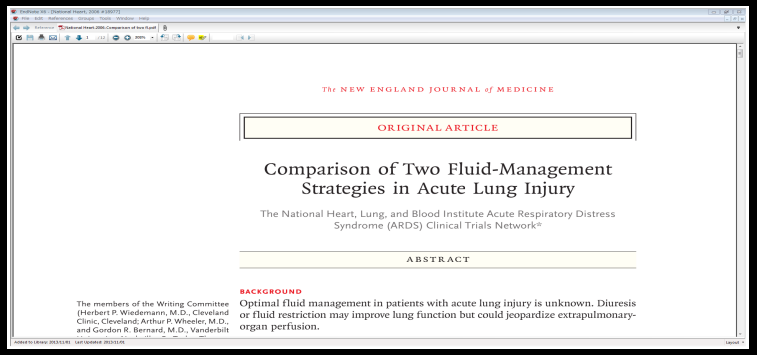


Surviving Sepsis Campaign

Fluid or Lung?



New Eng J Med 2006



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

The members of the Writing Committee (Herbert P. Wiedemann, M.D., Cleveland Clinic, Cleveland; Arthur P. Wheeler, M.D., and Gordon R. Bernard, M.D., Vanderbilt

ABSTRACT

BACKGROUND

Optimal fluid management in patients with acute lung injury is unknown. Diuresis or fluid restriction may improve lung function but could jeopardize extrapulmonary-organ perfusion.

30% of the cohort was shock

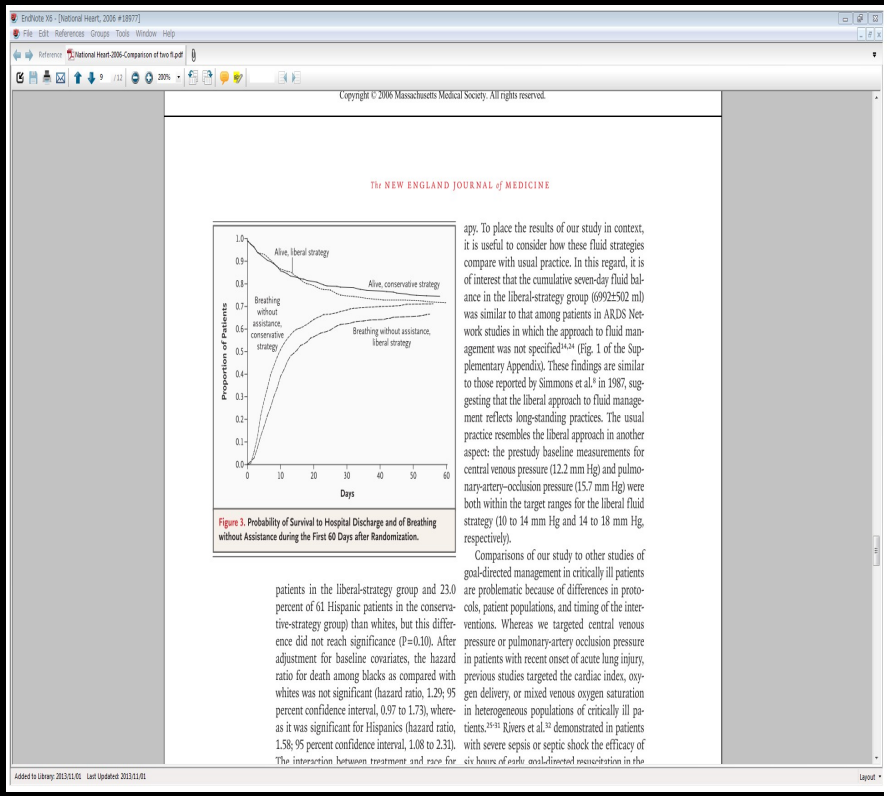
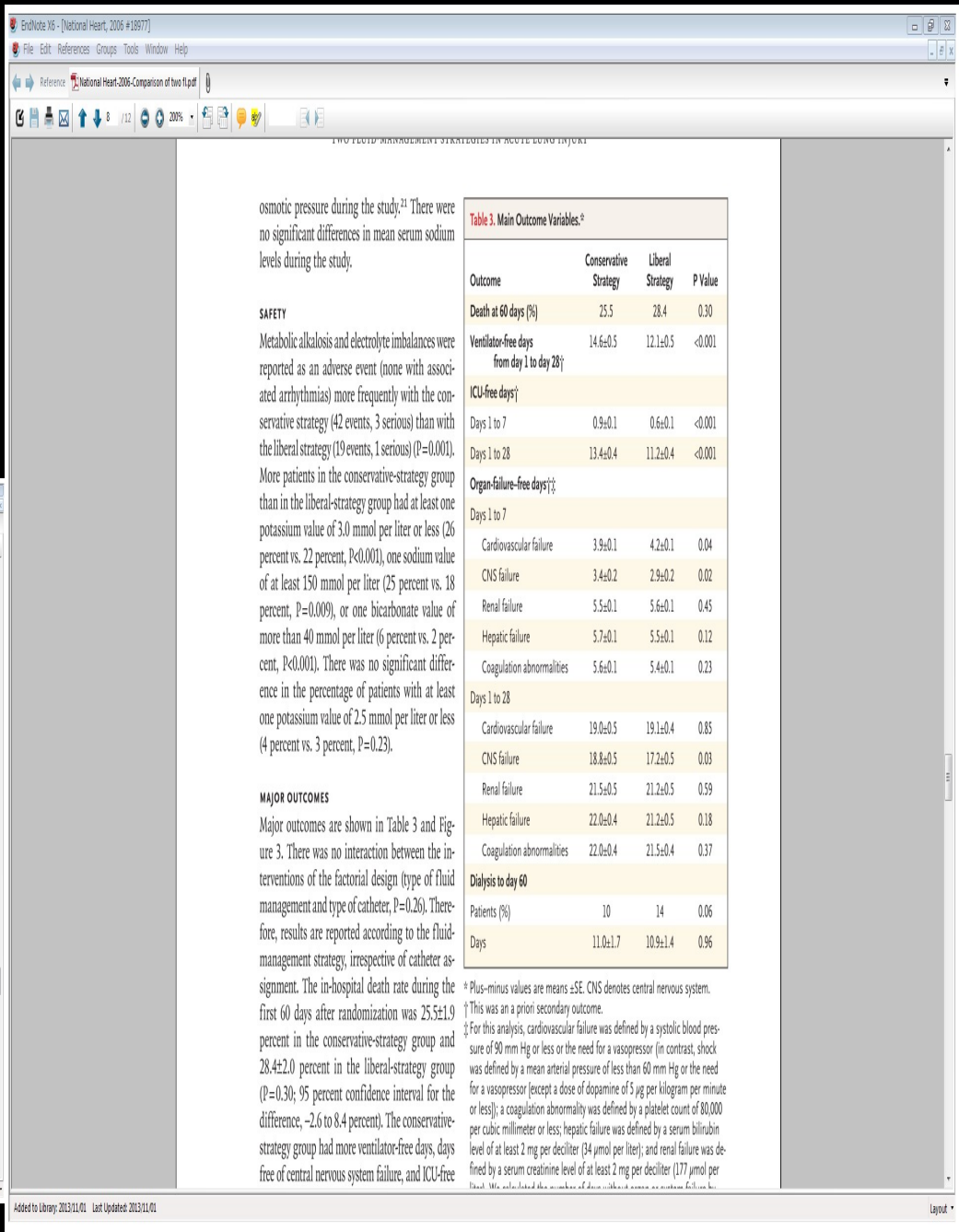


Figure 3. Probability of Survival to Hospital Discharge and of Breathing without Assistance during the First 60 Days after Randomization.

patients in the liberal-strategy group and 23.0 percent of 61 Hispanic patients in the conservative-strategy group) than whites, but this difference did not reach significance (P=0.10). After adjustment for baseline covariates, the hazard ratio for death among blacks as compared with whites was not significant (hazard ratio, 1.29; 95 percent confidence interval, 0.97 to 1.73), whereas it was significant for Hispanics (hazard ratio, 1.58; 95 percent confidence interval, 1.08 to 2.31). The interaction between treatment and race for

apy. To place the results of our study in context, it is useful to consider how these fluid strategies compare with usual practice. In this regard, it is of interest that the cumulative seven-day fluid balance in the liberal-strategy group (6992±502 ml) was similar to that among patients in ARDS Network studies in which the approach to fluid management was not specified[14,24] (Fig. 1 of the Supplementary Appendix). These findings are similar to those reported by Simmons et al.[8] in 1987, suggesting that the liberal approach to fluid management reflects long-standing practices. The usual practice resembles the liberal approach in another aspect: the prestudy baseline measurements for central venous pressure (12.2 mm Hg) and pulmonary-artery–occlusion pressure (15.7 mm Hg) were both within the target ranges for the liberal fluid strategy (10 to 14 mm Hg and 14 to 18 mm Hg, respectively).

Comparisons of our study to other studies of goal-directed management in critically ill patients are problematic because of differences in protocols, patient populations, and timing of the interventions. Whereas we targeted central venous pressure or pulmonary-artery occlusion pressure in patients with recent onset of acute lung injury, previous studies targeted the cardiac index, oxygen delivery, or mixed venous oxygen saturation in heterogeneous populations of critically ill patients.[25-31] Rivers et al.[32] demonstrated in patients with severe sepsis or septic shock the efficacy of six hours of early, goal-directed resuscitation in the



osmotic pressure during the study.[21] There were no significant differences in mean serum sodium levels during the study.

SAFETY

Metabolic alkalosis and electrolyte imbalances were reported as an adverse event (none with associated arrhythmias) more frequently with the conservative strategy (42 events, 3 serious) than with the liberal strategy (19 events, 1 serious) (P=0.001). More patients in the conservative-strategy group than in the liberal-strategy group had at least one potassium value of 3.0 mmol per liter or less (26 percent vs. 22 percent, P<0.001), one sodium value of at least 150 mmol per liter (25 percent vs. 18 percent, P=0.009), or one bicarbonate value of more than 40 mmol per liter (6 percent vs. 2 percent, P<0.001). There was no significant difference in the percentage of patients with at least one potassium value of 2.5 mmol per liter or less (4 percent vs. 3 percent, P=0.23).

MAJOR OUTCOMES

Major outcomes are shown in Table 3 and Figure 3. There was no interaction between the interventions of the factorial design (type of fluid management and type of catheter, P=0.26). Therefore, results are reported according to the fluid-management strategy, irrespective of catheter assignment. The in-hospital death rate during the first 60 days after randomization was 25.5±1.9 percent in the conservative-strategy group and 28.4±2.0 percent in the liberal-strategy group (P=0.30; 95 percent confidence interval for the difference, −2.6 to 8.4 percent). The conservative-strategy group had more ventilator-free days, days free of central nervous system failure, and ICU-free

Table 3. Main Outcome Variables.*

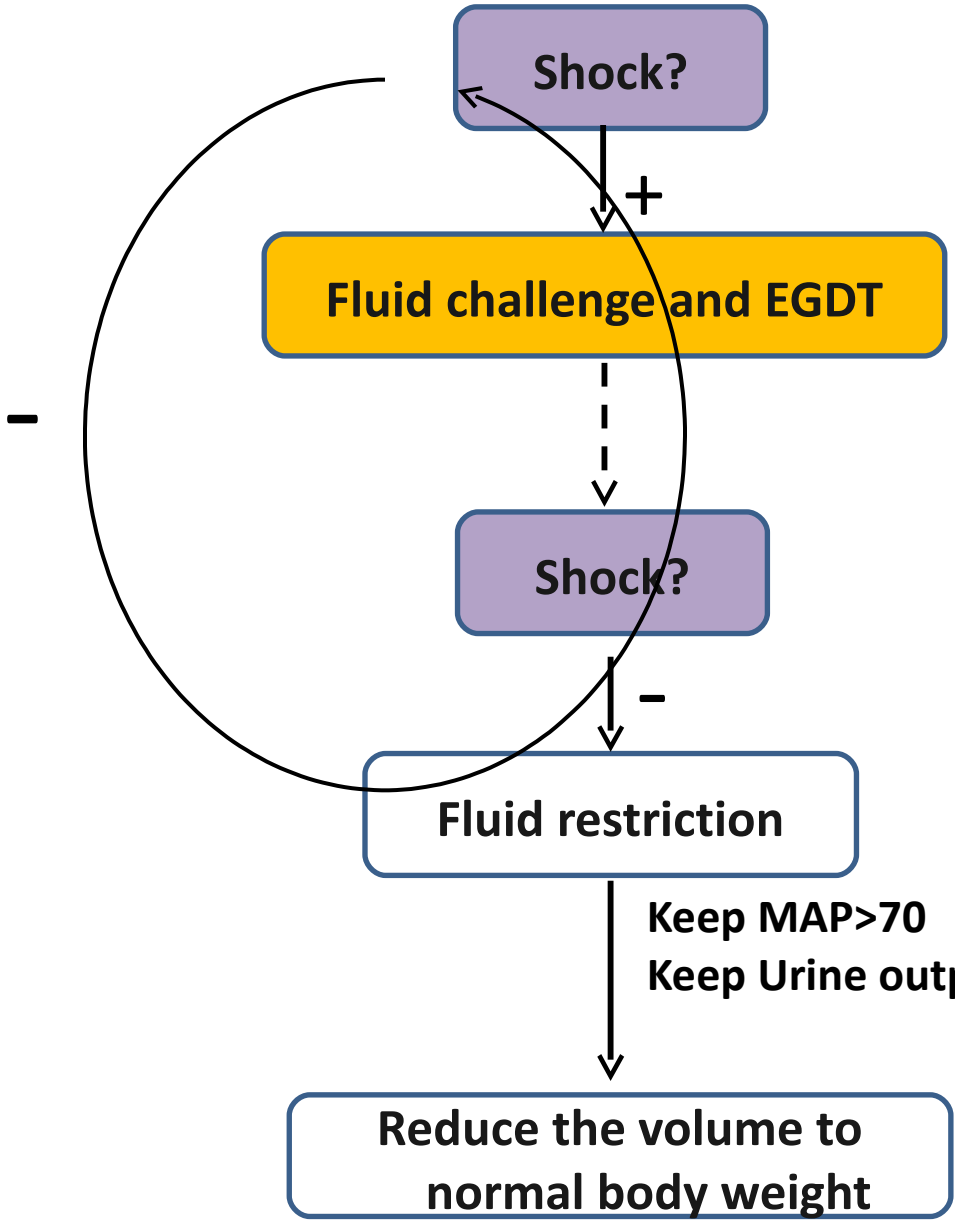
Outcome	Conservative Strategy	Liberal Strategy	P Value
Death at 60 days (%)	25.5	28.4	0.30
Ventilator-free days from day 1 to day 28†	14.6±0.5	12.1±0.5	<0.001
ICU-free days†			
Days 1 to 7	0.9±0.1	0.6±0.1	<0.001
Days 1 to 28	13.4±0.4	11.2±0.4	<0.001
Organ-failure-free days†‡			
Days 1 to 7			
Cardiovascular failure	3.9±0.1	4.2±0.1	0.04
CNS failure	3.4±0.2	2.9±0.2	0.02
Renal failure	5.5±0.1	5.6±0.1	0.45
Hepatic failure	5.7±0.1	5.5±0.1	0.12
Coagulation abnormalities	5.6±0.1	5.4±0.1	0.23
Days 1 to 28			
Cardiovascular failure	19.0±0.5	19.1±0.4	0.85
CNS failure	18.8±0.5	17.2±0.5	0.03
Renal failure	21.5±0.5	21.2±0.5	0.59
Hepatic failure	22.0±0.4	21.2±0.5	0.18
Coagulation abnormalities	22.0±0.4	21.5±0.4	0.37
Dialysis to day 60			
Patients (%)	10	14	0.06
Days	11.0±1.7	10.9±1.4	0.96

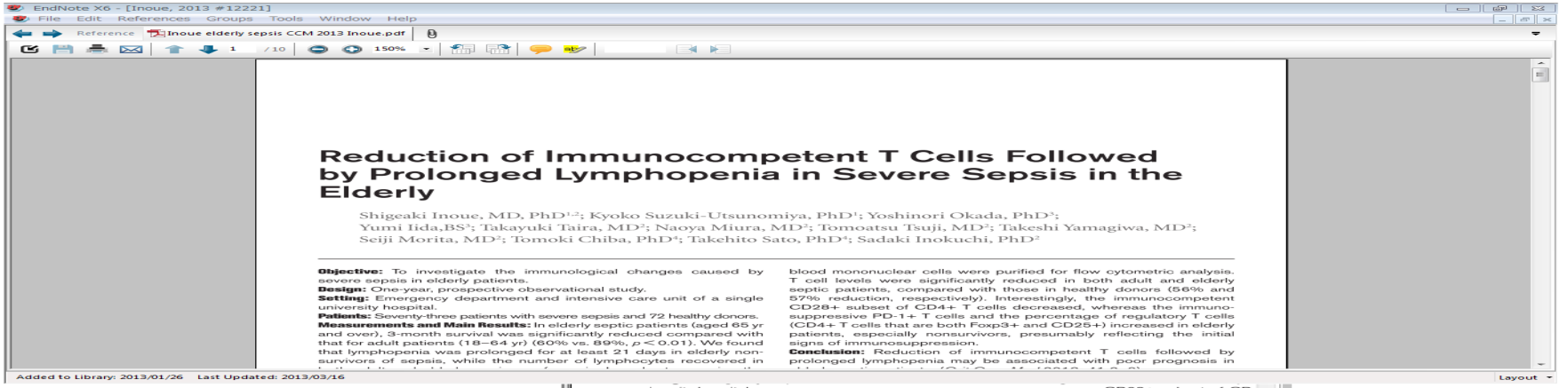
* Plus–minus values are means ±SE. CNS denotes central nervous system.
† This was an a priori secondary outcome.
‡ For this analysis, cardiovascular failure was defined by a systolic blood pressure of 90 mm Hg or less or the need for a vasopressor (in contrast, shock was defined by a mean arterial pressure of less than 60 mm Hg or the need for a vasopressor [except a dose of dopamine of 5 μg per kilogram per minute or less]); a coagulation abnormality was defined by a platelet count of 80,000 per cubic millimeter or less; hepatic failure was defined by a serum bilirubin level of at least 2 mg per deciliter (34 μmol per liter); and renal failure was defined by a serum creatinine level of at least 2 mg per deciliter (177 μmol per

Measured intravascular pressure (mm Hg)				MAP <60 mm Hg or a need for any vasopressor (except dopamine ≤5 μg/kg/min); consider correctable causes of shock first	MAP ≥60 mm Hg without vasopressors (except dopamine ≤5 μg/kg/min)			
CVP		PAOP[G]			Average urinary output <0.5 ml/kg/hr		Average urinary output ≥0.5 ml/kg/hr	
Conservative strategy	Liberal strategy	Conservative strategy	Liberal strategy		**Ineffective Circulation** Cardiac index <2.5 liters/min/m² or cold, mottled skin with capillary-refilling time >2 sec	**Effective Circulation** Cardiac index ≥2.5 liters/min/m² or absence of criteria for ineffective circulation	**Ineffective Circulation** Cardiac index <2.5 liters/min/m² or cold, mottled skin with capillary-refilling time >2 sec	**Effective Circulation** Cardiac index ≥2.5 liters/min/m² or absence of criteria for ineffective circulation
Range 1				1 Vasopressor[F] Fluid bolus[F]	3 KVO IV Dobutamine[A] Furosemide[B,1,2,4]	7 KVO IV Furosemide[B,1,2,4]	11 KVO IV Dobutamine[A] Furosemide[B,1,3,4]	15 KVO IV Furosemide[B,1,3,4]
>13	>18	>18	>24					
Range 2					4 KVO IV Dobutamine[A]	8 KVO IV Furosemide[B,1,2,4]	12 KVO IV Dobutamine[A]	16 KVO IV Furosemide[B,1,3,4]
9–13	15–18	13–18	19–24					
Range 3				2 Fluid bolus[F] Vasopressor[F]	5 Fluid bolus[C]	9 Fluid bolus[C]	13 Fluid bolus[C]	17 Liberal KVO IV
4–8	10–14	8–12	14–18					18 Conservative Furosemide[B,1,3,4]
Range 4					6 Fluid bolus[C]	10 Fluid bolus[C]	14 Fluid bolus[C]	19 Liberal fluid bolus
<4	<10	<8	<14					20 Conservative KVO IV

Figure 1. Overview of the Protocol for Conservative and Liberal Fluid Management in the Group Assigned to a Pulmonary-Artery Catheter (PAC) and the Group Assigned to a Central Venous Catheter (CVC).

Fluid therapy for ARDS





Reduction of Immunocompetent T Cells Followed by Prolonged Lymphopenia in Severe Sepsis in the Elderly

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Objective: To investigate the immunological changes caused by severe sepsis in elderly patients.
Design: One-year, prospective observational study.
Setting: Emergency department and intensive care unit of a single university hospital.
Patients: Seventy-three patients with severe sepsis and 72 healthy donors.
Measurements and Main Results: In elderly septic patients (aged 65 yr and over), 3-month survival was significantly reduced compared with that for adult patients (18–64 yr) (60% vs. 89%, $p < 0.01$). We found that lymphopenia was prolonged for at least 21 days in elderly non-survivors of sepsis, while the number of lymphocytes recovered in blood mononuclear cells were purified for flow cytometric analysis. T cell levels were significantly reduced in both adult and elderly septic patients, compared with those in healthy donors (56% and 57% reduction, respectively). Interestingly, the immunocompetent CD28+ subset of CD4+ T cells decreased, whereas the immunosuppressive PD-1+ T cells and the percentage of regulatory T cells (CD4+ T cells that are both Foxp3+ and CD25+) increased in elderly patients, especially nonsurvivors, presumably reflecting the initial signs of immunosuppression.
Conclusion: Reduction of immunocompetent T cells followed by prolonged lymphopenia may be associated with poor prognosis in

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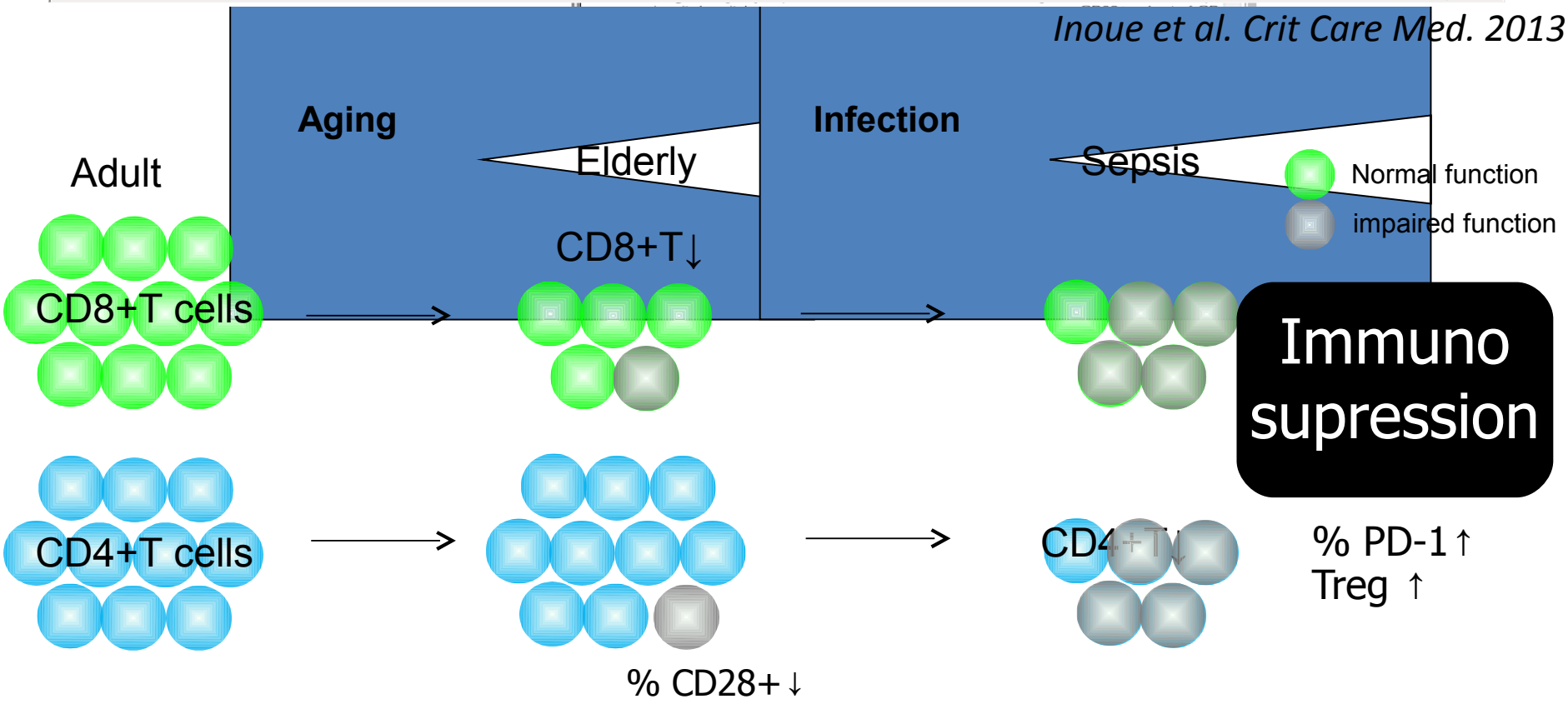
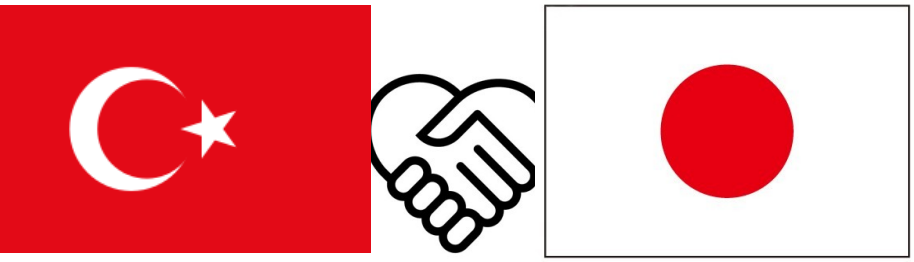
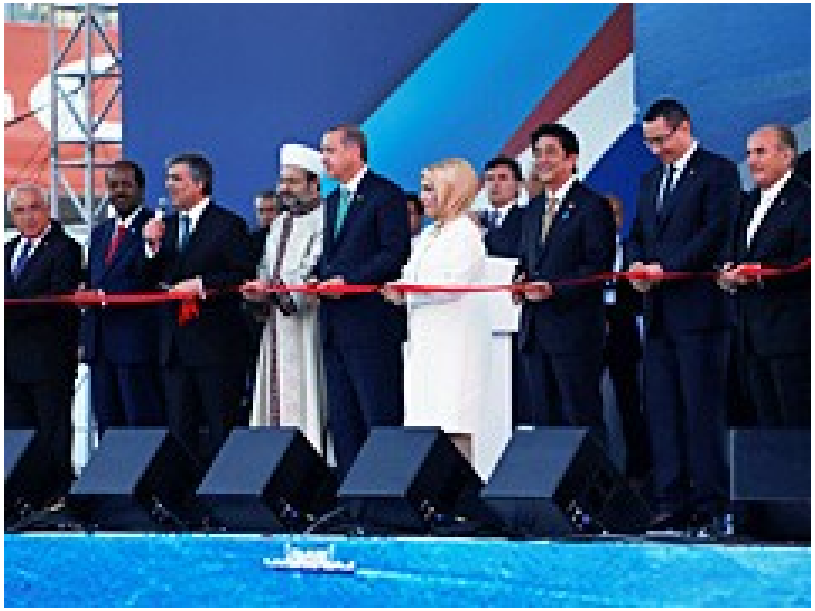


Reduction of immunocompetent T cells in elderly sepsis



Fatih Sultan Mehmet Köprüsü

Voyage of frigate Ertugrul to Japan



10/27 Opening ceremony of new metro in Istanbul Bogazi.

Acknowledgements

Tokai University School of Medicine Japan

Dept. of innovative science and technology
(Inoue's Labo)
Kyoko Suzuki-Utsunomiya
Sayuri Chiba
Yukako Komori

Teaching and Research Support Center
Yoshinori Okada *Yumi Iida*
Yoshiko Shinozaki *Kayoko Iwao*

Dept. of Immunology
Takehito Sato