Journal Club
敗血症治療バンドルの遵守と予後の関係

The Surviving Sepsis Campaign bundles and outcome: results from the International Multicentre Prevalence Study on Sepsis (the IMPreSS study)

IMPRESS (INTERNATIONAL MULTICENTRE PREVALENCE STUDY ON SEPSIS)

聖マリアンナ医科大学出向中
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2015/11/10

最近の敗血症治療の流れについて

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

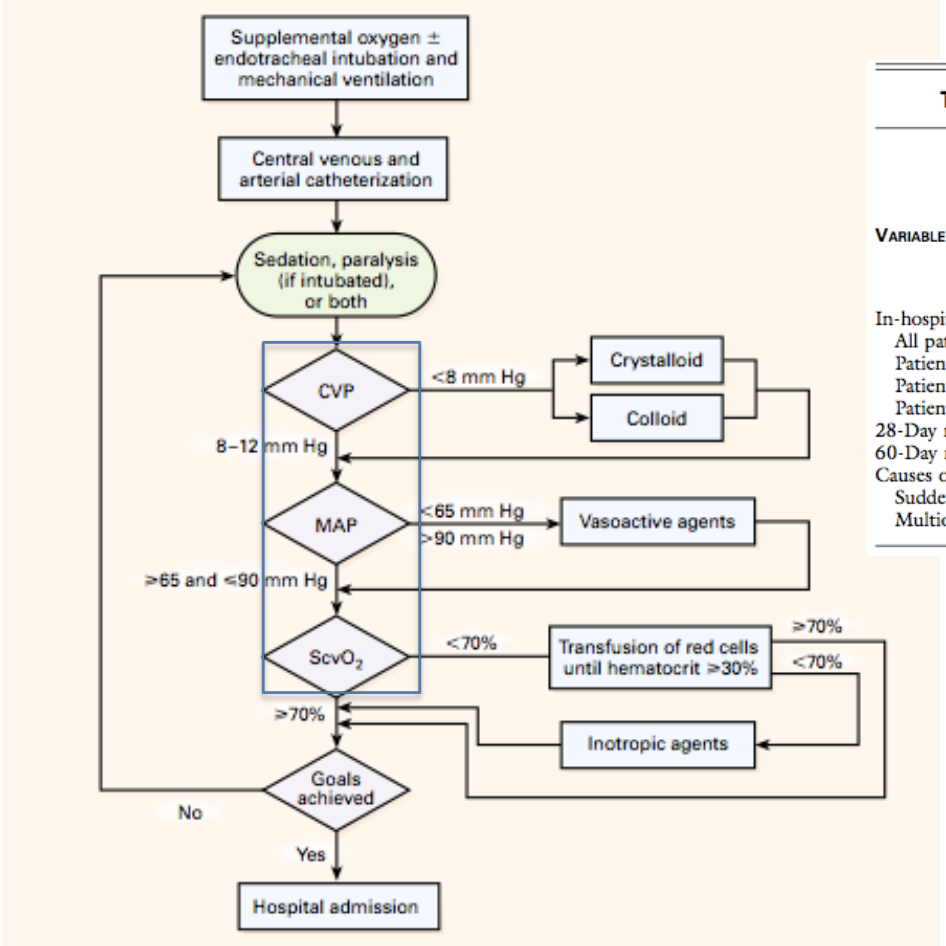


TABLE 3. KAPLAN–MEIER ESTIMATES OF MORTALITY AND CAUSES OF IN-HOSPITAL DEATH.*

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

単施設RCT
1997年3月～2000年3月
CVP、MAP、ScvO2を指標に6時間以内
→28日死亡率の減少

N Engl J Med. 2001;345: 1368-1377

ProCESS

アメリカの31の施設(N＝1351)

N Engl J Med 2014;370:1683-93

2008年3月～2013年5月

Inclusion:

・18歳以上 ・敗血症疑い ・SIRS≧2項目

・fluid challenge(＊)でもSBP<90mmHg or vasopressor使用 or 乳酸値 >4mmol/L

＊fluid challenge：>20ml/kg/30min >1000ml/30min

Primary Outcome：

60日以内の病院内死亡率

Secondary Outcome：

90日死亡率、90日と1年の積算死亡、vasopressor使用期間、ventilator使用期間、透析使用、入院期間、ICU滞在期間、転帰、重症合併症

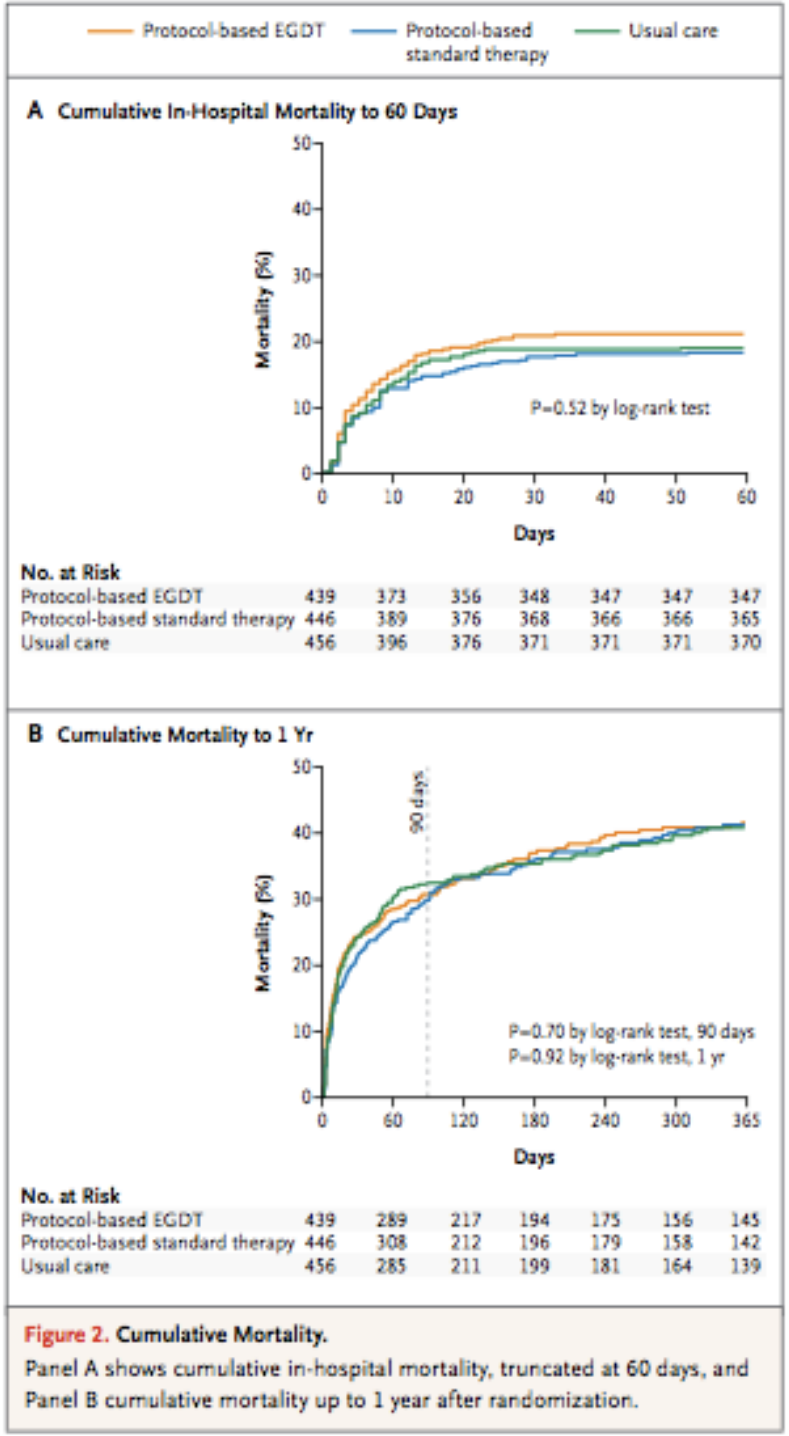


Figure 2. Cumulative Mortality.
Panel A shows cumulative in-hospital mortality, truncated at 60 days, and Panel B cumulative mortality up to 1 year after randomization.

Table 2. Outcomes.*

Outcome	Protocol-based EGDT (N=439)	Protocol-based Standard Therapy (N=446)	Usual Care (N=456)	P Value†
Death — no./total no. (%)				
In-hospital death by 60 days: primary outcome	92/439 (21.0)	81/446 (18.2)	86/456 (18.9)	0.83‡
Death by 90 days	129/405 (31.9)	128/415 (30.8)	139/412 (33.7)	0.66
New organ failure in the first week — no./total no. (%)				
Cardiovascular	269/439 (61.3)	284/446 (63.7)	256/456 (56.1)	0.06
Respiratory	165/434 (38.0)	161/441 (36.5)	146/451 (32.4)	0.19
Renal	12/382 (3.1)	24/399 (6.0)	11/397 (2.8)	0.04
Duration of organ support — days§				
Cardiovascular	2.6±1.6	2.4±1.5	2.5±1.6	0.52
Respiratory	6.4±8.4	7.7±10.4	6.9±8.2	0.41
Renal	7.1±10.8	8.5±12	8.8±13.7	0.92
Use of hospital resources				
Admission to intensive care unit — no. (%)	401 (91.3)	381 (85.4)	393 (86.2)	0.01
Stay in intensive care unit among admitted patients — days	5.1±6.3	5.1±7.1	4.7±5.8	0.63
Stay in hospital — days	11.1±10	12.3±12.1	11.3±10.9	0.25
Discharge status at 60 days — no. (%)				
Not discharged	3 (0.7)	8 (1.8)	2 (0.4)	0.82
Discharged to a long-term acute care facility	16 (3.6)	22 (4.9)	22 (4.8)	
Discharge to another acute care hospital	8 (1.8)	2 (0.4)	5 (1.1)	
Discharged to nursing home	71 (16.2)	93 (20.9)	88 (19.3)	
Discharged home	236 (53.8)	227 (50.9)	235 (51.5)	
Other or unknown	13 (3.0)	13 (2.9)	18 (3.9)	
Serious adverse events — no. (%)¶	23 (5.2)	22 (4.9)	37 (8.1)	0.32

- 死亡率に有意差なし
- EGDTでICU入室率が有意に高い
- 昇圧薬使用、人工呼吸器使用に有意差なし
- ICU滞在期間、入院期間、重大な合併症イベントに有意差なし

ARISE

N Engl J Med 2014;371:1496-506.

主にオーストラリア、ニュージーランドの51施設(N＝1600)
2008年10月5日～2014年4月23日

Inclusion:
・18歳以上 ・敗血症疑い ・SIRS≧2項目
・fluid challenge(補液1000ml以上投与1時間後)でも
SBP<90mmHg or MAP≦65mmHg or 乳酸値>4mmol/L

Primary Outcome：
90日死亡率

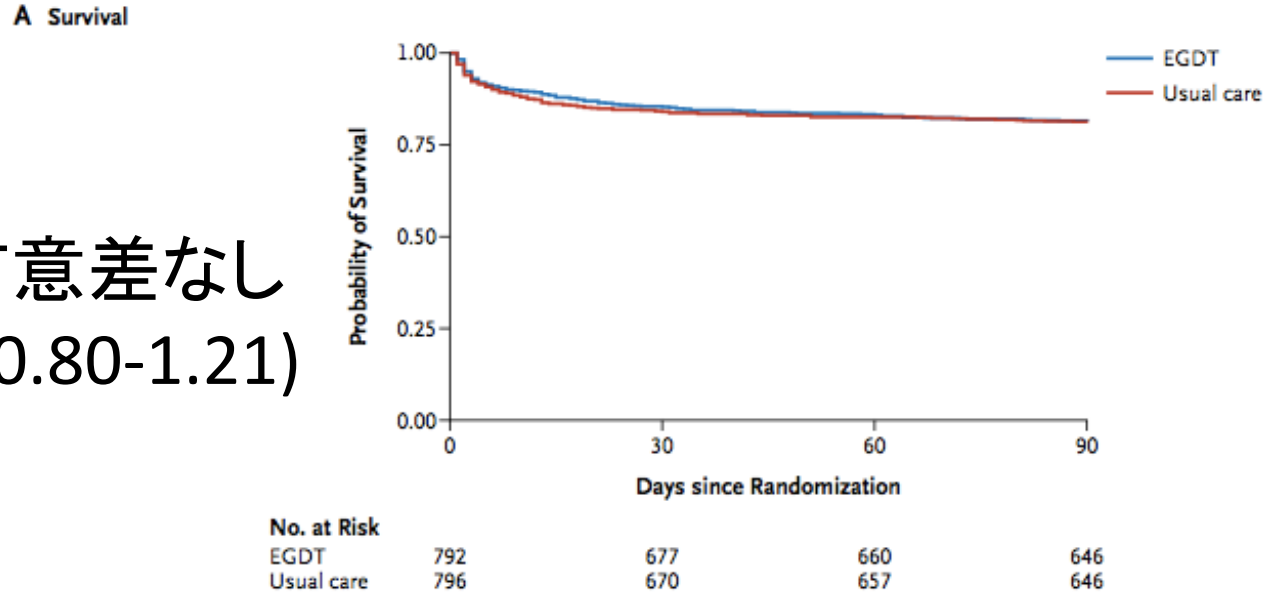
Secondary Outcome：
90日生存期間、ICU死亡率、28日死亡率、60日院内死亡率、vasopressor使用期間、ventilator使用期間、透析使用期間、ICU/ED滞在期間、転帰、副作用

Table 2. Study Outcomes.

Variable	EGDT (N=793)	Usual Care (N=798)	Relative Risk (95% CI)	Risk Difference (95% CI)*	P Value
				percentage points	
Primary outcome: death by day 90 — no./total no. (%)	147/792 (18.6)	150/796 (18.8)	0.98 (0.80 to 1.21)	−0.3 (−4.1 to 3.6)	0.90
Secondary outcomes					
Median duration of stay (IQR)†					
Emergency department — hr	1.4 (0.5–2.7)	2.0 (1.0–3.8)			<0.001
ICU — days	2.8 (1.4–5.1)	2.8 (1.5–5.7)			0.81
Hospital — days	8.2 (4.9–16.7)	8.5 (4.9–16.5)			0.89
Use and duration of organ support‡					
Invasive mechanical ventilation — no./total no. (%)	238/793 (30.0)	251/798 (31.5)	0.95 (0.82 to 1.11)	−1.4 (−6.0 to 3.1)	0.52
Median duration of invasive mechanical ventilation (IQR) — hr	62.2 (23.5–181.8)	65.5 (23.0–157.9)			0.28
Vasopressor support — no./total no. (%)	605/793 (76.3)	525/798 (65.8)	1.16 (1.09 to 1.24)	10.5 (6.1 to 14.9)	<0.001
Median duration of vasopressor support (IQR) — hr	29.4 (12.9–61.0)	34.2 (14.0–67.0)			0.24
Renal-replacement therapy — no./total no. (%)	106/793 (13.4)	108/798 (13.5)	0.99 (0.77 to 1.27)	−0.2 (−3.5 to 3.2)	0.94
Median duration of renal-replacement therapy (IQR) — hr§	57.8 (25.3–175.0)	85.9 (29.3–182.9)			0.40
Tertiary outcomes — no./total no. (%)					
Death by day 28	117/792 (14.8)	127/797 (15.9)	0.93 (0.73 to 1.17)	−1.2 (−4.7 to 2.4)	0.53
Death by the time of discharge from ICU	79/725 (10.9)	85/661 (12.9)	0.85 (0.64 to 1.13)	−2.0 (−5.4 to 1.5)	0.28
Death by the time of discharge from hospital¶	115/793 (14.5)	125/797 (15.7)	0.92 (0.73 to 1.17)	−1.2 (−4.7 to 2.3)	0.53

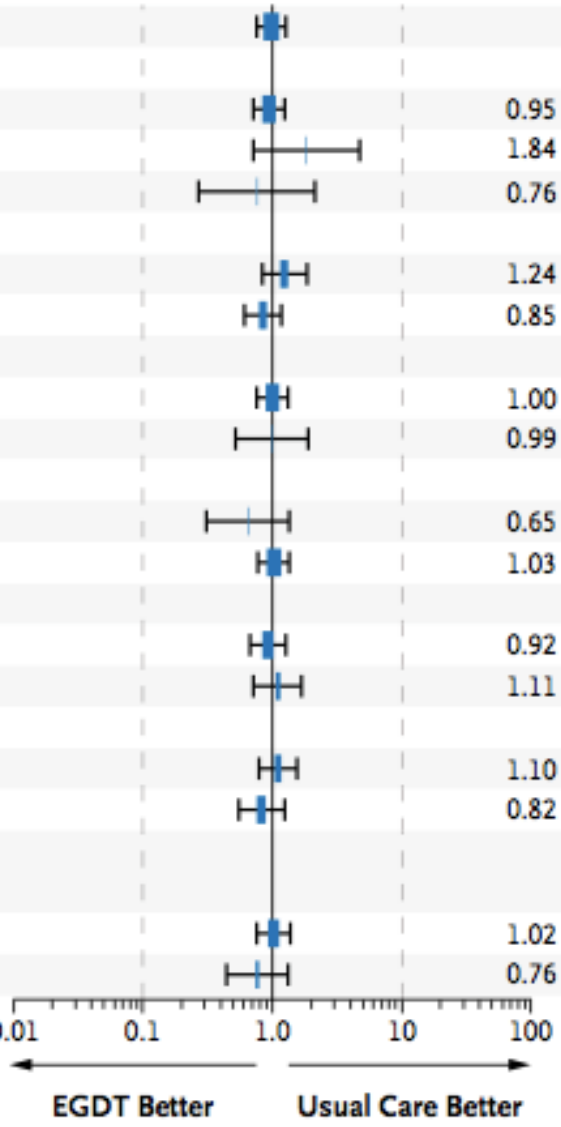
・EGDT群の方が有意にvasopressor使用率が高い。

90 日死亡率は有意差なし
Relative Risk0.98(0.80-1.21)
p=0.9



B Subgroup Analyses

Subgroup	EGDT	Usual Care	Odds Ratio (95% CI)	P Value	P Value for Interaction
	no. of events/total no. (%)				
Overall	147/792 (18.6)	150/796 (18.8)			
Country					0.38
Australia	126/677 (18.6)	132/679 (19.4)	0.95 (0.72–1.24)	0.70	
New Zealand	13/67 (19.4)	8/69 (11.6)	1.84 (0.71–4.76)	0.21	
Other	8/48 (16.7)	10/48 (20.8)	0.76 (0.27–2.13)	0.60	
Age					0.15
<65 yr	61/393 (15.5)	50/387 (12.9)	1.24 (0.83–1.85)	0.30	
≥65 yr	86/399 (21.6)	100/409 (24.4)	0.85 (0.61–1.18)	0.33	
APACHE II					0.98
<25	114/720 (15.8)	114/718 (15.9)	1.00 (0.75–1.32)	0.98	
≥25	33/72 (45.8)	36/78 (46.2)	0.99 (0.52–1.88)	0.97	
Invasive mechanical ventilation					0.25
Yes	19/71 (26.8)	23/64 (35.9)	0.65 (0.31–1.36)	0.25	
No	128/721 (17.8)	127/732 (17.3)	1.03 (0.78–1.35)	0.84	
Refractory hypotension					0.50
Yes	90/554 (16.2)	97/557 (17.4)	0.92 (0.67–1.26)	0.60	
No	57/238 (23.9)	53/239 (22.2)	1.11 (0.72–1.69)	0.65	
Hypofusion					0.27
Yes	99/365 (27.1)	93/369 (25.2)	1.10 (0.79–1.54)	0.55	
No	48/427 (11.2)	57/427 (13.3)	0.82 (0.55–1.24)	0.35	
IV fluid volume before randomization					0.41
≥20 ml/kg	106/574 (18.5)	104/572 (18.2)	1.02 (0.76–1.37)	0.90	
<20 ml/kg	28/181 (15.5)	35/181 (19.3)	0.76 (0.44–1.32)	0.33	



サブグループ解析でも、各項目で90日死亡率に有意差なし

ProMISe

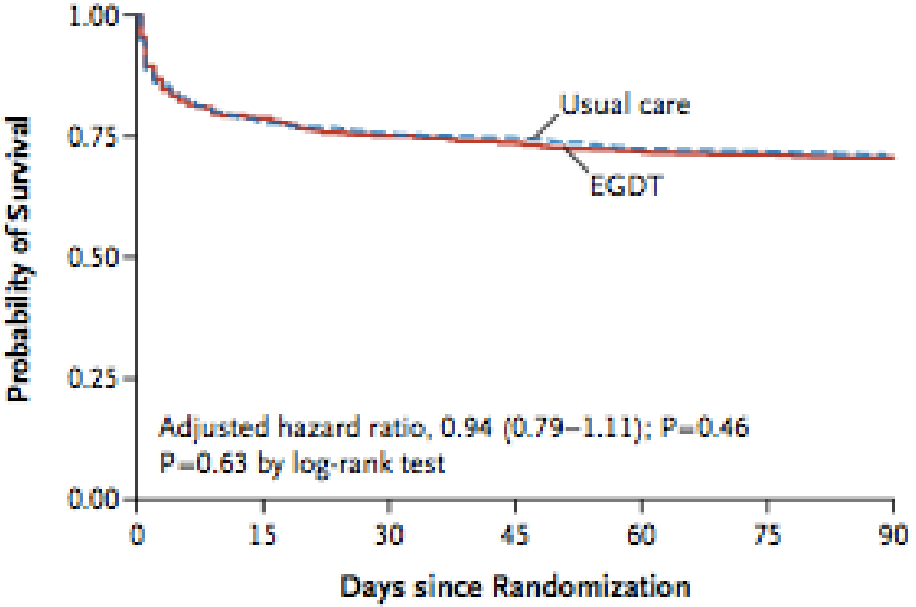
N Engl J Med 2015;372:1301-11.

Englandの56施設(N＝1260)
2011年2月16日～2014年7月24日

Inclusion:
・18歳以上 ・敗血症疑い ・SIRS≧2項目
・fluid challenge(補液1000ml以上投与1時間後)でもSBP<90mmHg or MAP≦65mmHg or 乳酸値>4mmol/L

Primary Outcome：
90日死亡率

Secondary Outcome：
28日後の補助(人工呼吸、昇圧薬、透析)、生存期間(28日、院内、1年)、滞在期間(ED、ICU、院内)、6-72時間後のSOFAスコア
European Quality of Life 5 Dimension、医療資源、費用
Quality-Adjusted Life-Years



No. at Risk							
EGDT	625	492	470	461	449	445	440
Usual care	626	487	469	464	448	445	439

Figure 2. Kaplan–Meier Survival Estimates.

Shown is the probability of survival for patients with severe sepsis receiving early, goal-directed therapy (EGDT) and those receiving usual care at 90 days.

死亡率に有意差なし

90日死亡率
EGDT VS Usual Care
29.5% VS 29.2%
RelativeRisk 1.01(0.85-1.20) p=0.90
AdjustedOR 0.95(0.74-1.24) p= 0.73
AdjustedHR 0.94(0.79–1.11)p= 0.46

Table 3. Study Outcomes.*

Outcome	EGDT (N=625)	Usual Care (N=626)	Incremental Effect (95% CI)	P Value
Clinical effectiveness				
Primary outcome: death from any cause at 90 days — no./total no. (%)	184/623 (29.5)	181/620 (29.2)		
Relative risk			1.01 (0.85 to 1.20)	0.90†
Absolute risk reduction — percentage points			−0.3 (−5.4 to 4.7)	
Unadjusted odds ratio			1.02 (0.80 to 1.30)	
Adjusted odds ratio			0.95 (0.74 to 1.24)	0.73
Secondary outcomes				
SOFA score‡				
At 6 hr	6.4±3.8	5.6±3.8	0.8 (0.5 to 1.1)§	<0.001
At 72 hr	4.0±3.8	3.7±3.6	0.4 (−0.0 to 0.8)§	0.056
Receipt of advanced cardiovascular support — no./total no. (%)	230/622 (37.0)	190/614 (30.9)	1.19 (1.02 to 1.40)¶	0.026†
Receipt of advanced respiratory support — no./total no. (%)	179/620 (28.9)	175/615 (28.5)	1.01 (0.85 to 1.21)¶	0.90†
Receipt of renal support — no./total no. (%)	88/620 (14.2)	81/614 (13.2)	1.08 (0.81 to 1.42)¶	0.62†
Days free from advanced cardiovascular support up to 28 days	20.3±11.9	20.6±11.8	−0.3 (−1.5 to 1.0)§	0.63
Days free from advanced respiratory support up to 28 days	19.6±12.1	19.8±12.0	−0.2 (−1.5 to 1.1)§	0.78
Days free from renal support up to 28 days	20.6±12.1	20.6±11.9	0.0 (−1.3 to 1.3)§	0.97
Median length of stay in emergency department (IQR) — hr	1.5 (0.4 to 3.1)	1.3 (0.4 to 2.9)		0.34‖
Median length of stay in ICU (IQR) — days	2.6 (1.0 to 5.8)	2.2 (0.0 to 5.3)		0.005‖
Median length of stay in hospital (IQR) — days	9 (4 to 21)	9 (4 to 18)		0.46‖
Death from any cause — no./total no. (%)				
At 28 days	155/625 (24.8)	152/621 (24.5)	1.01 (0.83 to 1.23)¶ 0.95 (0.73 to 1.25)**	0.90† 0.73
At hospital discharge	160/625 (25.6)	154/625 (24.6)	1.04 (0.86 to 1.26)¶ 0.98 (0.75 to 1.29)**	0.74† 0.90

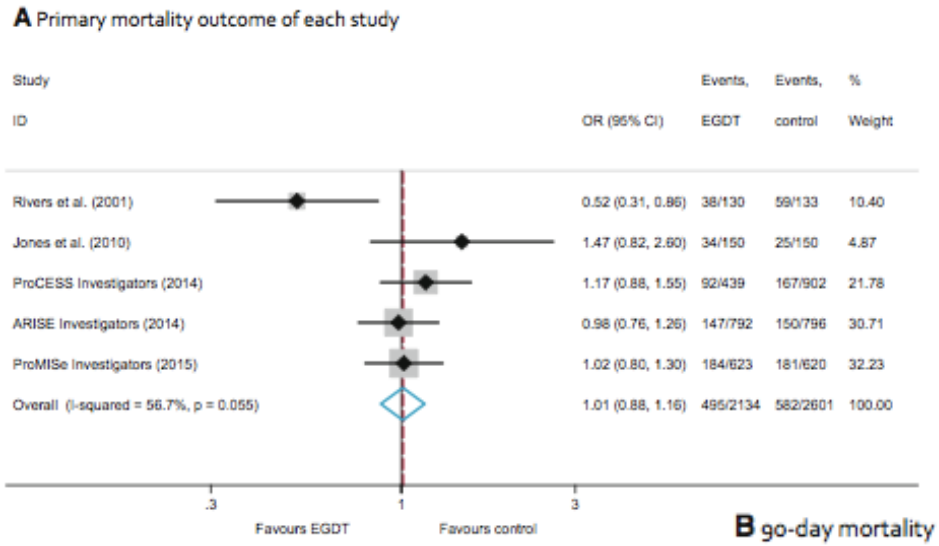
Table 3. (Continued.)

Outcome	EGDT (N=625)	Usual Care (N=626)	Incremental Effect (95% CI)	P Value
Cost-effectiveness				
Health-related quality of life on EQ-5D at 90 days††	0.609±0.319	0.613±0.312	−0.004 (−0.051 to 0.044)§	0.88
Quality-adjusted life-yr up to 90 days	0.054±0.048	0.054±0.048	−0.001 (−0.006 to 0.005)§	0.85
Costs up to 90 days				0.26
Pounds	12,414±14,970	11,424±15,727	989 (−726 to 2,705)§	
Dollars	17,647±21,280	16,239±22,356	1,406 (−1,032 to 3,845)§	
Incremental net benefit up to 90 days‡‡				0.25
Pounds	NA	NA	−1,000 (−2,720 to 720)§	
Dollars	NA	NA	−1,422 (−3,866 to 1,023)§	
Serious adverse events — no. (%)	30 (4.8)	26 (4.2)	1.16 (0.69 to 1.93)¶	0.58†

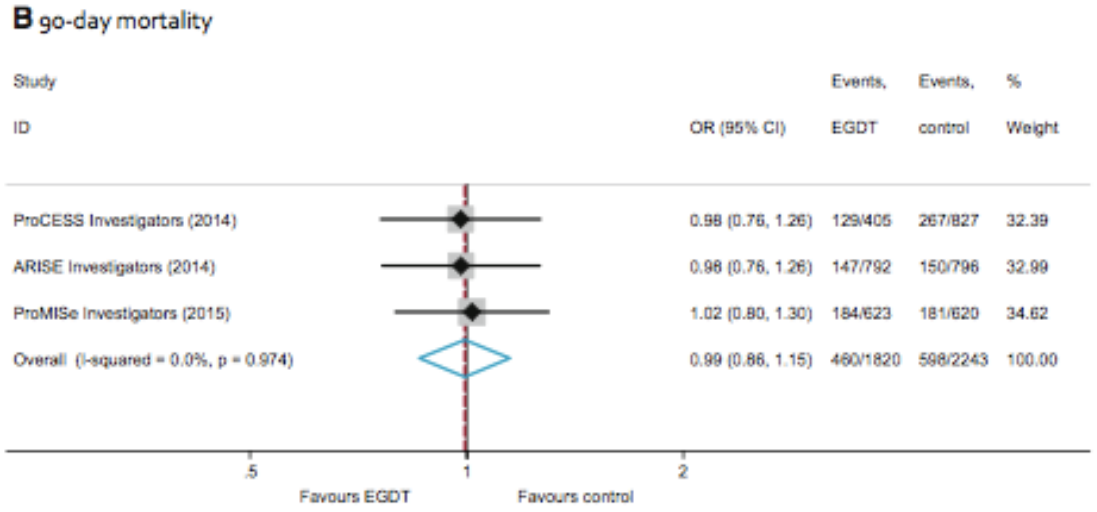
- SOFAスコアはUsual careの方が低い
- Organ Supportは有意差なし
- コストは、EGDTの方が高め
- 90日後のQOLは有意差なし

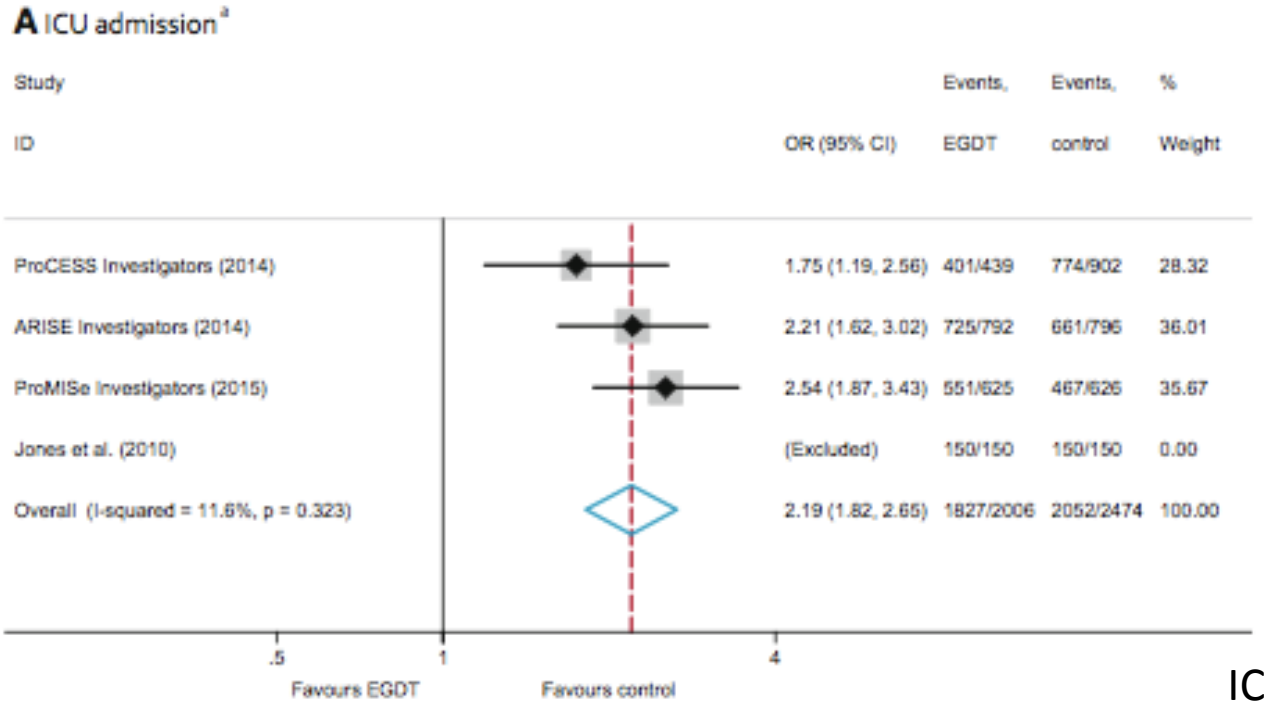
A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators

Intensive Care Med 2015 41:1549–1560

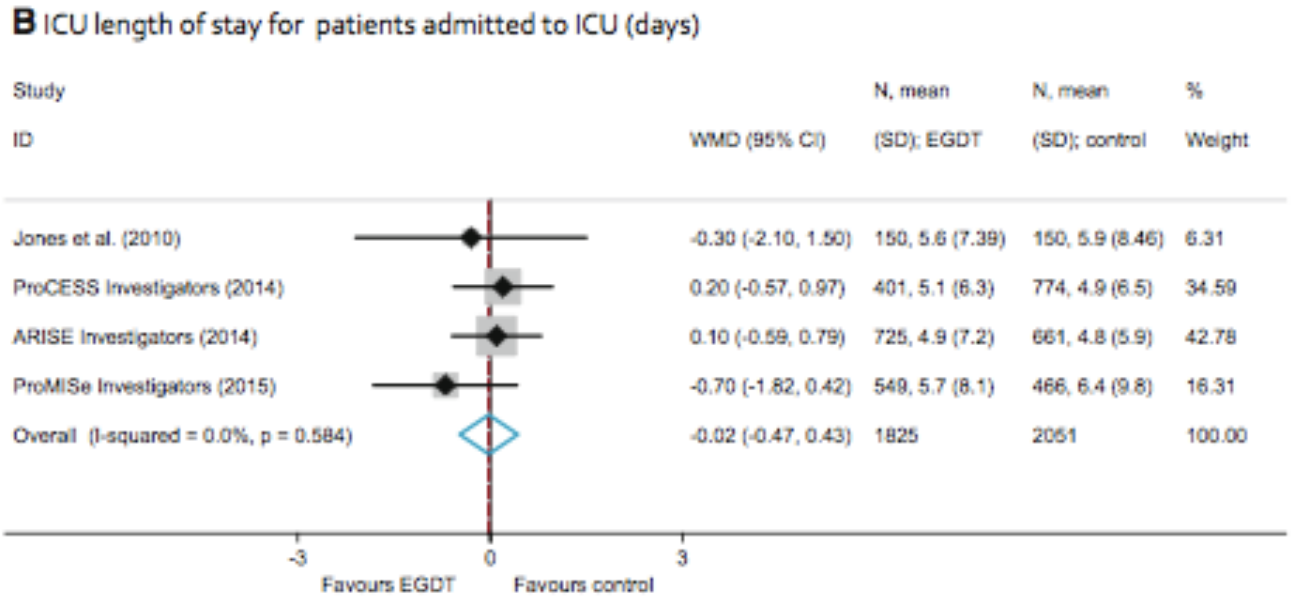


90日死亡率に有意差なし





ICU入室率、期間に有意差なし



2012 Bundles

SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4mmol/L

TO BE COMPLETED WITHIN 6 HOURS:

5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation ($Scvo_2$)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $Scvo_2$ of ≥70%, and normalization of lactate.

Figure 1. Surviving Sepsis Campaign Care Bundles.

Crit Care Med 2013; 41:580–637

2015 Bundle

TO BE COMPLETED WITHIN 3 HOURS OF TIME OF PRESENTATION*:

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30ml/kg crystalloid for hypotension or lactate ≥4mmol/L

* *"Time of presentation" is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review.*

TO BE COMPLETED WITHIN 6 HOURS OF TIME OF PRESENTATION:

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65mmHg
6. In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion and document findings according to Table 1.
7. Re-measure lactate if initial lactate elevated.

2015 Bundle Table1

EITHER

- Repeat focused exam (after initial fluid resuscitation) by licensed independent practitioner including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings.

OR TWO OF THE FOLLOWING:

- Measure CVP
- Measure $ScvO_2$
- Bedside cardiovascular ultrasound
- Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge

Introduction

The Surviving Sepsis Campaign(SSC)　Bundle遵守の質改善により
重症敗血症、敗血症性ショックの死亡率は低下するが
採用できている病院は少ないまま

Crit Care Med. 2015 ; 43:3-12

SSCに積極的に参加することと、ガイドライン遵守増加が認められ、
敗血症関連の死亡率改善にも関連する

Crit Care Med 2014;40:1623-33

SSCに長く参加し、performanceを改善すればするほど
アウトカムはより改善する

Introduction

前述のようなエビデンスがあるにもかかわらず、病院間において明らかな違いが認められる

世界中の病院でのSSCの浸透は限られている

敗血症における質改善のため、エビデンスに基づいたSSC Bundleが異なった地域でどの程度広く充分に使われ、どの程度アウトカムと関連するか理解する必要がある

現状を把握し、進行する臨床経過のギャップを明らかにする

PICO

P	18歳以上 重症敗血症or敗血症性ショック患者
I	The Surviving Sepsis Campaign(SSC) Bundle を守っている
C	守っていない
O	院内死亡率

方法

design：

世界的な前向き観察研究、質改善研究

期間：

2013年11月7日0:00～24:00

対象：

重症敗血症or敗血症性ショックにて救急外来かICUにて治療

SIRS2項目以上満たし感染が疑われる+急性臓器傷害±shockを伴う患

the European Society of Intensive Care Medicine (ESICM)

the Society of Critical Care Medicine (SCCM)

The Surviving Sepsis Campaign (SSC)

the networks of national and local coordinators

を通じて62ヵ国の618病院から選定後30日間or退院時まで追跡

除外基準：18歳未満

統計

・Fisher検定
カテゴリー変数：頻度、度数
（オセアニア地域は、Nが少ないため地域間比較から除外）
・ロジスティック回帰分析
連続変数：平均値+標準偏差(正常分配)　中央値+四分異数範囲

・調整前後のオッズ比は、ともに95%信頼区間で表現
（調整項目）
①年齢
②ICU入室(yes VS no)
③敗血症の状態(重症 VS　ショック)
④診断場所(ED or 一般病棟 or ICU or 不詳)
⑤感染場所(Community or Health care or Hospital or ICU)
⑥APACHE Ⅱ スコア

解析方法：Stata 13.1　StataCorp　College Station　TX

Study Flow Chart

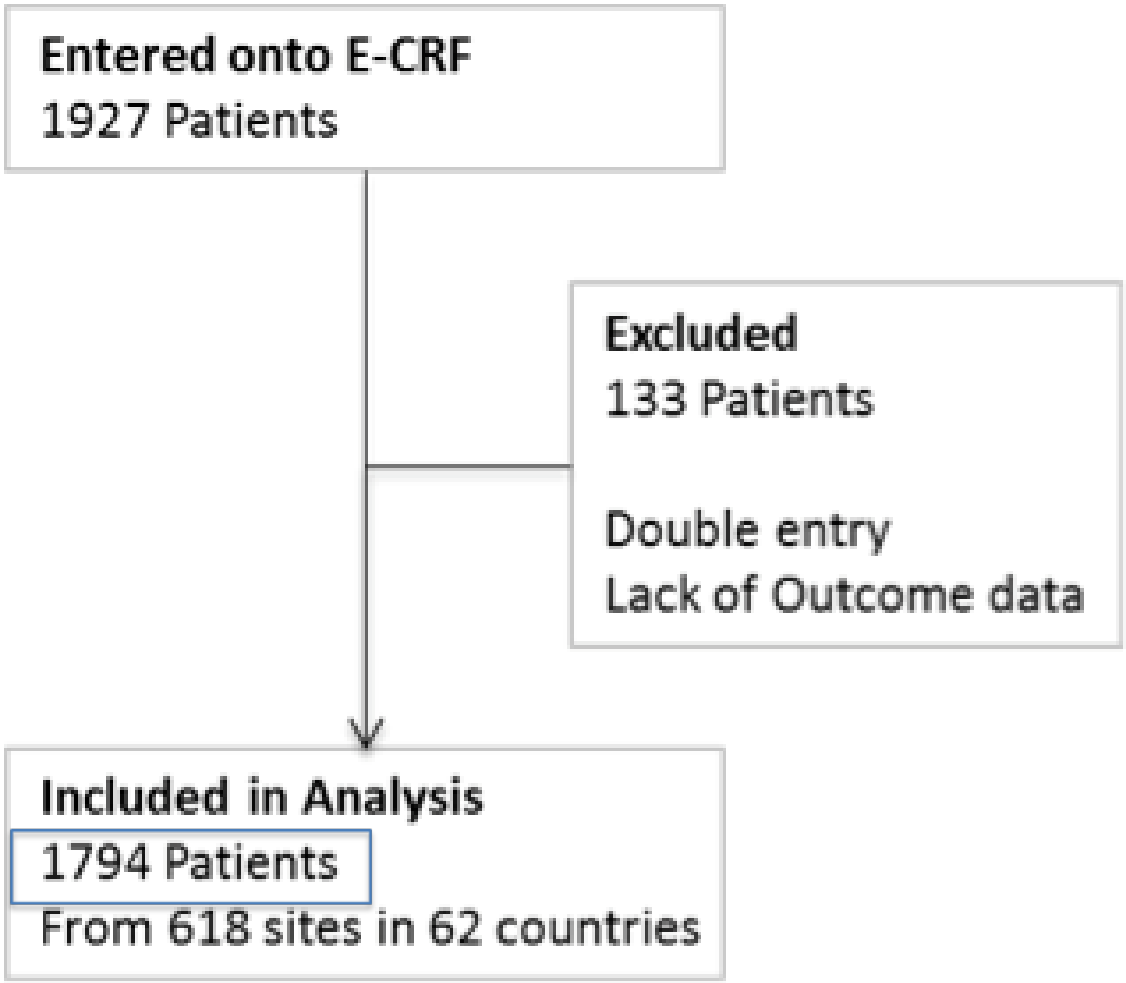


Table ESM 1

Table describing numbers of patients enrolled by country.

Country	N	%	Sites	Mortality
USA	489	27.3	125	24.1%
UK	199	11.1	67	25.1%
Malaysia	144	8.0	37	42.4%
Spain	141	7.9	51	21.3%
India	70	3.9	22	31.4%
Italy	57	3.2	28	35.1%
China	55	3.1	29	9.1%
Brazil	45	2.5	14	46.7%
Greece	43	2.4	20	41.9%
Belgium	41	2.3	10	26.8%
Argentina	34	1.9	16	47.1%
Japan	33	1.8	17	21.2%
Mexico	32	1.8	9	31.3%
France	29	1.6	15	31.0%
Netherlands	29	1.6	15	13.8%
Norway	26	1.4	11	23.1%
Germany	23	1.3	10	34.8%
Poland	17	0.9	10	47.1%
Ecuador	16	0.9	3	18.8%
Portugal	16	0.9	6	12.5%
Russian Federation	16	0.9	7	37.5%
Saudi Arabia	16	0.9	4	68.8%
Singapore	16	0.9	5	25.0%
Czech Republic	15	0.8	11	53.3%
South Korea	15	0.8	6	26.7%
Turkey	15	0.8	8	26.7%
Israel	13	0.7	3	23.1%
Canada	12	0.7	4	25.0%
Australia	11	0.6	3	18.2%
Colombia	11	0.6	4	18.2%
Bolivia	9	0.5	1	11.1%
Denmark	8	0.4	6	25.0%
Hungary	8	0.4	4	25.0%
Romania	8	0.4	3	62.5%
UAE	8	0.4	1	62.5%
Indonesia	6	0.3	1	16.7%
Lithuania	6	0.3	1	50.0%
Oman	6	0.3	2	0.0%
Serbia	6	0.3	1	83.3%
Peru	5	0.3	2	20.0%
Ireland	4	0.2	2	0.0%
Switzerland	4	0.2	2	0.0%
Brunei	3	0.2	1	0.0%
Cyprus	3	0.2	1	33.3%
Egypt	3	0.2	1	0.0%
Guatemala	3	0.2	1	0.0%
Nigeria	3	0.2	2	33.3%
Philippines	3	0.2	2	33.3%
Bosnia and Herzegovina	2	0.1	1	50.0%
Iceland	2	0.1	1	0.0%
Iran	2	0.1	1	0.0%
Sudan	2	0.1	1	100.0%
Tunisia	2	0.1	1	0.0%
Austria	1	0.1	1	0.0%
Bangladesh	1	0.1	1	0.0%
Croatia	1	0.1	1	0.0%
Estonia	1	0.1	1	0.0%
Martinique	1	0.1	1	100.0%
Slovakia	1	0.1	1	0.0%
Thailand	1	0.1	1	100.0%
Uganda	1	0.1	1	0.0%
Ukraine	1	0.1	1	100.0%
Total	1,794	100.0	618	28.4%

参加国が多い地域は、

①Western Europe(34.7%)

②North America(27.9%)

Table ESM 2

Baseline demographics of patients enrolled into the IMPreSS Study, markers of severity and outcomes . All numbers are presented as n (%) unless otherwise stated.

Detail	N (%)	Mortality n (%)
N	1794	510 (28.4)
Continent		
Asia	344 (19.2)	106 (30.8)
Oceania	14 (0.8)	2 (14.3)
West Europe	623 (34.7)	160 (25.7)
East Europe	100 (5.6)	44 (44.0)
North America	501 (27.9)	121 (24.1)
Central / South America	147 (8.2)	54 (36.7)
Africa and Middle East	65 (3.6)	23 (35.4)
Age		
< 65 years	952 (53.2)	252 (26.5)
≥65 and≤75 years	418 (23.3)	121 (28.9)
> 75 years	421 (23.5)	136 (32.3)
Gender		
Male	996 (55.5)	297 (29.8)
Female	798 (45.5)	213 (26.7)
Markers of severity		
Hypotension (systolic blood pressure < 90 mmHg)	1176 (65.6)	359 (30.5)
Creatinine > 176.8 mcmol/L and / or urine output < 0.5 ml/kg	827 (46.1)	286 (34.6)
Thrombocytopaenia < 100,000/mm³	358 (20.0)	132 (36.9)
Coagulopathy (INR > 1.5 or aPTT > 60 sec)	416 (23.2)	152 (36.5)
Bilirubin > 34.2mcmol/L	368 (20.5)	102 (27.7)
Lung infiltrates with PaO2 / FiO2 < 300 mmHg	1017 (56.7)	332 (32.6)
Mechanical ventilation (in first 24 hours)	1053 (58.7)	370 (35.1)
Renal replacement (in first 24 hours)	312 (17.4)	124 (39.7)
Lactate > 3mmo/L	641 (35.7)	218 (34.0)
Baseline lactate level (mmol/L) (mean (SD).	3.2 (3.5)	
APACHE II score (mean (SD))	22 (9)	
SOFA score (mean (SD))	7 (3)	
Severity of sepsis		
Severe sepsis	1047 (60.8)	280 (26.7)
Septic shock	674 (39.2)	207 (30.70
Outcomes for whole population		
Number admitted to intensive care (ICU)	1545 (86.1)	466 (30.2)
ICU mortality		405 (22.6)
Hospital length of stay, days (median (range))	13.7 (6.5 – 24.6)	
Hospital mortality		510 (28.4)

65歳以上が47%

59%で少なくとも1つの併存疾患あり

SHOCK 67%

ARDS 57%

AKI 46%

86.1%がICU入室

院内死亡率は28%

在院日数は中央値で13.7(6.5-24.6)

Table ESM 3
Baseline description of sepsis and description of co-morbid diseases as presentation for patients enrolled into the IMPreSS Study. All numbers are presented as n (%) unless otherwise stated.

Detail	N (%)	Mortality n (%)
Origin of sepsis		
Community acquired	1065 (59.9)	262 (24.6)
Health care acquired	291 (16.4)	84 (28.9)
Hospital acquired	273 (15.4)	104 (38.1)
ICU acquired	150 (8.4)	55 (36.7)
Source of infection		
Abdominal	402 (22.4)	132 (32.8)
Respiratory	716 (40.0)	215 (30.0)
Urinary tract	234 (13.0)	38 (16.2)
Central nervous system	22 (1.2)	4 (18.2)
Catheter related	45 (2.5)	8 (17.8)
Device related	13 (0.7)	5 (38.5)
Other	175 (9.8)	48 (27.4)
Unknown	187 (10.4)	60 (32.1)
Location in hospital at time of diagnosis		
Emergency department	972 (54.2)	239 (24.6)
Ward	352 (19.6)	117 (33.2)
Intensive Care Unit	383 (21.3)	136 (35.5)
Operating Theatre	17 (1.0)	2 (11.8)
Presenting with chronic illness	731 (40.8)	229 (31.3)
Rheumatic Heart Disease	98 (5.5)	26 (26.5)
Hypertension	868 (48.4)	267 (30.8)
Peptic ulcer disease	112 (6.2)	34 (30.4)
Mild diabetes	319 (17.8)	84 (26.3)
Severe diabetes	234 (13.0)	61 (26.1)
Mild liver disease	105 (5.9)	24 (22.9)
Previous myocardial infarction	135 (7.5)	41 (30.4)
Renal disease	296 (16.5)	98 (33.1)
Heart failure	255 (14.2)	77 (30.2)
Non metastatic tumour	173 (9.6)	48 (27.7)
Metastatic tumour	99 (5.5)	41 (41.4)
Cerebrovascular disease	150 (8.4)	51 (34.0)
Peripheral vascular disease	166 (9.3)	57 (34.3)
Lymphoma	39 (2.2)	17 (43.6)
Leukaemia	45 (2.5)	17 (37.8)
Dementia	131 (7.3)	36 (27.5)
AIDS	26 (1.5)	3 (11.5)
Chronic lung disease	376 (30.0)	127 (33.8)
Hemi / Paraplegia	84 (4.7)	28 (33.3)

Community acquired sepsisが最多

肺炎が最多

54%がEDで診断

①Western Europeで高齢傾向

②North Americaで慢性疾患が多い

Table 1 Presenting characteristics and outcomes for patients enrolled into the IMPreSS study split by geographic region

Detail	Asia	Oceania	West Europe	East Europe	North America	Central/South America	Africa and Middle East
N	344	14	623	100	501	147	65
Age >75 years	53 (15.4)	0 (0.0)	192 (30.9)	18 (18.1)	118 (23.7)	27 (18.4)	13 (20.0)
Presenting with chronic illness	101 (29.4)	5 (35.7)	239 (38.4)	40 (40.0)	253 (50.5)	60 (40.8)	33 (50.8)
Location in hospital of diagnosis							
Emergency department	180 (52.3)	7 (50.0)	324 (52.0)	26 (26.0)	318 (63.5)	84 (57.1)	33 (50.8)
Ward	82 (23.8)	2 (14.3)	136 (21.8)	18 (18.0)	72 (14.4)	29 (19.7)	13 (20.2)
Intensive care unit	66 (19.2)	1 (7.1)	135 (21.7)	44 (44.0)	100 (20.0)	27 (18.4)	10 (15.4)
Source of infection							
Abdominal	75 (21.8)	6 (42.9)	162 (26.0)	33 (33.0)	84 (16.8)	32 (21.8)	10 (15.4)
Respiratory	152 (44.2)	3 (21.4)	251 (40.3)	32 (32.0)	188 (37.5)	66 (44.9)	24 (36.9)
Urinary tract	14 (4.1)	0 (0.0)	81 (13.0)	7 (7.0)	104 (20.8)	18 (12.2)	10 (15.4)
Community-acquired	221 (64.4)	12 (85.7)	352 (56.7)	41 (41.0)	322 (64.4)	87 (60.4)	30 (52.6)
Septic shock	153 (45.8)	2 (15.4)	218 (36.0)	43 (43.0)	171 (35.9)	60 (42.0)	27 (48.2)
Baseline lactate (mmol/L) (mean (SD))	3.1 (2.7)	2.2 (1.5)	3.1 (3.4)	3.9 (3.4)	3.0 (4.2)	3.2 (3.6)	4.0 (2.9)
APACHE II score (mean (SD))	22.2 (8.5)	23.5 (9.7)	21.5 (8.2)	22.5 (9.7)	22.5 (9.1)	19.8 (8.2)	24.1 (8.8)
SOFA score	8.1 (3.2)	8.9 (3.8)	6.8 (3.4)	7.9 (3.2)	6.5 (3.2)	6.8 (3.0)	8.2 (2.9)
ICU admission	328 (95.4)	12 (85.7)	488 (78.3)	97 (97.0)	445 (88.8)	125 (85.0)	50 (76.9)
Hospital length of stay, days (median (range))	13.4 (7.0–22.2)	19.9 (7.3–26.2)	14.4 (7.2–28.1)	22.9 (14.2–36.4)	10.5 (5.0–19.4)	15.5 (8.0–27.0)	14.1 (5.3–24.0)
Hospital mortality (all patients)	106 (30.8)	2 (14.3)	160 (25.7)	44 (44.0)	121 (24.2)	54 (36.7)	23 (35.4)
Hospital mortality (septic shock)	42 (27.5)	0 (0)	59 (27.1)	21 (48.8)	43 (25.2)	29 (48.3)	13 (48.2)

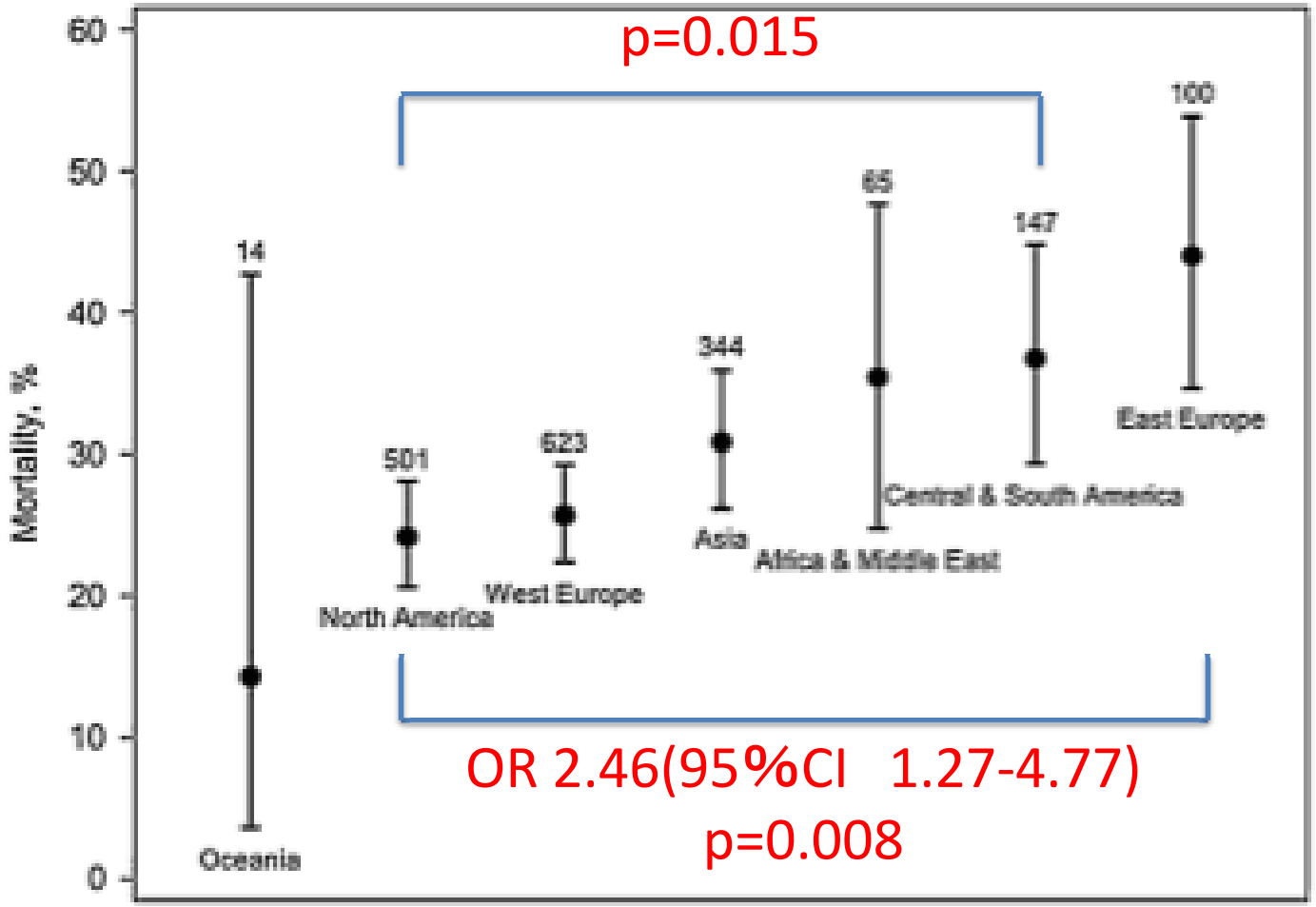
All numbers are presented as *n* (%) unless otherwise stated

③North AmericaではEDでの診断が多く、Asiaでは一般病棟、Eastern EuropeではICUで多い

④調整前の死亡率はEastern Europeで高く、Oceaniaで低い

OR 2.17(95%CI 1.16-4.03)

p=0.015



OR 2.46(95%CI 1.27-4.77)

p=0.008

Fig. 1 Estimated mortality and its associated 95 % CI by region where the number represents the observations within each region

Table 2 Surviving Sepsis Campaign bundle compliance and associated hospital mortality for patients enrolled into the IMPreSS study

Detail	
3-h bundle compliance (all patients, $n = 1794$)	
Measurement of lactate	1002 (55.9)
Obtain blood cultures before administration of antibiotics	883 (49.2)
Administer broad-spectrum intravenous antibiotics	1155 (64.4)
Administer 30 mL/kg crystalloid for hypotension	1017 (56.7)
Full bundle	340 (19.0)
Hospital mortality for 3-h bundle compliance	67/340 (19.7)
Hospital mortality for 3-h bundle non-compliance	443/1454 (30.5)*
6-h bundle compliance (all patients, $n = 1794$)	
Repeat the lactate measurement	1077 (60.0)
Application of vasopressors for hypotension	1479 (82.4)
Measurement of central venous pressure	1209 (67.4)
Measurement of central venous oxygen saturation	1070 (59.6)
Full bundle	637 (35.5)
Hospital mortality for 6-h bundle compliance	143/637 (22.4)
Hospital mortality for 6-h bundle non-compliance	367/1157 (31.7)*
6-h bundle compliance (for only patients with persistent hypotension (MAP <65 mmHg) and/or hyperlactataemia (>4 mmol/L) after volume administration ($n = 824$)	
Repeat the lactate measurement	530 (64.3)
Application of vasopressors for hypotension	544 (66.0)
Measurement of central venous pressure	274 (33.2)
Measurement of central venous oxygen saturation	135 (16.4)
Full bundle	90 (10.9)
Hospital mortality for 6-h bundle compliance	25/90 (27.8)
Hospital mortality for 6-h bundle non-compliance	261/734 (35.6)

All numbers are presented as n (%) unless otherwise stated
* Represents a p value of ≤ 0.0001 by the Fishers exact test for the mortality of bundle compliance versus non-compliance

①Overall compliance with all the 3-h bundle

19%

Hospital mortality
Compliance vs non-compliance

20% vs 31%(p＜0.001)

②Overall compliance with all the 6-h bundle

36%

Hospital mortality
Compliance vs non-compliance

22% vs 32%(p＜0.001)

6-hで低血圧継続or高乳酸血症を認めた患者でFull bundle
11% (90/824)

Table 3 Surviving Sepsis Campaign bundle compliance and hospital outcome for patients enrolled into the IMPreSS study split by geographic region

Detail	Asia	Oceania	West Europe	East Europe	North America	Central/South America	Africa and Middle East
N	344	14	623	100	501	147	65
3-h bundle compliance							
Measurement of lactate	166 (48.3)	6 (42.9)	376 (60.4)	48 (48.0)	318 (63.5)	64 (43.5)	24 (36.9)
Obtain blood cultures before administration of antibiotics	157 (45.6)	5 (42.9)	284 (45.6)	49 (49.0)	315 (62.9)	58 (39.5)	15 (23.1)
Administer broad-spectrum intravenous antibiotics	229 (66.6)	10 (71.4)	409 (65.7)	74 (74.0)	303 (60.5)	95 (64.6)	35 (53.8)
Administer 30 mL/kg crystalloid	187 (54.4)	11 (78.6)	340 (54.6)	53 (53.0)	312 (62.3)	76 (51.7)	38 (58.5)
Full bundle	50 (14.5)	1 (7.1)	108 (17.3)	14 (14.0)	146 (29.1)	14 (9.5)	7 (10.8)
Hospital mortality for bundle compliance	7 (14.0)	0 (0.0)	19 (17.6)	5 (35.7)	32 (21.9)	4 (28.6)	0 (0.0)
Hospital mortality for bundle non-compliance	99 (33.7)	2 (15.4)	141 (27.4)	39 (45.3)	89 (25.1)	50 (37.6)	23 (39.7)
6-h bundle compliance (all patients, $n = 1794$)							
Repeat the lactate measurement	187 (54.4)	10 (71.4)	434 (69.7)	55 (55.0)	290 (57.9)	74 (50.3)	27 (41.5)
Application of vasopressors for hypotension	308 (89.5)	13 (92.9)	511 (82.0)	89 (89.0)	382 (76.3)	123 (83.7)	53 (81.5)
Measurement of central venous pressure	253 (73.6)	10 (71.4)	427 (68.5)	67 (67.0)	312 (62.3)	99 (67.4)	41 (63.1)
Measurement of central venous oxygen saturation	214 (62.2)	9 (64.3)	377 (60.5)	58 (58.0)	286 (57.1)	89 (60.5)	37 (56.9)
Full bundle	126 (36.6)	7 (50.0)	255 (40.9)	28 (28.0)	163 (32.5)	41 (27.9)	17 (26.2)
Hospital mortality for bundle compliance	34 (27.0)	1 (14.3)	52 (20.4)	13 (46.4)	29 (17.8)	11 (26.8)	3 (17.6)
Hospital mortality for bundle non-compliance	72 (33.0)	1 (14.3)	108 (29.3)	31 (43.1)	92 (27.2)	43 (40.6)	20 (41.7)

All numbers are presented as *n* (%) unless otherwise stated

3-hでのFull bundle complianceは、
North Americaで最大(29%)、Central/South Americaで最低(9.5%)

6-hでのFull bundle complianceは、
West Europeで最大(41%)、Africa/Middle Eastで最低(26%)

Table 4 Hospital mortality odds ratios based on general estimating equation (GEE) population-averaged logistic regression models

Detail	Unadjusted hospital mortality odds ratio	95 % CI	*p* value	Adjusted hospital mortality odds ratio	95 % CI	*p* value
Model 1. Hospital mortality by geographic region[a]						
North America (reference)	1.00			1.00		
Asia	1.29	0.80–2.06	0.29	1.22	0.69–2.14	0.49
Oceania	0.52	0.11–2.51	0.41	0.28	0.03–2.67	0.27
West Europe	1.10	0.71–1.70	0.69	0.98	0.58–1.66	0.94
East Europe	2.47	1.41–4.31	0.001	2.46	1.27–4.77	0.008
Central/South America	1.77	1.05–3.00	0.033	2.17	1.16–4.03	0.015
Africa/Middle east	1.69	0.88–3.22	0.11	1.33	0.61–2/86	0.47
Model 2. Hospital mortality by Surviving Sepsis Campaign bundle compliance[b]						
Full 3-h bundle	0.60	0.45–0.80	<0.001	0.64	0.47–0.87	0.004
Full 6-h bundle	0.64	0.52–0.80	<0.001	0.71	0.56–0.90	0.005

①ICU入院②敗血症の状態(severe sepsis or septic shock)
③診断場所④APACHE Ⅱスコア⑤国
で調整後でも3-h、6-hでhospital mortalityに改善を認める

結果のまとめ

全体の院内死亡率28.4%

・28.4%の死亡率は、最近のRCTと比較すると高い

Bundleの遵守率は、3hで19%、6hで35.5%と低い

Bundleを遵守していた方が、有意に死亡率は低い

Limitation

・データにムラがある
(完全なデータから信頼性を保つ最小程度まで)

・サイト毎のNが比較的少ない
・多くの国で国毎の参加施設が少ない
→地域での臨床判断での入院数、疾患の季節での発症率の差
→外的妥当性の低下

・退院時までしかフォローしていない
→その後の情報が少ない

考察

・なぜ最近のRCTと逆に死亡率に改善が認められたか？

	ProCESS	ARISE Trial	ProMISe	IMPRESS
発表国	アメリカ	オーストラリア ニュージーランド	イギリス	62ヵ国
院内死亡率(＊)				
EGDT群	21.0%	14.5%	25.6%	22.4%
Usual care群	18.2%	15.7%	24.6%	31.7%

＊IMPRESSは6hバンドル遵守の院内死亡率

3つのRCTと比較し、多国籍で発展途上国も含まれており
Usual care（Bundleを守っていない群）の医療のレベルが低い

そもそもBundleは当然守るべき項目であり、本研究におけるBundleを守っている群と
3つのRCTのUsual care群が同じ群に相当すると言える

当然守るべきBundleを守らなければ予後は悪くなる、ということ

考察

医療レベルが低いところ(途上国、地域など)では、
積極的にEGDTを取り入れるとBETTER?

途上国、地域ほどCVP、ScvO2などのデバイスのアクセスは悪い

Bundle自体をACLSのようにより簡略化した方が良い？

Simplified Severe Sepsis Protocol: A Randomized Controlled Trial of Modified Early Goal-Directed Therapy in Zambia

Crit Care Med. 2014 November ; 42(11): 2315–2324

Zambiaで、JVPを指標にしたSimplified Severe Sepsis Protocol(SSSP)により
アウトカム改善されるか検討。

SSSP

最初の1時間で2Lの生理食塩水or乳酸リンゲル液をボーラス投与
投与後、MAP＜65mmHgであればDOA開始しMAP≧65mmHgを保つように調節

↓ JVP胸骨角より3cm未満

4時間でさらに2Lの補液

Baseline characteristics of Zambian patients with severe sepsis

	SSSP n=53	Control n=56	p
Age, years, mean (SD)	35.2 (1.3)	34.8 (1.4)	0.85
Male, n (%)	28 (52.8)	30 (53.6)	0.94
Admission Vital Signs, mean (SD)			
SBP, mmHg	102.6 (21.4)	101.6 (24.2)	0.83
DBP, mmHg	62.4 (14.4)	65.2 (17.2)	0.35
MAP, mmHg	75.8 (15.4)	77.3 (18.8)	0.64
RR, breaths/min	38.2 (10.9)	37.7 (11.2)	0.81
HR, beats/min	119.2 (15.8)	122.9 (22.3)	0.32
Temp, degrees C	37.3 (1.5)	37.9 (1.7)	0.07
GCS, median (IQR)	14 (11-15)	14 (10-15)	0.76
HIV positive, n (%)	42 (79.2)	46 (82.1)	0.70
CD4 count, median (IQR)+	40 (17-107)	70 (24-109)	0.41
On ARVs, n (% of HIV positive)	18 (42.9)	16 (35.6)	0.49
Suspected site of infection, n (%)			0.86
Pulmonary	31 (58.5)	32 (57.1)	
Central nervous system	19 (35.8)	15 (26.8)	
Abdomen	3 (5.7)	4 (7.1)	
Other ^	6 (11.3)	7 (12.5)	

Subgroups	SSSP*	Control*	RR (95% CI)	p-value#
HIV positive	29/42 (69.0)	29/46 (63.0)	1.10 (0.81-1.48)	0.70
HIV negative	5/11 (45.5)	5/10 (50.0)	0.91 (0.37-2.22)	
MAP>=65 mmHg	26/39 (66.7)	28/46 (60.9)	1.10 (0.79-1.51)	0.72
MAP <65 mmHg	8/14 (57.1)	6/10 (60.0)	0.95 (0.48-1.88)	
Respiratory rate>40 **	16/20 (80.0)	15/23 (65.2)	1.23 (0.85-1.78)	0.37
Respiratory rate<=40	18/33 (54.5)	18/32 (56.3)	0.97 (0.63-1.50)	
Hb<7 ***	8/13 (61.5)	5/8 (62.5)	0.98 (0.50-1.96)	0.83
Hb>=7	20/33 (60.6)	22/39 (56.4)	1.07 (0.73-1.59)	
SAPS3 >= median	22/28 (78.6)	20/29 (69.0)	1.14 (0.83-1.56)	0.52
SAPS3 < median	12/25 (48.0)	14/27 (51.9)	0.93 (0.54-1.60)	
Confirmed TB	10/15 (66.7)	12/16 (75.0)	0.89 (0.56-1.40)	0.39
No confirmed TB	24/38 (63.2)	22/40 (55.0)	1.15 (0.79-1.66)	
Hypoxemic respiratory distress †	8/8 (100.0)	7/10 (70.0)	1.43 (0.95-2.14)	0.17
No hypoxemic respiratory distress	26/45 (57.8)	27/46 (58.7)	0.98 (0.70-1.39)	
Overall	34/53 (64.2)	34/56 (60.7)	1.06 (0.79-1.41)	

院内死亡率

SSSP VS Usual

64.2% VS 60.7%

(RR1.05 95%CI0.79-1.41)

そもそも発展途上国は、HIV感染などベースが悪く死亡率自体が高い

結論

・SSC bundle complianceは、まだ低く地域差が大きい

→本研究では、6割弱が北米と欧州であり、人口分布を考えると世界情勢を反映しているかはわからない

結論

・SSC bundleを行うことで、院内死亡率が有意に低下する

→本研究では、3h-complianceも低くusual careの質が低いことが示唆され、3つのRCTとは比較できない

3つのRCTでは、usual careも乳酸値などを指標にmodified EGDTの様なcareがされており、死亡率が低い可能性がある

→非集中治療医が、治療に当たる場合はEGDTを積極的に用いた方が良いかもしれない