

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008;358:125-39.

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SUPPLEMENTARY METHODS

Inclusion criteria:

Severe sepsis was defined as the presence of microbiologically proven, clinically proven, or suspected infection; presence of Systemic Inflammatory Response Syndrome (SIRS); and development of at least one organ dysfunction within the last 24 hours. Diagnosis of SIRS required the fulfilment of at least two of the following criteria: hypo- ($\leq 36^{\circ}\text{C}$) or hyperthermia ($\geq 38^{\circ}\text{C}$), tachycardia (≥ 90 bpm); tachypnea (≥ 20 breaths/min) and/or an arterial $\text{pCO}_2 \leq 4.3$ kPa (32 mmHg) and/or mechanical ventilation; leukocytosis $\geq 12,000/\mu\text{l}$ or leukopenia $\leq 4,000/\mu\text{l}$ and/or a left shift in the differential white blood cell count $\geq 10\%$. For the diagnosis of organ dysfunction one of the following criteria had to be fulfilled: presence of acute encephalopathy with reduced vigilance, agitation, disorientation, delirium not explained by psychotropic medication; thrombocytopenia $\leq 100,000/\mu\text{l}$ or a drop in the thrombocyte count $>30\%$ within 24 hours not explained by hemorrhage; arterial hypoxemia with an arterial $\text{pO}_2 < 10$ kPa (75 mmHg) when breathing room air or an oxygenation index ($\text{paO}_2/\text{FiO}_2 \leq 33\text{kPa}$ (250 mmHg) not explained

by presence of a pulmonary or cardiac disease; arterial hypotension with a systolic blood pressure ≤ 90 mmHg or mean arterial blood pressure ≤ 70 mmHg for at least one hour despite adequate fluid loading not explained by other causes of shock; renal dysfunction with an urine output ≤ 0.5 ml/kg/h for at least one hour despite adequate fluid loading and/or increase of serum creatinine more than twofold above the reference range of the local laboratory; metabolic acidosis with a base deficit ≥ 5.0 mmol/l or a serum lactate ≥ 1.5 fold above the reference range of the local laboratory.

Septic shock was defined as the presence of infection and SIRS as defined in severe sepsis as well as presence of arterial hypotension with a systolic blood pressure ≤ 90 mmHg or a mean arterial blood pressure ≤ 70 mmHg for at least 2 hours or administration of a vasopressor (dopamin ≥ 5 $\mu\text{g kg}^{-1} \text{min}^{-1}$; norepinephrine, epinephrine, phenylephrine, or vasopressin in any dosage) to maintain systolic blood pressure ≥ 90 mmHg or mean arterial blood pressure ≥ 70 mmHg despite adequate fluid loading.

Exclusion criteria:

Treatment with >1000 ml of hydroxyethyl starch within 24 hours before study inclusion; pre-existing renal failure requiring dialysis or a serum creatinine level ≥ 320 $\mu\text{mol/l}$ (3,6 mg/dl), age < 18 years, pregnancy, known allergy against hydroxyethyl starch, intracerebral hemorrhage,

heart failure with NYHA IV, requirement of an inspiratory oxygen fraction of at least 0.7, immunosuppression from cytostatic chemotherapy, high dosage of steroids or AIDS, participation in another interventional trial, moribund due to coexisting disease, order to withhold or withdraw therapy.

Method of randomization

Patients were randomly assigned (stratified by hospital and using random permuted blocks with variable size) to receive either conventional or IIT and either 10% HES or buffered full electrolyte solution similar to RL.

Adverse events

Adverse events were defined per protocol as occurring in possible relation with the administration of study medication such as

- acute worsening of oxygenation under volume therapy (worsening of $\text{paO}_2/\text{FiO}_2$ ratio by 100 mmHg within 2 hours excluding extrapulmonary causes)
- bleeding complication if
 - life-threatening
 - needing transfusion of ≥ 3 RBC on two consecutive days

- intracranial
- allergic reaction to study medication (any anaphylactic/anaphylactoid reaction)
- hypoglycemia defined as blood glucose level ≤ 40 mg/dl (2,2 mmol/l).

Other adverse events related to study medication: any event which by judgment of the local investigator occurred in relation to the administration of the study medication.

Scores:

Sequential Organ Dysfunction Score (SOFA): scores can range from 0-24, with higher scores indicating more severe disease.

Acute Physiology And Chronic Health Evaluation (APACHE II): scores can range from 0-71, with higher scores indicating more severe disease.

Antimicrobial assessment definitions:

During the VISEP study, all investigators agreed to base their antibiotic management on International Sepsis Forum (ISF) recommendations, a published international guidelines for the diagnosis and treatment of severe sepsis.¹ Antimicrobial assessment was performed daily by the investigator on-site and data was entered into the electronic case report form of the VISEP-study.

Per protocol, therapy of antimicrobials was defined as:

- **Empirical:** a positive culture result was not available to guide therapy within the first 4 study days.

Empirical broad spectrum antibiotic therapy was specified to include a third- or fourth- generation cephalosporins, piperacillin/tazobactam, carbapenems, quinolones, alone or in combination with other antimicrobials. The site of infection, suspected causative agent and local resistance patterns were used to select from these antibiotic choices.

Empirical selective antimicrobials were given to some patients instead of broad spectrum antibiotics. This was because taking into account the site of infection, the suspected causative agent and local antibiotic resistance pattern, it was felt more selective antibiotics were in the patients' best interest.

- **Appropriate:** antimicrobial therapy based on bacterial or fungal culture results and susceptibility testing obtained within the first 4 study days).

Appropriate antimicrobial therapy required documentation of the infection microbiologically with the use of at least one antibiotic known to be active in vitro against the causative agent.² This was determined by the investigator on site. Such data was gathered on a daily basis throughout the study.

1. Guidelines for the management of severe sepsis and septic shock. The International Sepsis Forum. Intensive Care Med 2001;27 Suppl 1:S1-134.
2. Bochud PY, Glauser MP, Calandra T. Antibiotics in sepsis. Intensive Care Med 2001;27 Suppl 1:S33-48.

Volume study

Hemodynamic management:

Hemodynamic parameters were recorded at baseline and 1, 2, 4, 6, 8 and 12 h, and then 12 hourly until 96 h and then daily until the end of the treatment period.

In brief, during a period of 96 hours after randomisation, volume resuscitation was mandatory to achieve a central venous pressure (CVP) of 8 mmHg. If, within this time period, mean arterial blood pressure (MAP) was below 70 mmHg or central venous oxygen saturation (ScvO₂) was less than 70%, the treating physician decided on further measures (fluid repletion, vasopressors and/or inotropes) to raise MAP and ScvO₂ into prespecified ranges. According to protocol, HES was not to be used as a maintenance fluid. Decision on further fluid resuscitation for sepsis-related volume depletion after 96 hours was left to the discretion of the treating physician, however the study assignment had to be observed (in the HES group HES until a limit of 20 mL/kg/day, then preferentially Ringer's or other non-colloid fluids; in the RL group Ringer's lactate).

Use of non-study colloid fluids

18 of 275 patients (6.5%) in the RL group received HES at some time during the study period (median 750 mL over 21 days, [IQR 500;2000 ml]). 73 of 275 patients (26.6%) patients in the RL received “non-study colloids” which included albumin, dextran, gelatin and HES (median 900 mL over 21 days). 67 of 262 HES patients (25.6%) received “non-study colloids” (i.e. albumin, other HES solutions than the 10% HES 200/0.5, dextran and gelatin) (median dose 500 mL over 21 days). The full dose of non-study colloids did not differ significantly comparing study groups (P=0.38).

Study fluid composition:

Ringer’s Lactate (Sterofundin, B. Braun Melsungen, Germany). 1000 ml contain Na^+ 140.0 mmol, K^+ 4.0 mmol, Ca^{++} 2.5 mmol, Mg^{++} 1.0 mmol, Cl^- 106.0 mmol and lactate $^-$ 45.0 mmol.

10% hydroxyethyl starch (HES) with a substitution grade of 0.45-0.55 and a molecular weight of 200,000 Dalton (Hemohes 10%, B. Braun Melsungen AG, Melsungen, Germany. 1000 ml hydroxyethyl starch solution contain Na^+ 154 mmol and Cl^- 154 mmol.

Further details on statistical analyses:

The primary outcome analysis followed a method proposed by Kieser et al [Kieser M, Bauer P, Lehmacher W. Inference on multiple endpoints in clinical trials with adaptive interim analyses. *Biom J* 1999;41:261-77.], which combines multiple endpoint testing with a two-stage adaptive design, using the Bonferroni-Holm procedure to control the experimentwise error rate α . According to the two-by-two factorial design with two interventions and two (co-primary) endpoints, a total of four different null hypotheses had to be tested. For each intervention, null hypotheses were ordered on the basis of the resulting one-sided p-values and compared with critical boundaries α_0 and α_1 .

The null hypothesis was retained if $\alpha_0 \leq p_{\text{one-sided}} \leq 1-\alpha_0$ (futility threshold $\alpha_0=0.3$ for all four hypotheses) and was rejected if $p_{\text{one-sided}} \leq \alpha_1$ or $p_{\text{one-sided}} \geq 1-\alpha_1$ (early significance levels $\alpha_{1,A1}=0.00263$, $\alpha_{1,A2}=0.00582$, $\alpha_{1,B1}=0.00582$, $\alpha_{1,B2}=0.01308$, where A and B indicate the two interventions and 1 and 2 indicate the two endpoints). If the null hypothesis was neither rejected nor retained, the respective endpoint was planned to be continued in the second stage of the trial.

For secondary endpoints, the Chi-Square test, Fisher's exact test, Cochran-Armitage trend test, t-test, and Mann-Whitney U-test were applied to compare categorical and continuous variables where appropriate. The Kaplan-Meier method and log-rank test was used to analyze time to hemodynamic recovery and overall survival. Multiple logistic regression analysis was

used to identify risk factors for the need for renal replacement therapy, 28-day and 90-day mortality.

Acknowledgment

“Design of the Study: K.Reinhart, F. Brunkhorst, F. Bloos, A.Meier-Hellmann, M.Loeffler, C. Engel; Data Analysis: M. Loeffler, C. Engel, E. Kuhnt; Vouching for Data and Analysis: K.Reinhart, M.Loeffler; Writing Committee: K. Reinhart, C. Hartog, C. Natanson, F.M. Brunkhorst, C. Engel, M. Loeffler, E. Kuhnt; Decision to Publish: all authors listed under the title.

Following participants in the VISEP study gathered the data:

Department of Anesthesiology and Intensive Care Medicine, University Hospital Aachen, Rheinisch-Westfaelische

Technische Hochschule Aachen - D. Henzler, B. Werbelow, N. Zuremba, Department of Anesthesiology and

Critical Care Medicine, Klinikum Augsburg - I. Kreuzer, Department of Nephrology and Medical Intensive Care,

Charite, Campus Virchow-Klinikum, University Medical Center, Berlin - G. Weinberg, G. Kress, M. Vietzke, D.

Schrage, Department of Anesthesiology and Critical Care Medicine, Vivantes-Klinikum Neukoelln, Berlin - H.

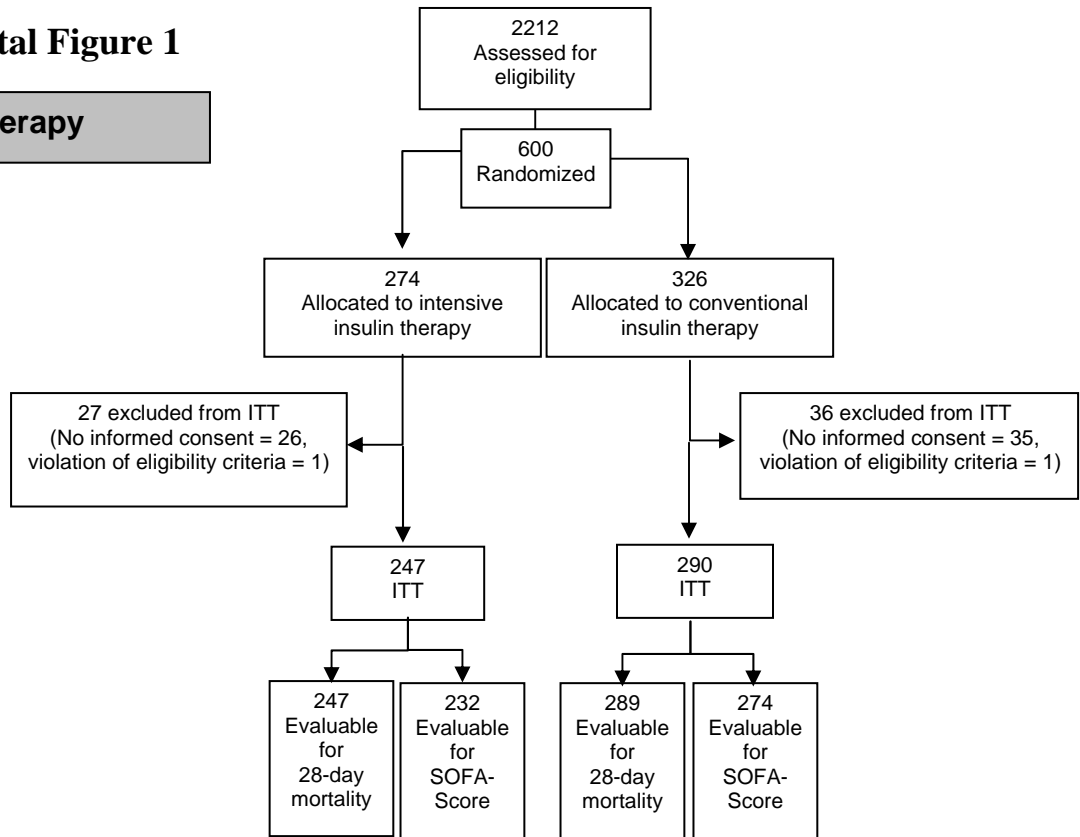
Gerlach, R. Maiazza, X. Bartenschlager, Department of Anesthesiology and Intensive Care Medicine, Staedtisches

Klinikum Brandenburg - M. Schaefer, S. Krueger, Department of Anesthesiology and Intensive Care Medicine,

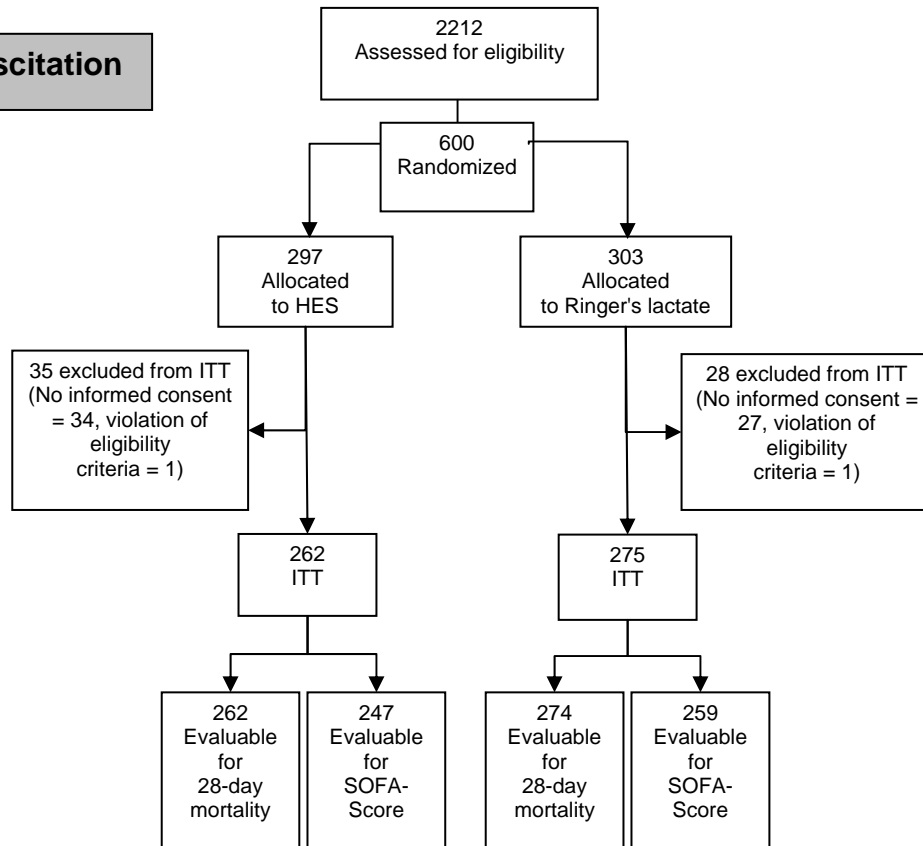
Rheinische Friedrich-Wilhelms-Universität Bonn - F. Stueber, M. Book, Department of Anesthesiology and Intensive Care Medicine, University Hospital of the Technical University of Dresden - K. Sengebusch, M. Albert, B. Gottschlich, Department of Anesthesiology and Intensive Care Medicine, HELIOS Klinikum, Erfurt - S. Hirn, Department of Nephrology and Hypertension, University of Erlangen-Nuremberg - K.-U. Eckardt, Ch. Forster, Department of Anesthesiology and Intensive Care Medicine, University of Goettingen - A. Kernchen, G. Ottersbach, J. Barwing, Department of Anesthesiology and Intensive Care Medicine, Ernst-Moritz-Arndt University, Greifswald - S.-O. Kuhn, L. Guderian, Department of Anesthesiology and Intensive Care Medicine, Martin-Luther-University, Halle-Wittenberg - A. Christl, H. Bromber, Department of Anesthesiology and Intensive Care Medicine, Friedrich-Schiller University of Jena - A. Braune, P. Bloos, U. Redlich, B. Korda, Department of Anesthesiology and Intensive Care Medicine, University Hospital Schleswig-Holstein, Campus Kiel, Kiel – J. Scholz, G. Schmitz, T. Meyer-Jark, D. Schädler, Department of Anesthesiology and Intensive Care Medicine, University Hospital Leipzig - T. Albert, Department of Pulmonary and Critical Care Medicine, University Otto-von-Guericke, Magdeburg - O. Burkhardt, Department of Anesthesiology and Intensive Care, University of Muenster - H.G. Bone, N. P. de Oliveira, A. David.

Supplemental Figure 1

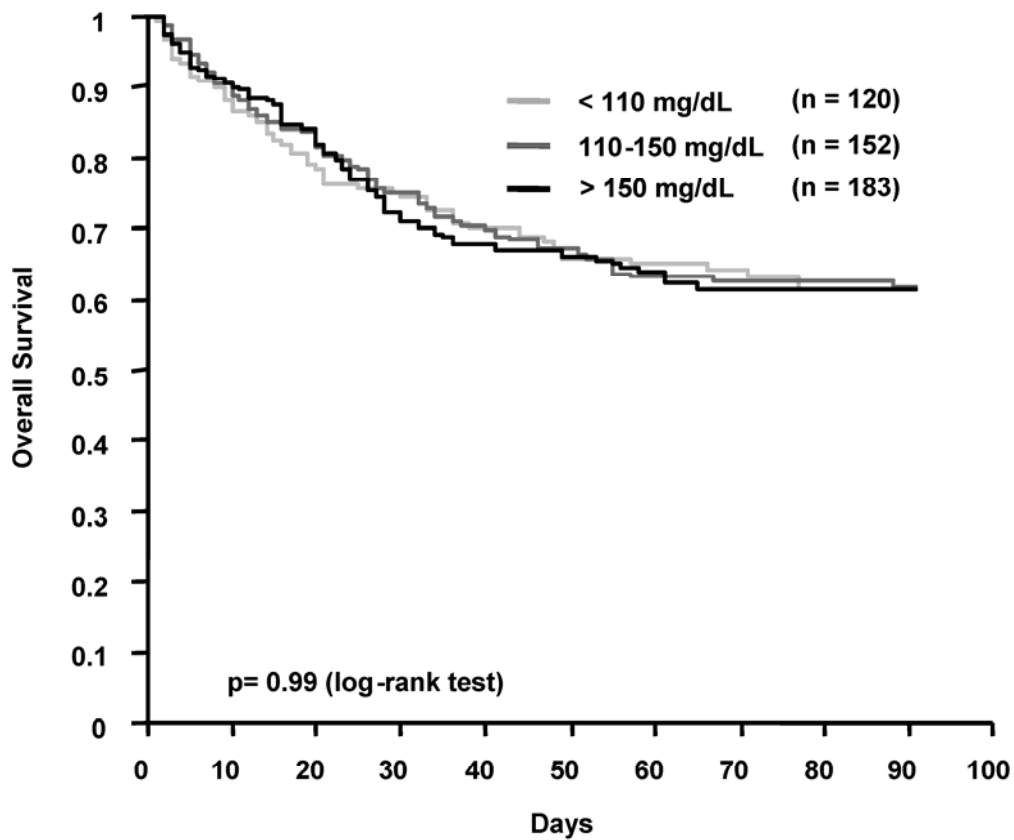
A: Insulin therapy



B: Volume resuscitation



Supplemental Figure 1: Patient flow in the two interventions

Supplemental Figure 2

Supplemental Figure 2: Kaplan-Meier survival curve in patients stratified by mean morning blood glucose levels (< 110 mg/dL, 110-150 mg/dL, >150 mg/dL)

Supplemental Table 1: Sources and causes of infection*

	All n = 537	Conventional insulin treatment n=290	Intensive insulin treatment n=247	p-value (conventional vs. intensive insulin)	Ringer's Lactate n=275	HES n=262	p-value (Ringer's Lactate vs. HES)
Source of infection				0.32			0.42
Community acquired	224 (41.7)	125 (43.1)	99 (40.1)		108 (39.3)	116 (44.3)	
Nosocomial; ICU acquired	122 (22.7)	69 (23.8)	53 (21.5)		64 (23.3)	58 (22.1)	
Nosocomial; hospital acquired	183 (34.1)	90 (31.0)	93 (37.7)		100 (36.3)	83 (31.7)	
missing	8 (1.5)	6 (2.1)	2 (0.8)		3 (1.1)	5 (1.9)	
Infection				0.19			0.10
microbiologically confirmed	344 (64.1)	193 (66.6)	151 (61.1)		167 (60.7)	177 (67.6)	
clinically proven or suspected	193 (35.9)	97 (33.4)	96 (38.9)		108 (39.3)	85 (32.4)	
Type of organism †							
Gram-positive	226 (42.1)	121 (41.7)	105 (42.5)	0.85	110 (40.0)	116 (44.3)	0.32
Staphylococcus aureus	60 (11.2)	29 (10.0)	31 (12.6)		31 (11.3)	29 (11.1)	
Other staphylococcus species	71 (13.2)	39 (13.5)	32 (13.0)		36 (13.1)	35 (13.4)	
Streptococcus pneumoniae	7 (1.3)	4 (1.4)	3 (1.2)		4 (1.5)	3 (1.2)	
Other streptococcus species	52 (9.7)	28 (9.7)	24 (9.7)		22 (8.0)	30 (11.5)	
Enterococcus species	87 (16.2)	50 (17.2)	37 (15.0)		39 (14.2)	48 (18.3)	
Other gram-positive	25 (4.7)	9 (3.1)	16 (6.5)		16 (5.8)	9 (3.4)	
Gram-negative	215 (40.0)	123 (42.4)	92 (37.3)	0.22	106 (38.6)	109 (41.6)	0.47
Escherichia coli	104 (19.4)	61 (21.0)	43 (17.4)		46 (16.7)	58 (22.1)	
Klebsiella species	49 (9.1)	28 (9.7)	21 (8.5)		31 (11.3)	18 (6.9)	
Pseudomonas species	37 (6.9)	20 (6.9)	17 (6.9)		19 (6.9)	18 (6.9)	
Enterobacter species	30 (5.6)	14 (4.8)	16 (6.5)		15 (5.5)	15 (5.7)	
Haemophilus influenzae	5 (0.9)	1 (0.3)	4 (1.6)		2 (0.7)	3 (1.2)	
Bacteroides species	24 (4.5)	13 (4.5)	11 (4.5)		12 (4.4)	12 (4.6)	

	All n = 537	Conventional insulin treatment n=290	Intensive insulin treatment n=247	p-value (conventional vs. intensive insulin)	Ringer's Lactate n=275	HES n=262	p-value (Ringer's Lactate vs. HES)
Other gram-negative	97 (18.1)	56 (19.3)	41 (16.6)		50 (18.2)	47 (17.9)	
Fungus	94 (17.5)	47 (16.2)	47 (19.0)	0.39	42 (15.3)	52 (19.9)	0.16
Candida albicans	66 (12.3)	33 (11.4)	33 (13.4)		31 (11.3)	35 (13.4)	
Other candida species	30 (5.6)	16 (5.5)	14 (5.7)		13 (4.7)	17 (6.5)	
Yeast	2 (0.4)	0	2 (0.8)		2 (0.7)	0	
Other fungus	9 (1.7)	6 (2.1)	3 (1.2)		2 (0.7)	7 (2.7)	
Other	3 (0.6)	1 (0.3)	2 (0.8)	0.60	1 (0.4)	2 (0.8)	0.62
Polymicrobial (based on patients with microbiologically confirmed infection)	103 / 344 (29.9)	56 / 193 (29.0)	47 / 151 (31.1)	0.67	52 / 167 (31.1)	51 / 177 (28.8)	0.64

* Data are presented as absolute frequencies and percentages in brackets.

† Microbial culture results from day 1-4; patients may have had more than one organism cultured.

Supplementary Table 2: Concomitant medication*

Variable	All n=537	Conventional insulin treatment n=290	Intensive insulin treatment n=247	P Value †	Ringer's lactate n=275	HES n=262	P Value †
Hydrocortisone							
No. (%) - patients treated	319 (59.4)	175 (60.3)	144 (58.3)	0.63	161 (58.6)	158 (60.3)	0.68
Total dose (mg) ‡	883 [500 – 1411]	826 [482 – 1306]	1040 [507 – 1601]	0.09	875 [500 – 1400]	891 [500 – 1476]	0.72
Mean daily dose (mg) ‡	148.5 [117.0 – 186.3]	148.5 [113.6 – 185.0]	150.0 [122.9 – 189.7]	0.31	150.0 [117.0 – 185.5]	147.9 [117.3 – 188.7]	0.81
Days on treatment ‡	6 [4 – 10]	6 [4 – 9]	6 [3 – 10]	0.30	5 [4 – 9]	6 [4 – 10]	0.41
High dose steroids §							
No. (%) - patients treated	17 (3.2)	10 (3.5)	7 (2.8)	0.69	7 (2.6)	10 (3.8)	0.40
Days on treatment ‡	2 [1 – 8]	2.5 [1 – 9]	2.0 [1 – 8]	0.58	2 [1 – 9]	2.5 [1 – 8]	0.88
Activated Protein C							
No. (%) - patients treated	32 (6.0)	14 (4.8)	18 (7.3)	0.23	16 (5.8)	16 (6.1)	0.89

Variable	All n=537	Conventional insulin treatment n=290	Intensive insulin treatment n=247	P Value †	Ringer's lactate n=275	HES n=262	P Value †
Antithrombin							
No. (%) - patients treated	64 (11.9)	38 (13.1)	26 (10.5)	0.36	24 (8.7)	40 (15.3)	0.02
Total dose (IU) ‡	2000 [1000 – 3500]	2000 [1500 – 4000]	2000 [1000 - 3000]	0.62	2000 [1250 – 3750]	2000 [1000 – 3500]	0.80
Mean daily dose (IU) ‡	1667 [1000 – 2000]	1667 [1000 – 2000]	1667 [1000 – 2400]	0.81	1667 [1000 – 2000]	1625 [1000 – 2000]	0.96
Immunoglobulins							
No. (%) - patients treated	3 (0.6)	3 (1.0)	0	0.25	2 (0.7)	1 (0.4)	1.0

* Data are presented as absolute frequencies and percentages in brackets, or median and IQR.

† P Values calculated by Chi-square test or Fisher's exact test, as appropriate, and Mann-Whitney-U-test.

‡ per patient when administered

§ > 5 mg prednisolone equivalent / day

Supplemental Table 3a: Insulin therapy**Mortality *and mean SOFA Score**

Variable	All n = 537	Conventional insulin treatment n=290	Intensive insulin treatment n=247	P Value
28-Day mortality – no. (%)	136 / 536 (25.4)	75 / 289 (26.0)	61 / 247 (24.7)	0.74
28-Day mortality according to APACHE II quartile – no. (%) of patients				
< 16	12 / 137 (8.8)	7 / 73 (9.6)	5 / 64 (7.8)	0.71
16 – 20	32 / 157 (20.4)	19 / 86 (22.1)	13 / 71 (18.3)	0.56
21 – 24	32 / 122 (26.2)	19 / 67 (28.4)	13 / 55 (23.6)	0.56
> 24	60 / 120 (50.0)	30 / 63 (47.6)	30 / 57 (52.6)	0.58
28-Day mortality according to diagnostic category – no. (%)				
Neurological	50 / 158 (31.7)	31 / 95 (32.6)	19 / 63 (30.2)	0.74
Respiratory	60 / 229 (26.2)	32 / 128 (25.0)	28 / 101 (27.7)	0.64
Cardiovascular	61 / 198 (30.0)	37 / 115 (32.2)	24 / 83 (28.9)	0.62
Renal	48 / 135 (35.6)	30 / 77 (39.0)	18 / 58 (31.0)	0.34
Hematological	17 / 50 (34.0)	7 / 24 (29.2)	10 / 26 (38.5)	0.49
Gastrointestinal	57 / 204 (27.9)	28 / 106 (26.4)	29 / 98 (29.6)	0.61
Metabolic	67 / 238 (28.2)	37 / 133 (27.8)	30 / 105 (28.6)	0.90
Others	34 / 133 (25.6)	19 / 69 (27.5)	15 / 64 (23.4)	0.59
28-Day mortality in patients with diabetes – no. (%)				
No history of diabetes	89 / 373 (23.9)	46 / 198 (23.2)	43 / 175 (24.6)	0.76
History of diabetes	47 / 163 (28.8)	29 / 91 (31.9)	18 / 72 (25.0)	0.34
NIDDM	22 / 90 (24.4)	15 / 50 (30.0)	7 / 40 (17.5)	0.17
IDDM	25 / 73 (34.3)	14 / 41 (34.2)	11 / 32 (34.4)	0.98

Variable	All n = 537	Conventional insulin treatment n=290	Intensive insulin treatment n=247	P Value
28-Day mortality according to length of ICU-stay – no. (%) of patients				
≥ 3 days	118 / 514 (23.0)	63 / 273 (23.1)	55 / 241 (22.8)	0.95
≥ 5 days	105 / 473 (22.2)	56 / 251 (22.3)	49 / 222 (22.1)	0.95
≥ 10 days	85 / 361 (23.6)	45 / 188 (23.9)	40 / 173 (23.1)	0.86
28-Day mortality according to antimicrobial therapy study day 1 – no. (%) of patients				
Empirical selective	28 / 121 (23.1)	16 / 62 (25.8)	12 / 59 (20.3)	0.48
Empirical broad spectrum	69 / 263 (26.2)	39 / 143 (27.3)	30 / 120 (25.0)	0.68
Appropriate	37 / 146 (25.3)	19 / 80 (23.8)	18 / 66 (27.3)	0.63
90-Day mortality – no. (%)	200 / 535 (37.4)	102 / 288 (35.4)	98 / 247 (39.7)	0.31
90-Day mortality according to APACHE II quartile – no. (%)				
< 16	27 / 137 (19.7)	13 / 73 (17.8)	14 / 64 (21.9)	0.55
16 – 20	54 / 157 (34.4)	28 / 86 (32.6)	26 / 71 (36.6)	0.59
21 – 24	50 / 122 (41.0)	28 / 67 (41.8)	22 / 55 (40.0)	0.84
> 24	69 / 119 (58.0)	33 / 62 (53.2)	36 / 57 (63.2)	0.27
90-Day mortality, according to diagnostic category – no. (%)				
Neurological	71 / 158 (44.9)	42 / 95 (44.2)	29 / 63 (46.0)	0.82
Respiratory	83 / 228 (36.4)	38 / 127 (29.9)	45 / 101 (44.6)	0.02
Cardiovascular	83 / 198 (41.9)	48 / 115 (41.7)	35 / 83 (42.2)	0.95
Renal	60 / 135 (44.4)	34 / 77 (44.2)	26 / 58 (44.8)	0.94
Hematological	24 / 50 (48.0)	9 / 24 (37.5)	15 / 26 (57.7)	0.15
Gastrointestinal	80 / 204 (39.2)	39 / 106 (36.8)	41 / 98 (41.8)	0.46
Metabolic	92 / 237 (38.8)	46 / 132 (34.9)	46 / 105 (43.8)	0.16
Others	50 / 132 (37.9)	27 / 68 (39.7)	23 / 64 (35.9)	0.66

Variable	All n = 537	Conventional insulin treatment n=290	Intensive insulin treatment n=247	P Value
90-Day mortality in patients with diabetes – no. (%)				
No history of diabetes	133 / 372 (35.8)	64 / 197 (32.5)	69 / 175 (39.4)	0.16
History of diabetes	67 / 163 (41.1)	38 / 91 (41.8)	29 / 72 (40.3)	0.85
NIDDM	32 / 90 (35.6)	19 / 50 (38.0)	13 / 40 (32.5)	0.59
IDDM	35 / 73 (48.0)	19 / 41 (46.3)	16 / 32 (50.0)	0.76
90-Day mortality according to length of ICU-stay – no. (%) of patients				
≥ 3 days	182 / 513 (35.5)	90 / 272 (33.1)	92 / 241 (38.2)	0.23
≥ 5 days	169 / 472 (35.8)	83 / 250 (33.2)	86 / 222 (38.7)	0.21
≥ 10 days	145 / 360 (40.3)	70 / 187 (37.4)	75 / 173 (43.4)	0.25
90-Day mortality according to antimicrobial therapy – no. (%) of patients				
Empirical selective	37 / 121 (30.6)	18 / 62 (29.0)	19 / 59 (32.2)	0.71
Empirical broad spectrum	102 / 263 (38.8)	54 / 143 (37.8)	48 / 120 (40.0)	0.71
Appropriate	59 / 146 (40.4)	29 / 80 (36.3)	30 / 66 (45.5)	0.26
Mean SOFA according to antimicrobial therapy – no, mean 95%CI				
Empirical selective	110 7.5 [6.7; 8.2]	57 7.6 [6.5;8.7]	53 7.4 [6.3;8.4]	0.75
Empirical broad spectrum	250 7.7 [7.2; 8.2]	1367.8 [7.1;8.4]	114 7.6 [6.9;8.4]	0.80
Appropriate	143 8.0 [7.4; 8.6]	78 7.7 [6.9;8.6]	65 8.4 [7.5;9.2]	0.29

* 1 patient for 28-day mortality, 2 patients for 90-day mortality and 1 patient for length of ICU-stay were not evaluable.

Supplemental Table 3b: Volume therapy**Mortality * and mean SOFA Score**

Variable	All n = 537	Ringer's lactate n=275	HES n=262	P value
28-Day mortality according to antimicrobial therapy – no. (%) of patients				
Empirical selective	28 / 121 (23.1)	17 / 63 (27.0)	11 / 58 (19.0)	0.30
Empirical broad spectrum	69 / 263 (26.2)	34 / 137 (24.8)	35 / 126 (27.8)	0.59
Appropriate	37 / 146 (25.3)	15 / 72 (20.8)	22 / 74 (29.7)	0.22
90-Day mortality according to antimicrobial therapy – no. (%) of patients				
Empirical selective	37 / 121 (30.6)	22 / 63 (34.9)	15 / 58 (25.9)	0.28
Empirical broad spectrum	102 / 263 (38.8)	48 / 137 (35.0)	54 / 126 (42.9)	0.19
Appropriate	59 / 146 (40.4)	23 / 72 (31.9)	36 / 74 (48.7)	0.04
Mean SOFA according to antimicrobial therapy – no, mean 95%CI				
Empirical selective	110 7.5 [6.7; 8.2]	56 7.5 [6.5;8.6]	54 7.4 [6.3;8.5]	0.88
Empirical broad spectrum	250 7.7 [7.2; 8.2]	132 7.6 [6.9;8.2]	118 7.9 [7.1;8.6]	0.54
Appropriate	143 8.0 [7.4; 8.6]	70 7.5 [6.6;8.3]	73 8.6 [7.7;9.5]	0.06

* 1 patient for 28-day mortality, 2 patients for 90-day mortality and 1 patient for length of ICU-stay were not evaluable.

Supplementary Table 4: Insulin Therapy**Nutritional intake, insulin dose and blood glucose control***

Variable	All n=537	Conventional insulin treatment n=290	Intensive insulin treatment n=247	P Value †
Nutrition ‡				
Mean daily caloric intake (kcal/day)	1236 ± 534	1253 ± 524	1217 ± 546	0.47
Glucose (g/day)	144 ± 92	144 ± 90	144 ± 94	1.0
Mean daily amount of nutritional protein (g/day)	51.9 ± 39.4	48.3 ± 31.8	56.4 ± 47.2	0.14
Insulin therapy				
Number of patients treated with insulin – no. (%)	458 (85.3)	215 (74.1)	243 (98.4)	< 0.001
Insulin dose – IU per ICU day	19 [3 – 38]	5 [0 - 22]	32 [20 - 50]	< 0.001
Insulin dose – IU per ICU day ‡	43 [23 – 64]	29 [15 - 51]	52 [32 - 73]	< 0.001
Blood glucose control §				
Mean morning blood glucose (mg/dL)	133 ± 34	151 ± 33	112 ± 18	< 0.001
Mean morning blood glucose (mg/dL) ¶	141 ± 38	173 ± 30	113 ± 18	< 0.001
Mean morning blood glucose (mg/dL) in patients with diabetes	145 ± 39	169 ± 35	115 ± 19	< 0.001
Hypoglycemia (≤ 40 mg/dL)				
Patients experiencing hypoglycemia – no. (%)	54 (10.1)	12 (4.1)	42 (17.0)	< 0.001
Patients experiencing two or more hypoglycemic events – no. (%)	19 (3.6)	2 (0.7)	17 (6.9)	< 0.001
Lowest levels of blood glucose during hypoglycemia (mg/dL) §	31 ± 9	28 ± 10	31 ± 9	0.30

* Data are presented as mean \pm SD, absolute frequencies and percentages in brackets, or median and IQR.

† P Values calculated by t-Test or Mann-Whitney-U-test and Chi-square test or Fisher's exact test, as appropriate.

‡ values per patient were calculated only for days on which nutrition or insulin, respectively, was given.

§ multiply by 0.0551 to convert glucose values to mmol/L

|| values were calculated for all patients and all ICU days

¶ values per patient were calculated only for days on which insulin was given

Supplemental Table 5: Volume resuscitation**Fluid loading during preceding 12 hours**

	All n = 537		Ringer's lactate n=275		HES n=262		P value*
	No. of patients	Value (Median [IQR])	No. of patients	Value (Median [IQR])	No. of patients	Value (Median [IQR])	
Crystalloids (ml)	446	2000 [1000 – 3500]	231	2000 [1000 - 3600]	215	2000 [1000 - 3500]	1.0
Colloids (ml)	315	850 [500 – 1000]	160	725 [500 - 1000]	155	979 [500 - 1000]	0.76

* P value for comparison of dose administered.

Supplemental Table 6: Volume resuscitation

Multivariate analysis						
Risk Factor / Covariate	Renal replacement therapy		28-Day mortality		90-Day mortality	
	Odds Ratio (95% CI) *	p-value	Odds Ratio (95% CI) *	p-value	Odds Ratio (95% CI) *	p-value
Constant		0.56		0.09		0.65
Total dose HES†	1.155 (1.093-1.221)	<.0001	0.998 (0.940-1.060)	0.95	1.116 (1.058-1.178) ‡	<.0001
Total dose RL†	1.013 (0.995-1.031)	0.17	1.000 (0.981-1.018)	0.97	1.022 (1.005-1.039) ‡	0.01
Intensive Insulin Therapy	1.295 (0.841-1.994)	0.24	0.894 (0.582-1.375)	0.61	1.121 (0.759-1.657)	0.57
APACHE II without MAP and Creatinine	1.033 (0.995-1.072)	0.09	1.116 (1.075-1.159)	<.0001	1.088 (1.051-1.127)	<.0001
Creatinine Clearance [ml/min]	0.982 (0.974-0.990)	<.0001	0.986 (0.979-0.993)	0.0001	0.986 (0.981-0.992)	<.0001
MAP [mmHg]	0.984 (0.971-0.998)	0.02	0.989 (0.976-1.002)	0.10	0.987 (0.975-0.999)	0.03
Dose of all Colloids [ml/kg] 12 hours before start of therapy	0.992 (0.963-1.021)	0.57	1.002 (0.974-1.031)	0.88	0.991 (0.965-1.017)	0.48

RL: Ringer's lactate, HES: Hydroxyethyl starch, MAP: Mean arterial pressure; CVP: central venous pressure

Multivariable logistic regression analysis was used to analyze disease and therapy related risk factors for need for renal replacement therapy, 28-day and 90-day mortality. In a pilot analysis, we found that low baseline CVP and the dose of saline given before randomization were predictive for HES high dosage during therapy (adjusted for other pre-randomization factors such as APACHE-II, creatinine clearance and HES dose). Since the final models shown in Table 3 included the HES dose as a therapy related factor, pre-randomization CVP and saline dose were not included to avoid colinearities.

* Odds ratio per unit increase

† calculated in steps of 20 ml/kg bodyweight

‡ Both the cumulative RL and HES dose are significantly associated with 90-day mortality, but the effect is significantly stronger for effect of HES than Ringer's lactate ($p = 0.002$)

Supplemental Table 7: Antimicrobial therapy on study day 1 and day 1-4

Antimicrobial	RL n = 275	HES n = 262	P-value	CIT n = 290	IIT n = 247	P-value
Day 1						
Appropriate	72 (26.2)	74 (28.2)	0.55	80 (27.6)	66 (26.7)	0.79
Empirical	201 (73.1)	184 (70.2)		206 (71.0)	179 (72.5)	
- broad spectrum *	138/201 (68.7)	126/184 (68.5)	0.97	144/206 (69.9)	120/179 (67.0)	0.55
- selective *	63/201 (31.3)	58/184 (31.5)		62/206 (30.1)	59/179 (33.0)	
Days 1-4						
Appropriate	140 (50.9)	139 (53.1)	0.55	160 (55.2)	119 (48.2)	0.11
Empirical	134 (48.7)	120 (45.8)		128 (44.1)	126 (51.0)	
- broad spectrum *	95/134 (70.9)	84/120 (70.0)	0.88	94/128 (73.4)	85/126 (67.5)	0.30
- selective *	39/134 (29.1)	36/120 (30.0)		34/128 (26.6)	41/126 (32.5)	

RL Ringer's lactate, HES hydroxyethylstarch, CIT conventional insulin therapy, IIT intensive insulin therapy

* based on all patients with empirical therapy