Endocrine Response after Trauma – Surgeon View

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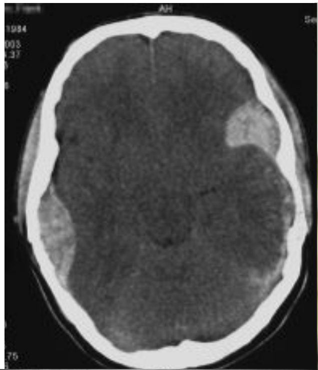
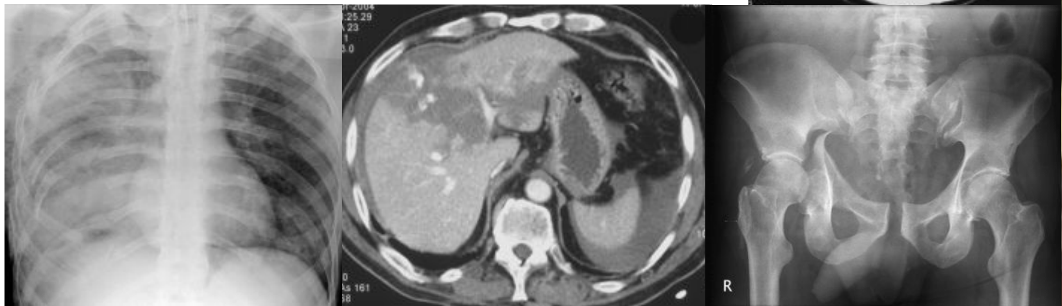
3rd swiss trauma & Resuscitation Day

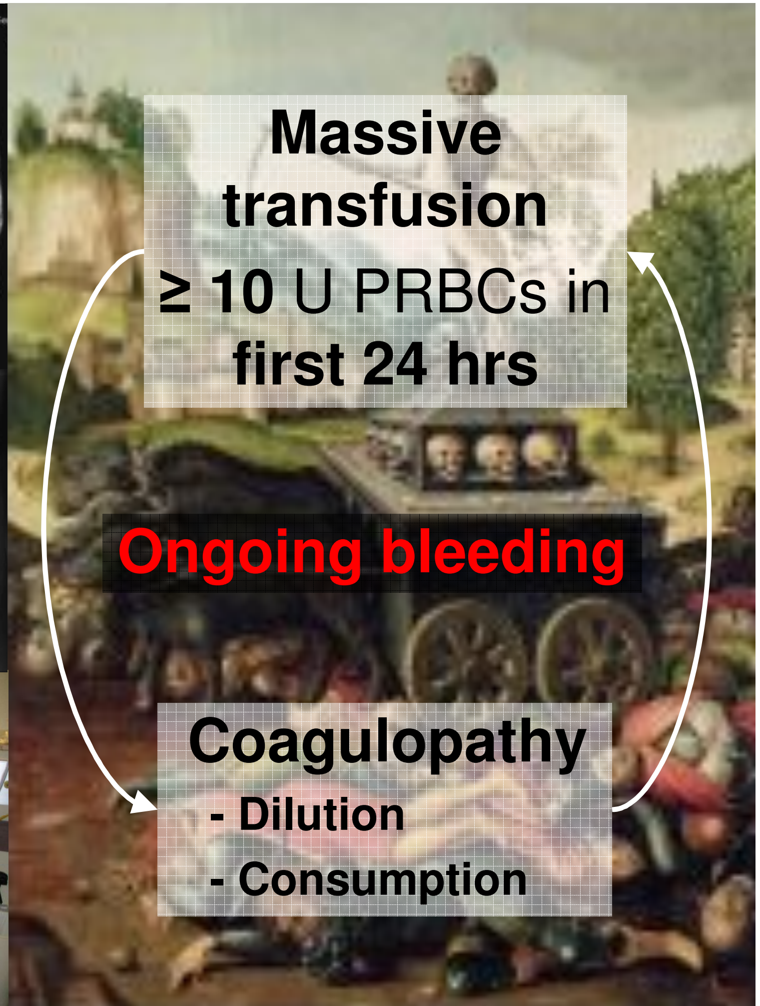
„Killers“ in Polytrauma

Keel et al. ***n=1191,*** *1.96-9.04;* ***ISS≥17pts.***

- Head injury (66%)
- Hemorrhagic shock (21%)

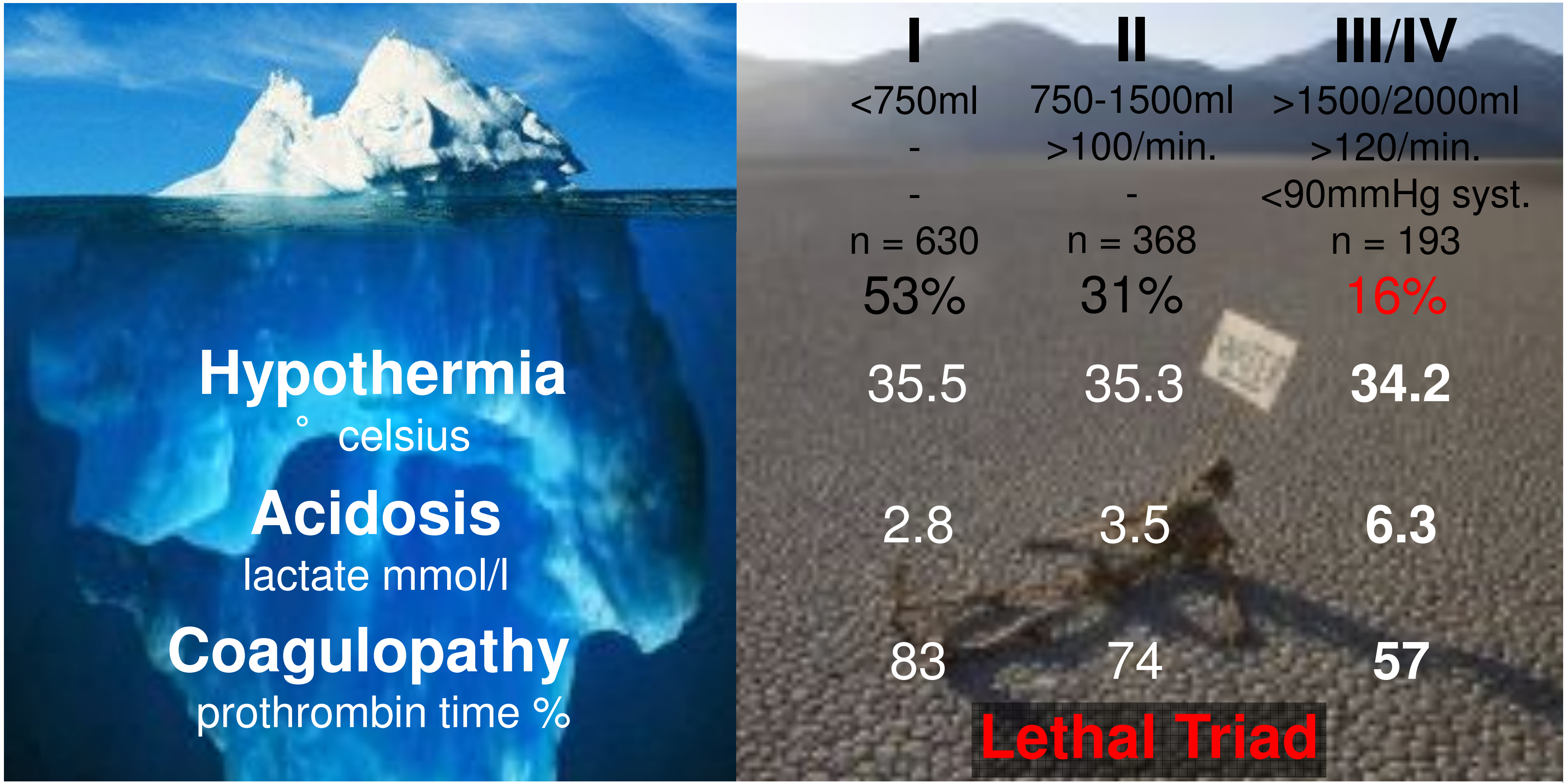






- Sepsis, MOF (13%)

Hemorrhagic Shock and Mortality

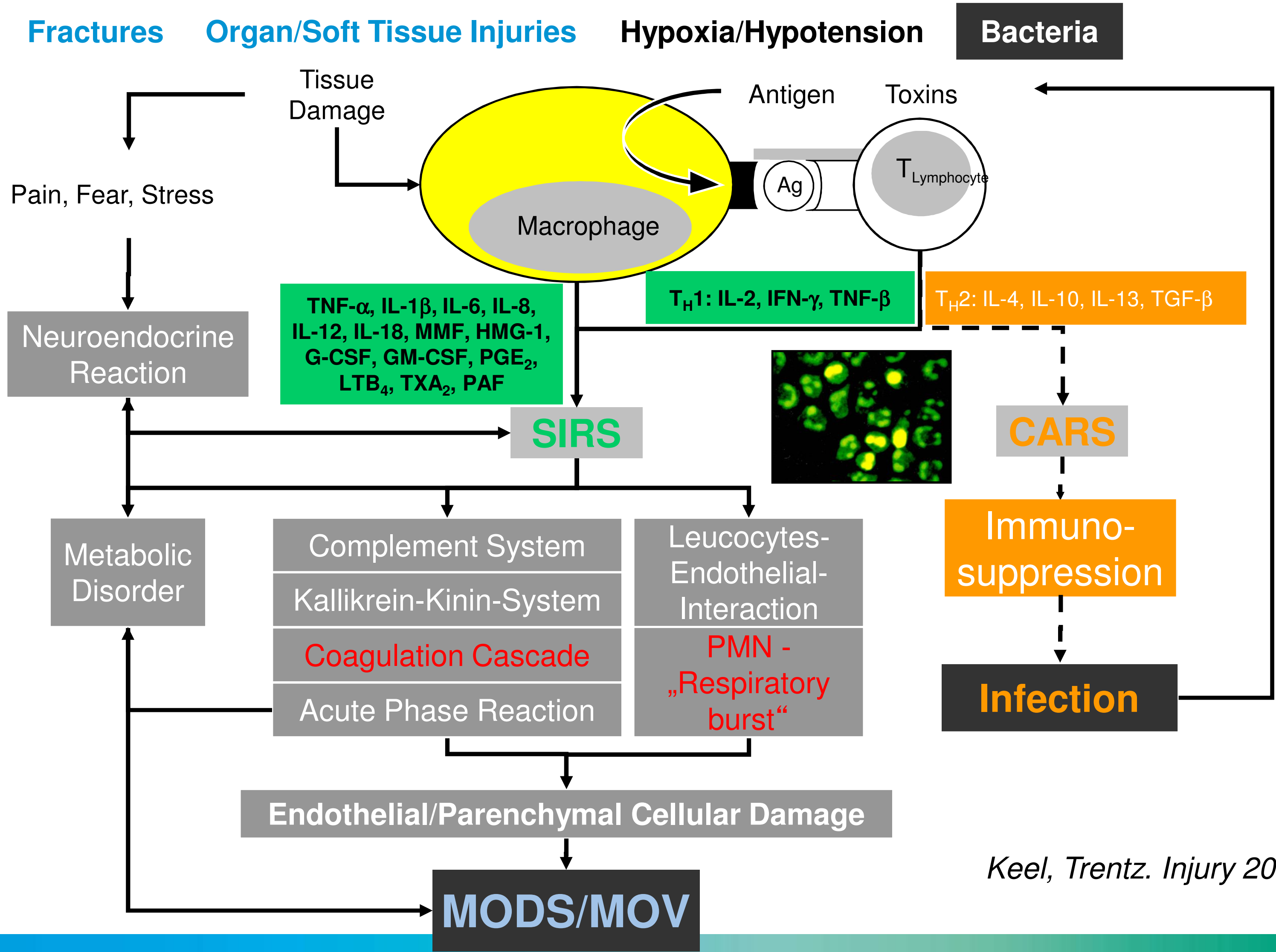


	I	II	III/IV
	<750ml	750-1500ml	>1500/2000ml
	-	>100/min.	>120/min.
	-	-	<90mmHg syst.
	n = 630	n = 368	n = 193
	53%	31%	16%
Hypothermia ° celsius	35.5	35.3	**34.2**
Acidosis lactate mmol/l	2.8	3.5	**6.3**
Coagulopathy prothrombin time %	83	74	**57**
Mortality (36%):	28%	33%	**67%**

Lethal Triad

Keel et al. ***n=1191,*** *1.96-9.04; ISS≥17pts.*

Pathophysiological Cascade



Keel, Trentz. Injury 2005; 36:691

„Two Hit“ – Model

Moore et al. J Trauma 1996;40:501

Keel, Trentz. Injury 2005;36:691

First Hits

- Hypoxia
- Hypotension
- **Organ injuries**
- **Soft tissue injuries**
- **Fractures**

Second Hits

Endogen (antigenic):
- **Hypoxia**
- **Hypotension**, **Acidosis**
- Ischemia/Reperfusion
- Cellular detritus
- Contamination/Infection

Exogen (interventional):
- **Surgery with blood loss, tissue damage, hypothermia**
- **Neglected/Missed injuries**
- **Prolonged diagnostic workup**
- **Massive transfusions**

Systemic Inflammatory Response Syndrome (SIRS)

- Temperature
- Pulse
- Breathing
- Leukocytes

Crit Care Med 1992;20:864

Host Defense Response
- reversible -

Multiple Organ Dysfunction Syndrome (MODS)

Sepsis

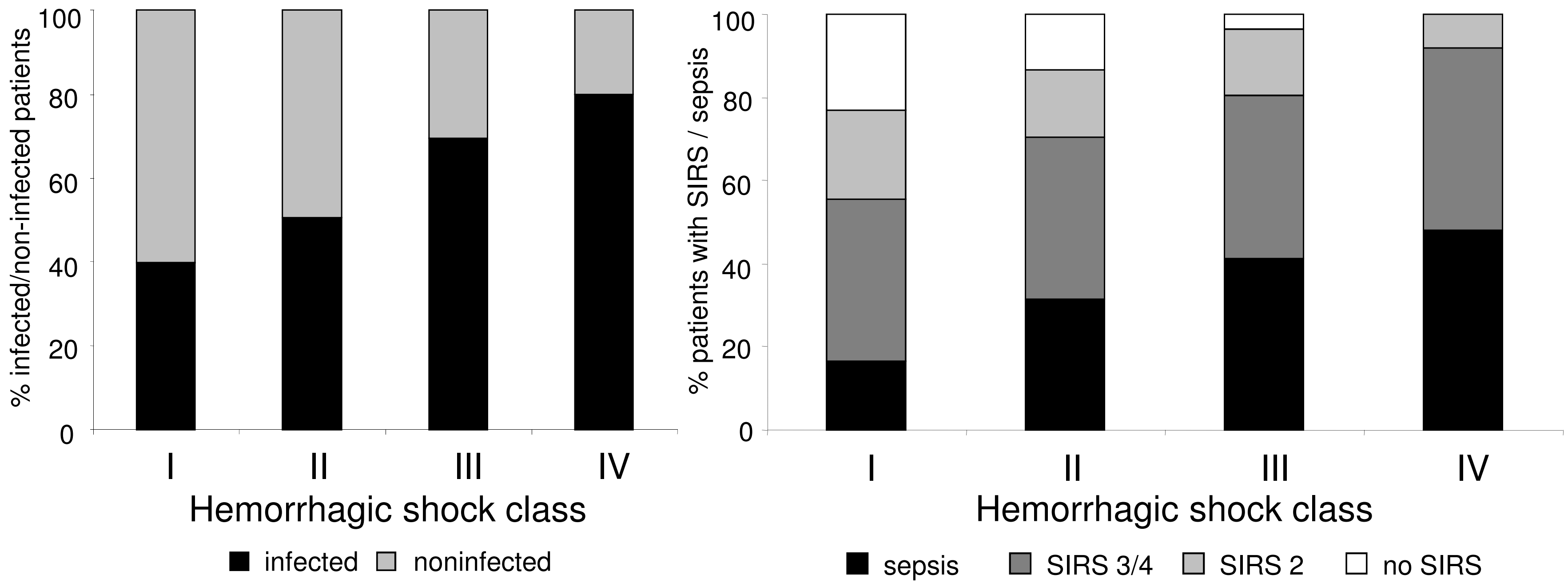
+Bacteria

Host Defense Failure Disease - irreversible -

Multiple Organ Failure (MOF)

Hemorrhagic Shock – Morbidity

- Inclusion: **ISS ≥17 pts.**, **survival >72 hrs**
- N=**972** (age: 40.2 y; ISS: 31.9 pts.; late mortality: 10.5%; blunt trauma: 91.4%)
- Hemorrhagic shock: I (n=582) – II (n=309) – III (n=56) – IV (n=25)



Lustenberger et al. Eur J Trauma Emerg Surg 2009

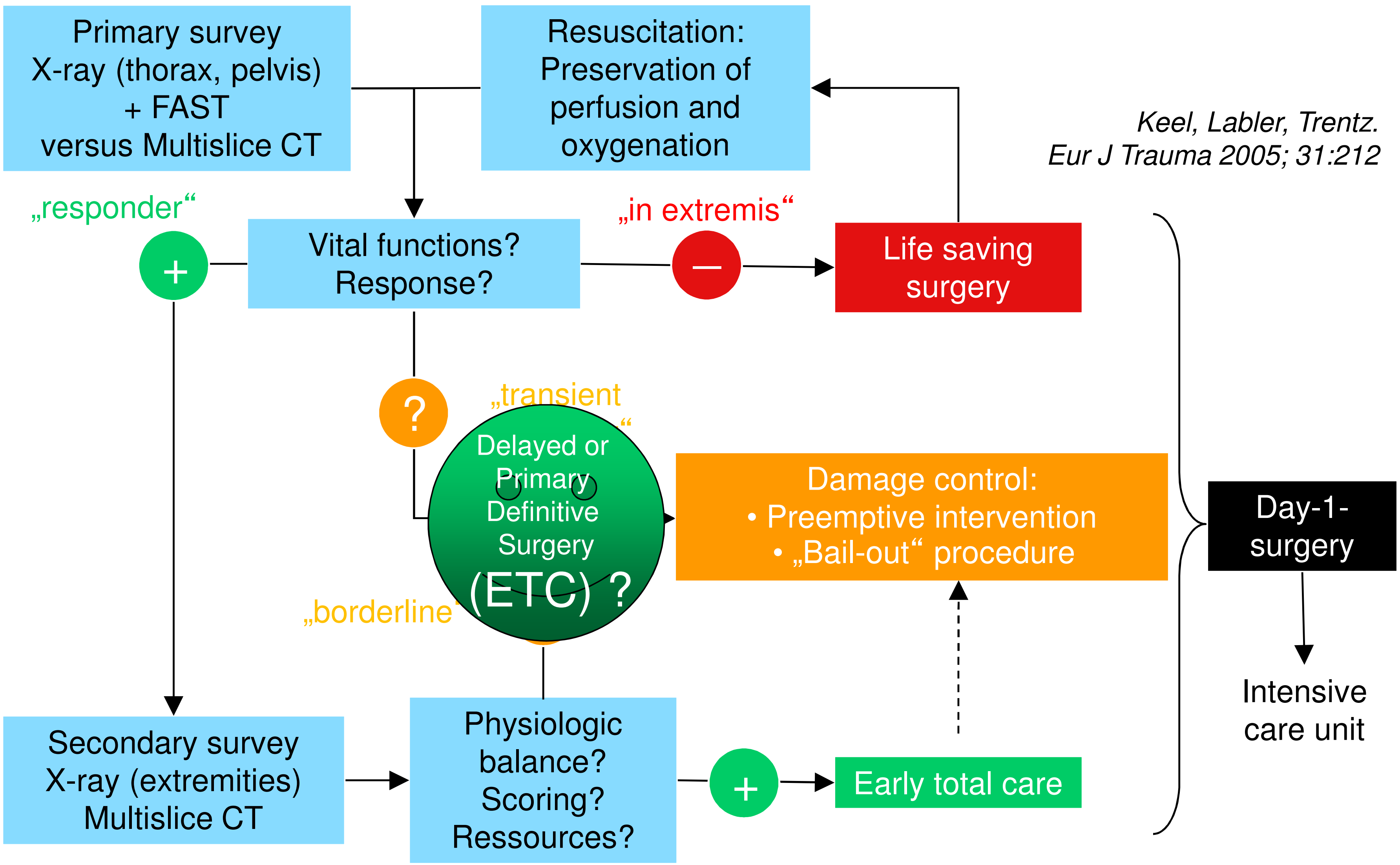
Damage Control – History – US Navy

- …keeping afloat a badly damaged ship by procedures to limit flooding, stabilize the vessel, isolate fires and explosions and avoid their spreading…

History: Damage Control Surgery

- Pringle-maneuver — *Pringle. Ann Surg. 1908; 48:541*
- Intra-abdominal packing — *Feliciano et al. J Trauma. 1981; 21:285*
- Damage Control as approach — *Rotondo et al. J Trauma. 1993; 35:375*
- Early packing – outcome — *Garrison et al. J Trauma. 1996; 40:923*
- **Timing of fracture treatment – DCO (Damage Control Orthopedic Surgery)** — *Pape et al. Am J Surg. 2002; 183:622*

Strategies of Trauma Care



Classification of Severely Injured Patients

	Stable	Borderline	Unstable	In Extremis
Shock:				
Blood pressure (mmHg)	>100	80-100	60-90	<50-60
Blood units	0-2	2-8	5-15	>15
Lactate	normal range	approx 2.5	>2.5	severe acidosis
Urine output (mL/h)	>150	50-150	<100	<50
Coagulation:				
Platelet (/mL)	>110,000	90,000-110,000	<70,000-90,000	<70,000
Fibrinogen (g/dL)	>1	approx. 1	<1	DIC
D-Dimer	normal range	abnormal	abnormal	DIC
Temperature:				
(° Celsius)	>34	33-35	30-32	<30
Injuries:				
Lung function (PaO2/FiO2)	>350	300	200-300	<200
Chest (AIS)	1 oder 2	2 oder >2	2 oder >2	3 oder >3
Abdominal (Moore)	<= II	<= III	III	IV
Pelvic trauma (AO)	A	B oder C	C	C
Extremities (AIS)	1 oder 2	2 oder 3	3 oder 4	Crush

Pape, Giannoudis, Krettek, Trentz. JOT 2005; 19:551

Damage control in severely injured trauma patients – A ten-year experience

Andreas Frischknecht, Thomas Lustenberger[1], Marko Bukur[1], Matthias Turina, Adrian Billeter, Ladislav Mica, Marius Keel[2]

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Table 1: Comparison of clinical and demographic characteristics of early survivors and early deaths

Clinical/ demographic characteristic	All patients (n=319)	Early survivors (n=267)	Early deaths (n=52)	P value
Age (years), mean±SEM	39.3±1.0	38.5±1.0	43.2±2.9	0.076
Age ≥55 years	19.4% (62/319)	17.2% (46/267)	30.8% (16/52)	0.024
Male	71.8% (229/319)	71.9% (192/267)	71.2% (37/52)	0.912
Penetrating MOI	8.8% (28/319)	9.0% (24/267)	7.7% (4/52)	1.000
GCS ≤ 8	55.7% (176/316)	50.0% (133/266)	86.0% (43/50)	<0.001
SBP < 90 mmHg	8.7% (26/299)	7.1% (18/253)	17.4% (8/46)	0.041
ISS, mean±SEM	36.6±0.7	35.3±0.7	43.4±2.1	<0.001
ISS ≥ 25	85.6% (273/319)	84.3% (225/267)	92.3% (48/52)	0.131
Head AIS ≥ 3	47.6% (152/319)	43.1% (115/267)	71.2% (37/52)	<0.001
Chest AIS ≥ 3	58.9% (188/319)	57.3% (153/267)	67.3% (35/52)	0.180
Abdomen AIS ≥ 3	65.8% (210/319)	65.9% (176/267)	65.4% (34/52)	0.941
Extremity AIS ≥ 3	67.1% (214/319)	68.9% (184/267)	57.7% (30/52)	0.115

MOI: Mechanism of Injury; GCS: Glasgow Coma Scale; SBP: Systolic Blood Pressure; ISS: Injury Severity Score; AIS: Abbreviated injury scale; SEM: Standard Error of the Mean

Table 2: Damage control procedures performed in 319 patients

Damage control procedure	All patients (*n*=319)	Early survivors (*n*=267)	Early deaths (*n*=52)	*P* value
Chest				
Intrathoracic packing	4.7% (15/319)	4.1% (11/267)	7.7% (4/52)	0.280
Abdomen				
Intra-abdominal packing	25.7% (82/319)	22.5% (60/267)	42.3% (22/52)	0.003
Retroperitoneal packing	6.9% (22/319)	4.9% (13/267)	17.3% (9/52)	0.004
Pelvis				
C-Clamp	10.3% (33/319)	9.7% (26/267)	13.5% (7/52)	0.420
External fixation	2.5% (8/319)	2.6% (7/267)	1.9% (1/52)	1.000
Extremities				
External fixation	60.5% (193/319)	64.4% (172/267)	40.4% (21/52)	0.001
External fixation upper extremity	13.5% (43/319)	14.2% (38/267)	9.6% (5/52)	0.372
External fixation lower extremity	53.6% (171/319)	57.7% (154/267)	32.7% (17/52)	0.001

Table 4: Independent risk factors at hospital admission for early mortality in patients undergoing damage control management

Variable	Odds ratio (95% CI)	*P* value	R^2
INR >1.2	10.64 (1.32-83.33)	0.026	0.184
Base deficit >3 mmol/L	4.85 (1.10-23.81)	0.040	0.111
AIS head ≥3	4.27 (1.55-11.76)	0.005	0.051
Body temperature <35°C	3.68 (1.15-11.76)	0.029	0.044
Lactate >6 mmol/L	2.96 (1.00-9.09)	0.050	0.032
Hemoglobin <7 g/dL	2.76 (1.02-7.46)	0.045	0.031

Variables in the equation: Hemoglobin <7 g/dL, Hematocrit < 20%, pH <7.3, AIS Head/Chest/Extremity ≥3, ISS ≥ 25, Age ≥55 Years, Systolic blood pressure <90 mmHg, INR >1.2, Base Deficit >3 mmol/L, Body temperature <35°C, Lactate >6 mmol/L. INR: International Normalized Ratio; AIS: Abbreviated Injury Scale; CI: Confidence Interval; C: Celsius; ISS: Injury Severity Score

Table 5: Independent risk factors at ICU admission for early mortality in patients undergoing damage control management

Variable	Odds ratio (95% CI)	*P* value	R^2
Lactate > 4 mmol/L	8.70 (1.81-41.67)	0.007	0.260
PRBC transfusion > 10 Units	7.14 (1.29-40.00)	0.025	0.113

Variables in the equation: Base deficit >6 mmol/L, INR >1.2, Platelet count <75, pH<7.3, Lactate >4 mmol/L, PRBC transfusion >10 Units, Operation time >120 minutes. ICU: Intensive Care Unit; PRBC: Packed Red Blood Cells; CI: Confidence Interval

Damage Control Concept – Limitations of Second Hits

Stop the bleeding –
Life **S**aving **S**urgery
Damage **C**ontrol **S**urgery (**DCO**)

- Surgical control of hemorrhage
- Angiographic control of hemorrhage
  (Transcatheter arterial embolisation (TAE))

Mitigate the lethal triad –
Damage **C**ontrol **R**esuscitation

- **Massive transfusion protocols** (MTPs)
- Correction of **coagulopathy**
- Correction of hypothermia

Definitive Treatment of Trauma

Immune response -
Window of opportunity

Trauma =  *Disease*

Multidisciplinary approach

Influence of Age on Damage Control Surgery ?

Impact of Advanced Age on Outcomes Following Damage Control Interventions for Trauma *World J Surg 2011*

Thomas Lustenberger · Peep Talving · Beat Schnüriger · Barbara M. Eberle · Marius J. B. Keel

Increased mortality !

Table 5 Overall mortality and mortality in DC subgroups

Groups	Total	≥55 years	<55 years	*P*	OR (95% CI)	Adj. *P*	Adj. OR (95% CI)
Overall	10.1% (16/158)	29.4% (10/34)	4.8% (6/124)	< 0.001	8.19 (2.72 – 24.70)	0.001[a]	7.09 (2.30–21.74)[a]
Damage control							
Extremity	6.7% (8/119)	19.2% (5/26)	3.2% (3/93)	0.012	7.14 (1.58–32.27)	0.032[b]	5.95 (1.16–30.30)[b]
Pelvis	18.5% (5/27)	25.0% (2/8)	15.8% (3/19)	0.616	1.78 (0.24–13.41)	–[c]	–[c]
Laparotomy	18.9% (7/37)	55.6% (5/9)	7.1% (2/28)	0.005	16.25 (2.32–114.06)	–[c]	–[c]

OR odds ratio; *CI* confidence interval; *Adj.* adjusted

[a] Adjusted for external fixator lower extremity, fibrinogen 24 h

[b] Adjusted for external fixator lower extremity, systolic blood pressure <90 mmHg

[c] No statistically significant confounders between the compared groups

Impact of Advanced Age on Outcomes Following Damage Control Interventions for Trauma

World J Surg 2011

Thomas Lustenberger · Peep Talving · Beat Schnüriger · Barbara M. Eberle · Marius J. B. Keel

Identical morbidity if surviving the early course !

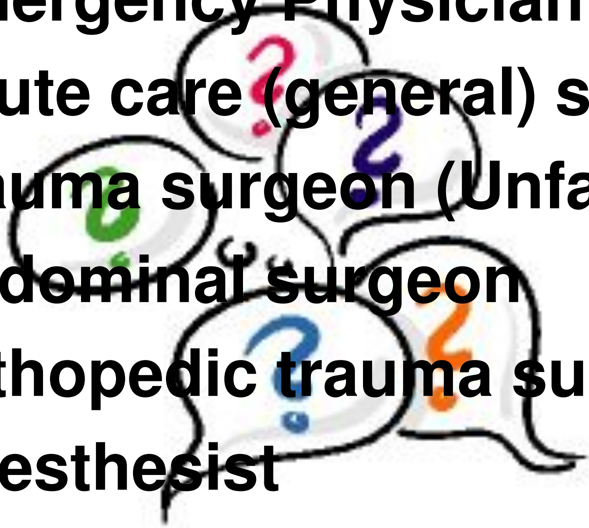
Table 4 Clinical outcomes for elderly and young trauma patients undergoing DC procedures

Clinical outcome	Total ($n = 158$)	≥55 years ($n = 34$)	<55 years ($n = 124$)	P
Ventilator days (survivors), mean ± SEM	7.0 ± 0.6	7.3 ± 1.7	6.9 ± 0.7	0.735
SICU LOS (survivors) (days), mean ± SEM	12.9 ± 1.0	14.7 ± 2.9	12.6 ± 1.0	0.402
Hospital LOS (days), mean ± SEM				
Survivors	40.6 ± 2.2	41.2 ± 4.5	40.4 ± 2.5	0.409
Nonsurvivors	9.1 ± 3.0	11.6 ± 4.3	5.0 ± 3.6	0.147
SIRS				
0	13.9% (22)	11.8% (4)	14.5% (18)	0.787
2	27.2% (43)	26.5% (9)	27.4% (34)	0.912
3/4	32.9% (52)	38.2% (13)	31.5% (39)	0.456
Sepsis	25.9% (41)	23.5% (8)	26.6% (33)	0.716
Overall infection	47.5% (75)	52.9% (18)	46.0% (57)	0.471
Pneumonia	23.4% (37)	26.5% (9)	22.6% (28)	0.635
Wound infection	25.9% (41)	20.6% (7)	27.4% (34)	0.421
Intraabdominal abscess	7.0% (11)	5.9% (2)	7.3% (9)	1.000
Acute renal failure	3.2% (5)	5.9% (2)	2.4% (3)	0.293
Deep venous thrombosis	5.1% (8)	5.9% (2)	4.8% (6)	0.682
ARDS	1.9% (3)	0% (0)	2.4% (3)	1.000
MOF (Goris ≥6)	37.3% (59)	47.1% (16)	34.7% (43)	0.186

SICU surgical intensive care unit; *LOS* length of stay; *SIRS* systemic inflammatory response syndrome; *ARDS* acute respiratory distress syndrome; *MOF* multiple organ failure

Trauma Leader in
- Acute Care
- Definitive Care

- Emergency Physician
- Acute care (general) surgeon
- Trauma surgeon (Unfallchirurg)
- Abdominal surgeon
- Orthopedic trauma surgeon
- Anesthesist
- ICU



Glycemic Control in the trauma patient

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The New England Journal of Medicine

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VOLUME 345 November 8, 2001 NUMBER 19

INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

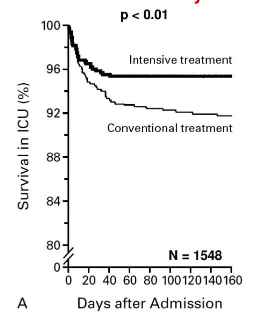
Greet Van den Berghe, M.D., Ph.D., Pieter Wouters, M.Sc., Frank Weekers, M.D., Charles Verwaest, M.D., Frans Bruyninckx, M.D., Miet Schetz, M.D., Ph.D., Dirk Vlasselaers, M.D., Patrick Ferdinande, M.D., Ph.D., Pieter Lauwers, M.D., and Roger Bouillon, M.D., Ph.D.

Background Hyperglycemia and insulin resistance are common in critically ill patients, even if they have not previously had diabetes. Whether the normalization of blood glucose levels with insulin therapy improves the prognosis for such patients is not known.

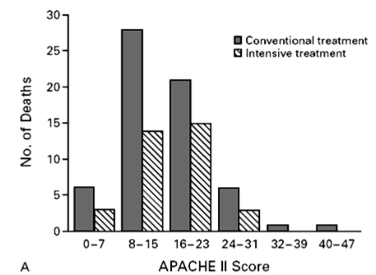
RCT in Surgical patients
BG 80 - 110 mg/dl
vs.
BG 180 . 200 mg/dl

Glycemic control (< 110 mg/dl) in post cardiac surgery ICU patients

ICU mortality



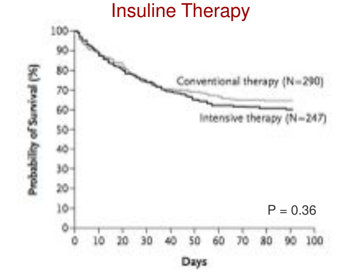
ICU death according to disease severity

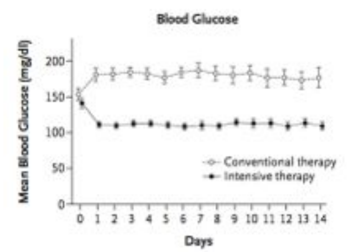


Van de Berghe G NEJM 2001, 345:1359

Insuline Therapy in Severe Sepsis
Brunkhorst et al NEJM 2008, 358:125

Insuline Therapy





Brunkhorst et al NEJM 2008, 358:125

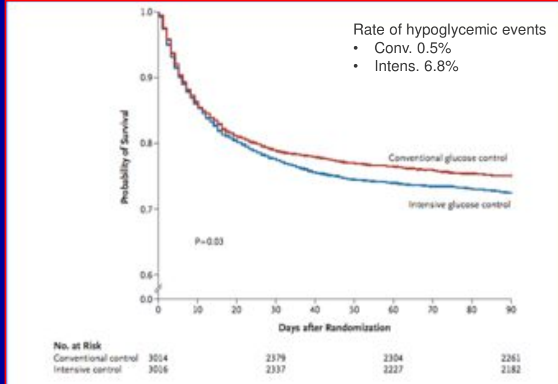
VISEP Adverse & Serious Adverse Events

Variable	Insulin Therapy All Patients (N=537)	Conventional (N=290)	Intensive (N=247)	P Value†
Adverse event				
Patients with at least one adverse event				<0.001
No. of patients	80	25	55	
Percent (95% CI)	14.9 (11.9–17.9)	8.6 (5.4–11.9)	22.3 (17.1–27.5)	
Hypoglycemia (≤40 mg/dl)				<0.001
No. of patients	54	12	42	
Percent (95% CI)	10.1 (7.5–12.6)	4.1 (1.9–6.4)	17.0 (12.3–21.7)	
Serious adverse event				
Patients with at least one serious adverse event				0.01
No. of patients	42	15	27	
Percent (95% CI)	7.8 (5.6–10.1)	5.2 (2.6–7.7)	10.9 (7.0–14.8)	
Hypoglycemia (≤40 mg/dl)¶				
Any				0.005
No. of patients	26	7	19	
Percent (95% CI)	4.8 (3.0–6.7)	2.4 (0.7–4.2)	7.7 (4.4–11.0)	
Life-threatening				0.05
No. of patients	19	6	13	
Percent (95% CI)	3.5 (2.0–5.1)	2.1 (0.4–3.7)	5.3 (2.5–8.1)	
Resulting in prolonged hospitalization				0.05
No. of patients	7	1	6	
Percent (95% CI)	1.3 (0.3–2.3)	0.3 (0–1.0)	2.4 (0.5–4.4)	

Brunkhorst et al NEJM 2008, 358:125

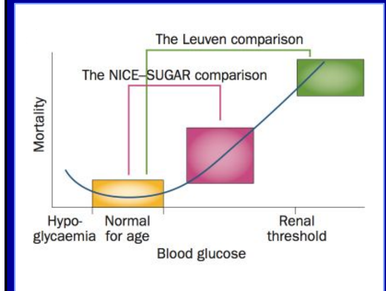
NICE-SUGAR Trial

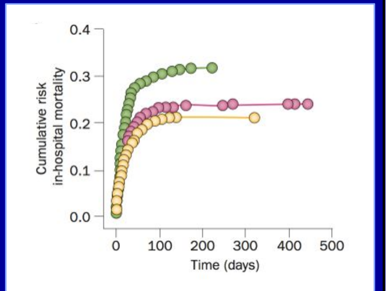
N Engl J Med 2009 360:1263



Relationship between blood glucose and mortality Leuven vs NICE-SUGAR studies

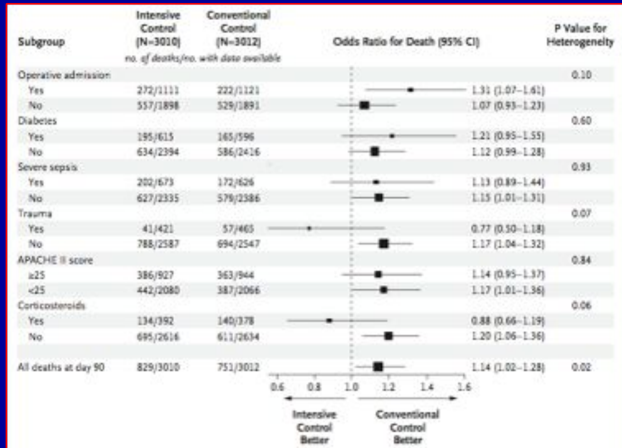
Wasen't the NICE-SUGAR study underpowered to conclude on mortality?





Van der Berghe G et. al. Nat Rev Endoc 2012 EPub

NICE-SUGAR Trial



Subgroup	Intensive Control (N=3010)	Conventional Control (N=3012)	Odds Ratio for Death (95% CI)	P Value for Heterogeneity
	no. of deaths/no. with data available			
Operative admission				0.10
Yes	272/1111	222/1121	1.31 (1.07–1.61)	
No	557/1898	529/1891	1.07 (0.93–1.23)	
Diabetes				0.60
Yes	195/615	165/596	1.21 (0.95–1.55)	
No	634/2394	586/2416	1.12 (0.99–1.28)	
Severe sepsis				0.93
Yes	202/673	172/626	1.13 (0.89–1.44)	
No	627/2335	579/2386	1.15 (1.01–1.31)	
Trauma				0.07
Yes	41/421	57/465	0.77 (0.50–1.18)	
No	788/2587	694/2547	1.17 (1.04–1.32)	
APACHE II score				0.84
≥25	386/927	363/944	1.14 (0.95–1.37)	
<25	442/2080	387/2066	1.17 (1.01–1.36)	
Corticosteroids				0.06
Yes	134/392	140/378	0.88 (0.66–1.19)	
No	695/2616	611/2634	1.20 (1.06–1.36)	
All deaths at day 90	829/3010	751/3012	1.14 (1.02–1.28)	0.02

N Engl J Med 2009 360:1263

Blood Glucose Levels in Trauma Patients on Admission

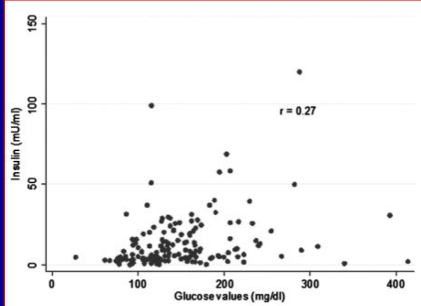


Figure 1. Scatter plot and Pearson's correlation coefficient for values of insulin and glucose at admission to ICU.

De La Rosa G. et al. J Trauma 2013 74:270

Blood Glucose Levels in Trauma Patients on Admission

TABLE 2. Logistic Regression Analysis for In-Hospital Mortality

Variable	Simple Logistic Regression OR (95% CI)	Multiple Logistic Regression OR (95% CI)	*p* (Wald test)
Insulin level, μU/mL			
5–15	1 (Reference)		
<5	2.14 (0.93–4.95)	1.68 (0.62–4.54)	0.233
>15	3.89 (1.60–9.44)	3.58 (1.18–10.84)	0.016
Intensive therapy with insulin	0.82 (0.43–1.56)	0.80 (0.36–1.77)	0.448
Age (each year)	1.01 (1.00–1.03)	1.00 (0.99–1.02)	0.492
Sex, male	0.43 (0.22–0.85)	0.58 (0.26–1.29)	0.257
History of diabetes	0.76 (0.19–3.07)	0.23 (0.04–1.28)	0.317
APACHE II (each point)	1.07 (1.02–1.13)	1.05 (0.99–1.11)	0.651
SOFA score (each point)	1.01 (0.99–1.02)	1.01 (0.98–1.02)	0.773
Blood glucose at admission, mg/dL	1.00 (1.00–1.01)	1.00 (1.00–1.01)	0.052
Creatinine at admission, mg/dL	0.96 (0.79–1.16)	0.78 (0.56–1.08)	0.176
Diagnosis of sepsis	2.61 (1.26–5.37)	2.42 (1.03–5.65)	0.020
ICU admission (each hour)	1.12 (0.99–1.27)	1.08 (0.94–1.23)	0.435
Hypoglycemia (≤40 mg/dL)	1.85 (0.36–9.49)	1.80 (0.27–11.6)	0.585
Variability of blood glucose (each unit)*	1.04 (1.01–1.06)	1.04 (1.01–1.07)	0.010
HOMA (each unit)†	1.03 (0.99–1.07)	0.99 (0.94–1.04)	0.495

*Variability = SD of the blood glucose values at 6:00 AM for each patient within their ICU stay.
†HOMA = FI × FG / 22.5. FI is measured in microunits per milliliter and FG is measured in millimoles per liter.

De La Rosa G. et al. J Trauma 2013 74:270

Systemic glucose levels in traumatic brain injury

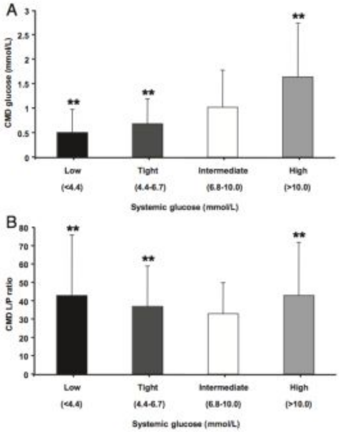
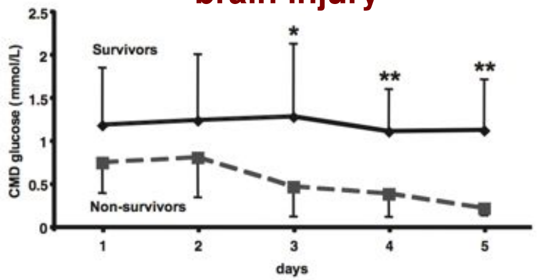


Table 6. Predictors of mortality

Variable	Adjusted odds ratio (95% confidence interval)	*p*
Brain energy crisis	7.36 (1.37–39.51)	0.02
Glasgow Coma Scale	1.12 (0.96–1.30)	0.15
Cerebral perfusion pressure	1.01 (0.97–1.04)	0.66
Intracranial pressure	1.00 (0.99–1.01)	0.91

Oddo M. et al CCM 2008 36:3222

Systemic glucose levels in traumatic brain injury



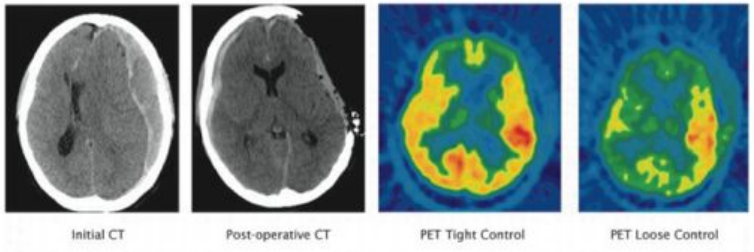
Variable	Survivors (n = 14)	Nonsurvivors (n = 6)	*p*
CMD glucose (mmol/L)	1.04 ± 0.56	0.46 ± 0.23	0.03
Systemic glucose (mmol/L)	7.3 ± 0.8	7.6 ± 0.4	0.40
Insulin dose (U/h)	1.3 ± 0.6	1.8 ± 0.6	0.10

Data are expressed as means ± SD.

Oddo M. et al CCM 2008 36:3222

Tight glycemic control increases metabolic distress in traumatic brain injury: A randomized controlled within-subjects trial*

Paul Vespa, MD; David L. McArthur, PhD, MPH; Nathan Stein, BS; Sung-Cheng Huang, PhD; Weber Shao, BA; Maria Filippou, MD; Maria Etchepare, BS; Thomas Glenn, PhD; David A. Hovda, PhD

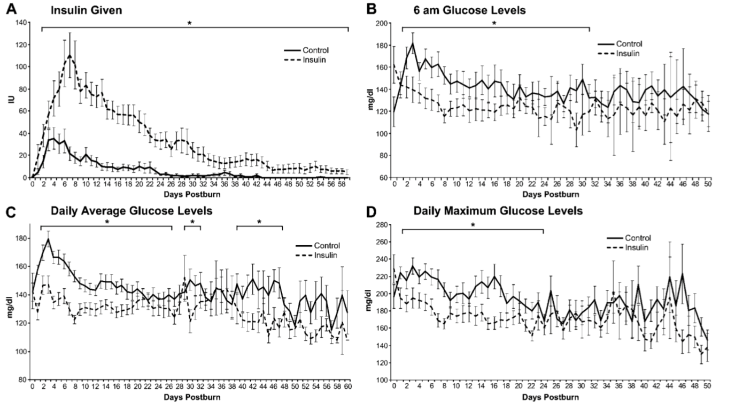


Crit Care Med 2012; 40: 1923–1929

Intensive Insulin Therapy in Severely Burned Pediatric Patients

A Prospective Randomized Trial

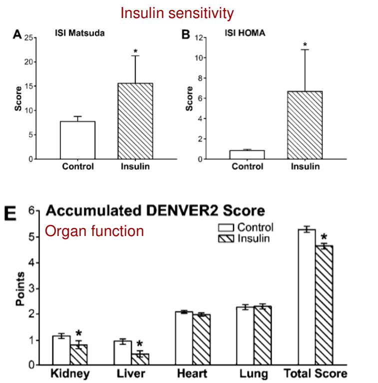
Jeschke MG AJRCCM 2010 182:351

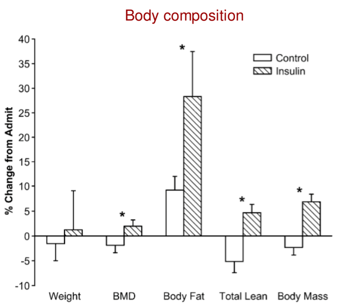


Intensive Insulin Therapy in Severely Burned Pediatric Patients

A Prospective Randomized Trial

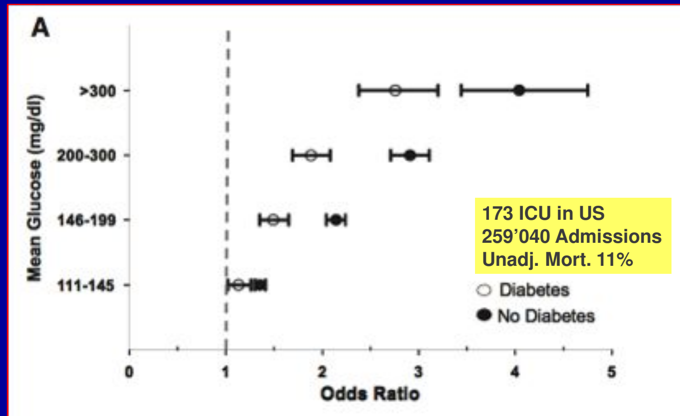
Jeschke MG AJRCCM 2010 182:351





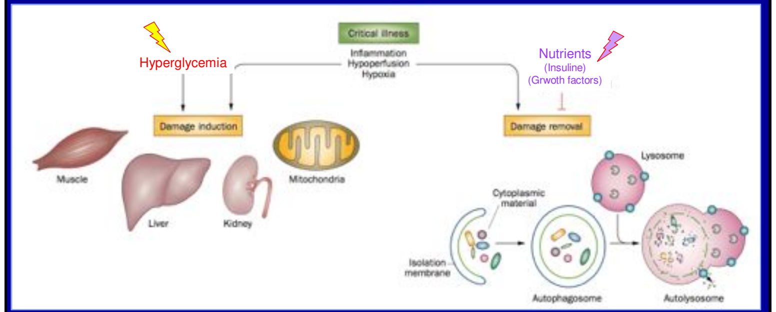
Intensive insulin therapy my improve morbidity in severe burn patients

Hyperglycemia



Falciglia et al.CCM 2009 37:3001

Toxicity of hypoglycemia in the critically ill patient



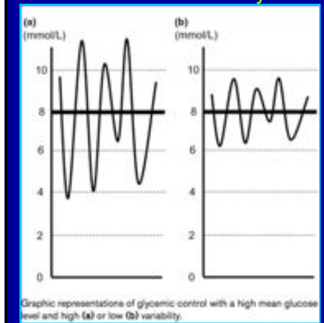
Van der Berghe G et. al. Nat Rev Endoc 2012 EPub

Toxicity of hyperglycemia

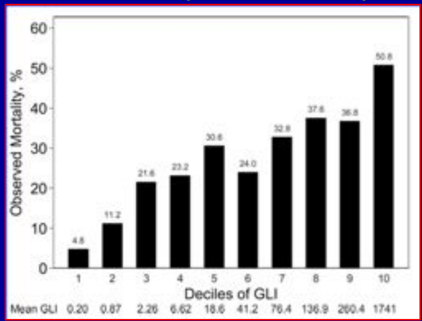
- **Possible factors**
  - ➢ **Oxydative stress**
  - ➢ **Endothelial dysfunction**
    - enhanced polyol activity, causing sorbitol and fructose accumulation
    - increased formation of advanced glycation end products
    - activation of protein kinase C and nuclear factor-kappa-B
    - increased hexosamine pathway flux
  - ➢ **Enhance monocyte adhesion to endothelial cells**
  - ➢ **Induce apoptosis**

Blood Glucose Variability and Mortality

Glucose Variability



Glucose liability Index & Mortality



Ali et al. CCM 2008 36:2316

Glucose variability negatively impacts long-term functional outcome in patients with traumatic brain injury☆,☆☆

Kazuhide Matsushima MD[a,*], Monica Peng BS[b], Carlos Velasco BS[b], Eric Schaefer MS[c], Ramon Diaz-Arrastia MD, PhD[d], Heidi Frankel MD, FACS, FCCM[e]

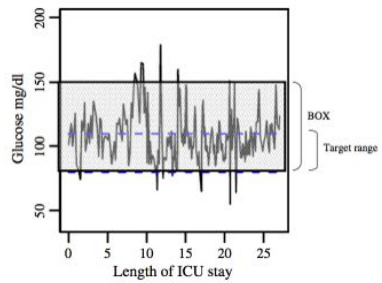


Table 5 Multivariable ordinal logistic regression results for the 4-level GOSE score

Variable	OR (95% CI)	*P*	c-index
POE <200, 10% increase	2.49 (0.99-6.22)	.05	0.754
POE <150, 10% increase	1.47 (1.14-1.91)	.004	0.768
POE <110, 10% increase	1.05 (0.88-1.26)	.59	0.746
POE >80, 10% increase	1.34 (0.73-2.46)	.34	0.743
POE >60, 1% increase	1.56 (1.15-2.12)	.004	0.765
POE 80-110, 10% increase	1.09 (0.89-1.34)	.39	0.746
POE 80-150, 10% increase	1.49 (1.16-1.91)	.002	0.767
Single episode of glucose <60 mg/dL	3.72 (1.60-8.65)	.002	0.767
Glucose mean, 10 mg/dL increase	1.28 (0.98-1.67)	.07	0.758
Glucose SD, 10 mg/dL increase	1.80 (1.23-2.63)	.002	0.771

Each variable was modeled separately while adjusting for age, sex, GCS at ED, ISS, ICP monitoring, and surgical procedure.

Glucose variability was significantly associated with poorer long-term functional outcome in patients with TBI as measured by the GOSE score.

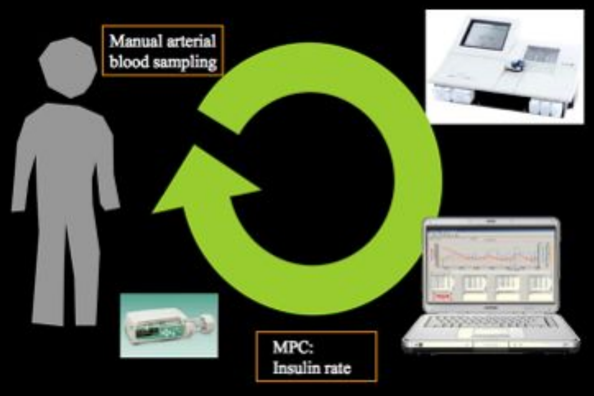
Mutsushima K. et al. J Crit Care 2012 27:125

Blood glucose variability and Hospital mortality

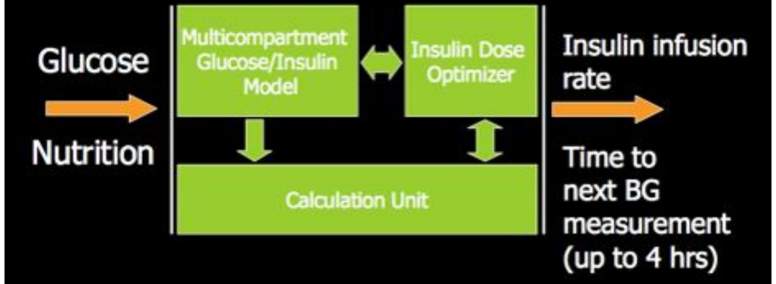
Blood glucose	Incidence (%)	Hospital mortality OR (95% CI)	
		Crude	Adjusted§
Early hypoglycemia			
Two episodes	1409 (2.1)	2.7 (2.4 to 3.0)	2.2 (1.9 to 2.5)
One episode only	7713 (11.7)	1.7 (1.6 to 1.8)	1.2 (1.1 to 1.3)
No hypoglycemia¶	57062 (86.2)	1.0	1.0
BG variability			
BG variability	1913 (2.9)	2.4 (2.1 to 2.6)	1.4 (1.3 to 1.5)□
Hypoglycemia	7209 (10.97)	1.7 (1.6 to 1.8)	1.2 (1.0 to 1.4)□
Neither¶	57062 (86.2)	1.0	1.0□

Bagshow et al. Crit Care 2009 13:R91

Computerized Glucose Control



Automated Glucose control

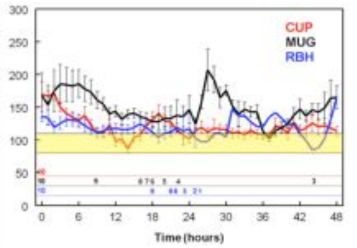


Glucose Control Unit Window

Controlling target blood glucose level and variability

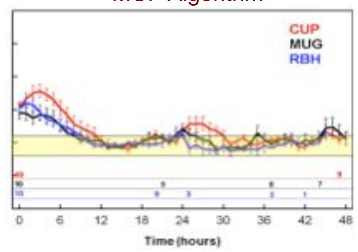
3 ICUs – RT post cardiac surgery

Standard Care



Hourly glucose measurements

MCP Algorithm



Computerized control

Comparison with an other Study center using the same device

TABLE 2. GLUCOSE CONTROL (PERCENTAGE OF TIME WITHIN BLOOD GLUCOSE RANGES AND MEAN ARTERIAL BLOOD GLUCOSE LEVEL) AND SAMPLING INTERVAL FOR INDIVIDUAL STUDY DAYS AND OVERALL

		Percentage of time (%)					
Study day	n	*2.2–3.2 mmol/L*	*3.3–4.3 mmol/L*	*4.4–8.3 mmol/L (target range)*	*>8.3 mmol/L*	*Mean glucose (mmol/L)*	*Sampling interval (h)*
1	20	0	3.7±7.6	67.9±19.2	28.4±19.4	7.6±0.9	1.6±0.3
2	20	0	1.1±2.3	84.4±20.1	14.5±20.1	6.9±0.9	2.3±0.8
3	20	0	1.3±2.3	84.2±16.6	14.4±16.7	6.8±0.7	2.2±0.6
4	19	0	1.6±3.2	82.8±19.6	15.6±20.1	6.8±1.0	2.2±0.7
5	15	0	2.3±3.8	87.3±15.4	10.4±13.7	6.6±0.6	2.3±0.6
6	12	0.2±0.8	0.7±1.2	86.9±13.4	12.2±13.3	6.7±0.6	2.2±0.5
7	9	0.1±0.4	2.9±3.5	85.0±14.7	12.0±12.2	6.8±0.5	2.1±0.6
8 and later	8	0.1±0.1	1.4±1.6	88.4±6.8	10.1±6.4	6.7±0.3	2.1±0.4
Total	20	0.03±0.07	2.1±1.8	83.4±8.9	14.5±8.3	6.8±0.4	2.0±0.4

Data are mean±SD values.

Amrein K Diab Tech & Terap 2012

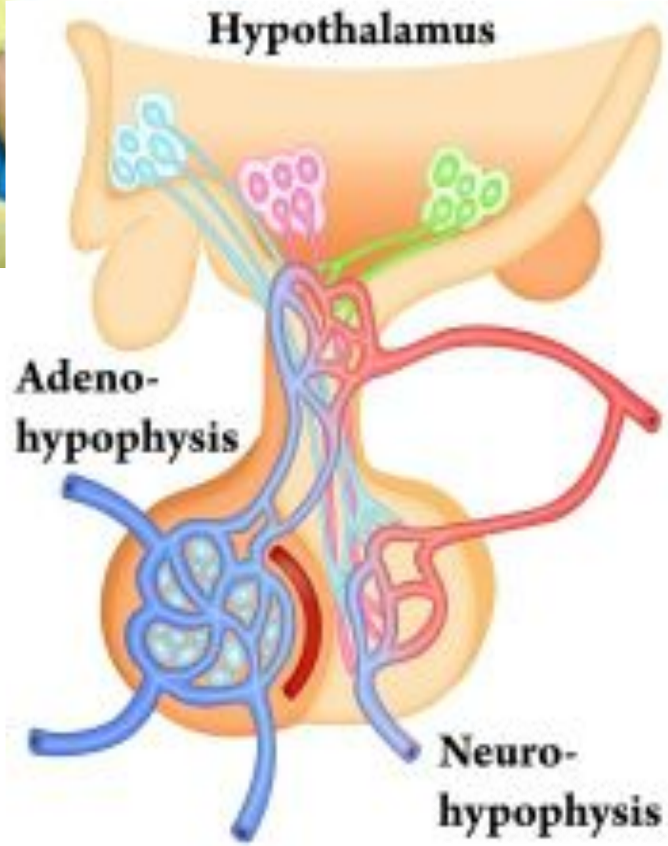
Insulin Therapy in the ICU what should we aim for?

- Target
  - General: 6 – 9 mmol/l (108 – 160 mg/dl)
  - to be adapted in selected groups of ICU patients
    - Cardiac surgery patients with parenteral nutrition
    - Brain trauma patients
    - Burn patients
  - Decrease blood glucose variability
- Close-loop glycemic control
  - Control for hypo- and hyperglycemic events
  - Decrease blood glucose variability

Endocrine response after trauma – the endocrinologists‘ perspective - focus on pituitary function

Bern 28.2.2014

Dr. Paul Kirchner
Oberarzt Poliklinik für Endokrinologie und Diabetologie
Inselspital Bern


Hypothalamus
Adeno-
hypophysis
Neuro-
hypophysis

Case report 1

- 37yr old nurse, one daughter (10 yrs)
- hospitalisation due to abdominal pain, vomiting
  - labor
    - Sodium 123mmol/l, Cortisol 42nmol/l
    - TSH 2.7mU/l (0.35-4.5)
  - MRI: empty sella
- 2 weeks later on Endocrinology outpatient clinic
  - no symptoms with 30mg hydrocortisone/day
  - labor
    - fT4 7.3 pmol/l (9.5-25), fT3 1.5pmol/l (2.9-6.5)
    - Oestradiol < 20pmol/l, LH 4.7 U/l, FSH 12.5 U/l
    - IGF1 <25ng/ml (94-252)
  - after delivery 10 years ago
    - heavy bleeding, severe headache, breastfeeding not possible
    - oligo-/amenorhea, fatigue, diminshed physical strength

- Anterior Pituitary Insufficiency with subtle onset after Sheehan Syndrom

- cortisol deficiency is a cause of hyponatremia
- recognition of symptomatic pituitary insufficiency could be difficult
- ischemia is a possible reason for pituitary insufficiency

Wie harmlos sind Kopfbälle? Hypogonadotroper Hypogonadismus nach leichten Schädel-Hirn-Traumata bei einem Profi-Fußballspieler

Isolated gonadotropic deficiency after multiple concussions in a professional soccer player

Autoren M. Auer[1] G.K. Stalla[1] A.P. Athanasoulia[1]

Institut [1] Abteilung für Innere Medizin, Endokrinologie und Diabetes, Max-Planck-Institut für Psychiatrie, München

Dtsch Med Wochenschr 2013

Case report 2

- 29yr old soccer professional
- diminshed physical strength over the last years, libido loss, erectile dysfunction
- testis each about 10ml
- labor
  - testosterone total 2.9nmol/l (12-22)
  - LH 1.3 U/l (1.7-8.6)
  - FSH 8.4 U/l(1.5-12.4)
- other pituitary function normal
- MRI sella: normal

- Frequency of headers (500 per week) as cause of hypogonadotropic hypogonadism**?**

- cortisol deficiency is a cause of hyponatremia
- recognition of symptomatic pituitary insufficiency could be difficult
- ischemia is a possible reason for pituitary insufficiency
- shearing lesions after (repetitive) concussions are discussed as a possible reason for pituitary insufficiency
- one low value does not define a hormone deficiency

Source	No. of Adults	No. (%) [95% CI]					
		Growth Hormone	LH/FSH	Adrenocorticotropic Hormone	TSH	Hypopituitarism	Multiple Deficiencies
TBI							
Bondanelli et al,[12] 2004	50	4 (8.0) [0.5-15.5]	7 (14.0) [4.4-23.6]	0	5 (10.0) [1.7-18.3]	14 (28.0) [15.6-40.5]	6 (12.0) [3.0-21.0]
Aimaretti et al,[14] 2005	70	14 (20.0) [10.6-29.4]	8 (11.4) [4.0-18.9]	5 (5.7) [0.3-11.2]	4 (7.1) [1.1-13.2]	16 (22.9) [13.0-32.7]	7 (10.0) [3.0-17.0]
Agha et al,[15,16] 2004	102	11 (10.8) [4.8-16.8]	12 (11.8) [5.5-18.0]	13 (12.7) [6.3-19.2]	1 (1.0) [0-2.9]	29 (28.4) [19.7-37.2]	6 (5.9) [1.3-10.5]
Popovic et al,[17] 2004	67	10 (14.9) [6.4-23.5]	6 (9.0) [2.1-15.8]	5 (7.5) [1.2-13.8]	3 (4.5) [0-9.4]	23 (34.3) [23.0-45.7]	7 (10.4) [3.1-17.8]
Leal-Cerro et al,[18] 2005	170	10 (5.9) [2.3-9.3]	29 (17.1) [11.4-22.7]	11 (6.5) [2.8-10.2]	10 (5.9) [2.4-9.4]	42 (24.7) [18.2-31.2]	15 (8.8) [4.6-13.1]
Agha et al,[19,20] 2005	48	5 (10.4) [1.8-19.1]	6 (12.5) [3.1-21.9]	9 (18.8) [7.7-29.8]	1 (2.1) [0-6.1]	Not reported	Not reported
Schneider et al,[21] 2006	70	7 (10.0) [3.0-17.0]	14 (20.0) [10.6-29.4]	6 (8.6) [2.0-15.1]	2 (2.9) [0-6.8]	25 (35.7) [24.5-46.9]	3 (4.3) [0-9.0]
Tanriverdi et al,[22] 2006	52	17 (32.7) [19.9-45.4]	4 (7.7) [0.5-14.9]	10 (19.2) [8.5-29.9]	3 (5.8) [0 12.1]	26 (50.0) [36.4-63.6]	5 (9.6) [1.6-17.6]
Herrmann et al,[23] 2006	76	6 (7.9) [1.8-14.0]	13 (17.1) [8.6-25.6]	2 (2.6) [0-6.2]	2 (2.6) [0-6.2]	18 (23.7) [14.1-33.2]	5 (6.6) [1.0-12.2]
Klose et al,[29] 2007	104	16 (15.4) [8.5-22.3]	2 (1.9) [0-4.6]	5 (4.8) [0.7-8.9]	2 (1.9) [0-4.6]	16 (15.4) [8.5-22.3]	6 (5.8) [1.3-10.3]

Harald Jörn Schneider, MD
Ilonka Kreitschmann-Andermahr, MD
Ezio Ghigo, MD
Günter Karl Stalla, MD
Amar Agha, MD

Hypothalamopituitary Dysfunction Following Traumatic Brain Injury and Aneurysmal Subarachnoid Hemorrhage
A Systematic Review

JAMA. 2007;298(12):1429-1438

Table 5. Prospective Studies of Anterior Pituitary Function After Traumatic Brain Injury

Study	No. of Patients	Growth Hormone	LH/FSH	Adrenocorticotropic Hormone	Thyroid-Stimulating Hormone
Acute Phase					
Agha et al,[19,20] 2005	50			8	1
Tanriverdi et al,[22] 2006	52			5	3
Total No.	102	19	60	13	4
Total %	100	18.6	58.8	12.7	3.9
3 Months					
Aimaretti et al,[14] 2005	70	16	12	6	4
Schneider et al,[21] 2006	78	7	24	15	6
Total No.	148	23	36	21	10
Total %	100	15.5	24.3	14.2	6.8
6 Months					
Agha et al,[19,20] 2005[a]	48	6	11	9	1
Total %	100	12.5	22.9	18.8	2.1
12 Months					
Agha et al,[19,20] 2005[b]	48	5	6	9	1
Tanriverdi et al,[22] 2006[c]	52	17	4	10	3
Aimaretti et al,[14] 2005[d]	70	14	8	5	4
Schneider et al,[21] 2006[e]	70	7	14	6	2
Total No.[f]	240	43	32	30	10

Cortisol after GST <450nmol/l

Cortisol basal < 194nmol/l

Harald Jörn Schneider, MD
Ilonka Kreitschmann-Andermahr, MD
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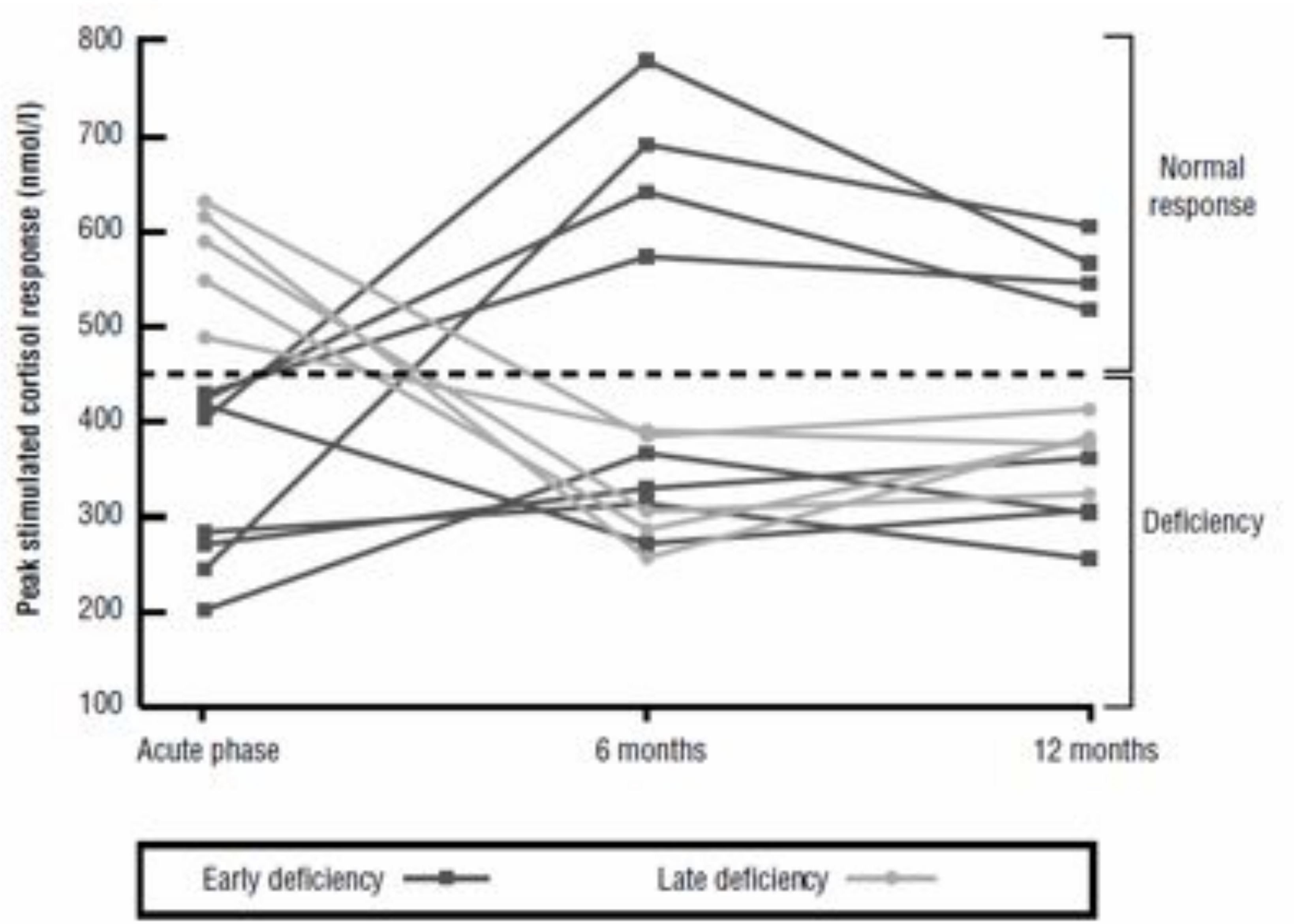
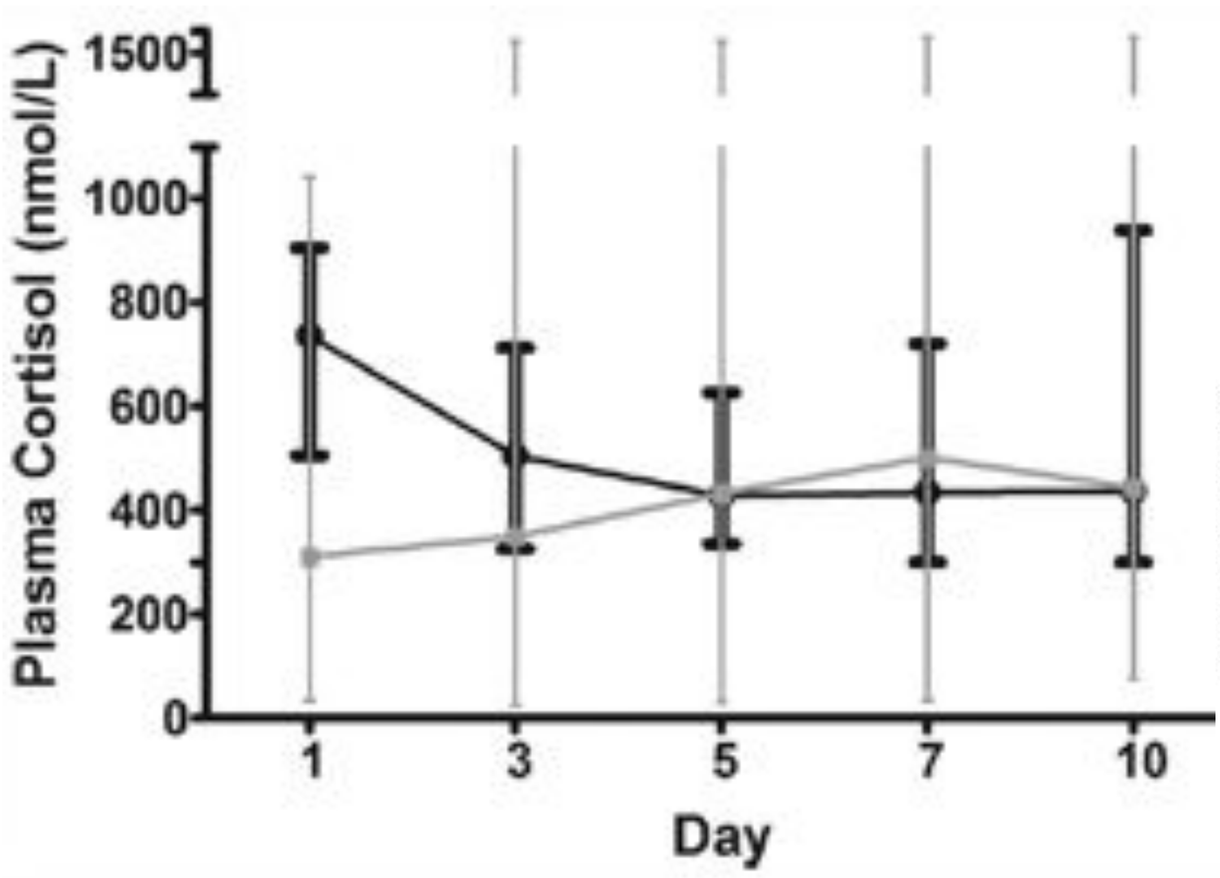
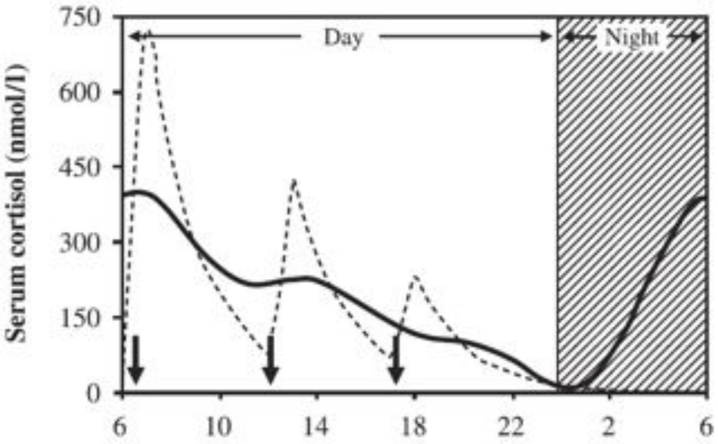
Hypothalamopituitary Dysfunction Following Traumatic Brain Injury and Aneurysmal Subarachnoid Hemorrhage
A Systematic Review

JAMA. 2007;298(12):1429-1438



Amar Agha, MD,[a] Jack Phillips,
Christopher J. Thompson, MD[a]
The natural history of post-traumatic hypopituitarism: Implications for assessment and treatment
The American Journal of Medicine (2005) 118, 1416.e1-1416.e7





Peak M. Man
Clinical Endocrinology (2004) **61**, 367–375

- 100 Patients after traumatic brain injury (TBI)
  - mean GCS 8.6, 33yrs, mortality 19%
- vs. 15 Controls
  - patients after aortic surgery, 68yrs
- Cortisol levels between 8 and 9 am

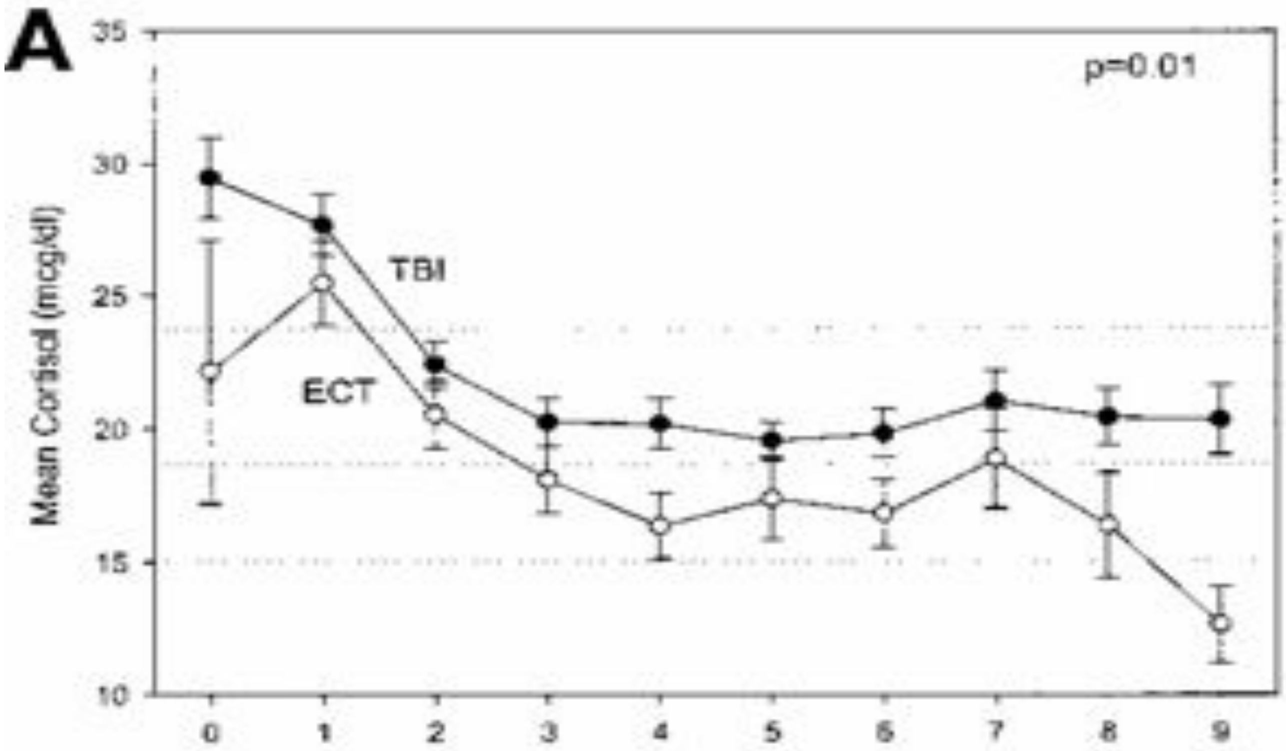
M. J. Hannon, R. K. Crowley, L. A. Behan, E. P. O'Sullivan, M. M. C. O'Brien, M. Sherlock, D. Rawluk, R. O'Dwyer, W. Tormey, and C. J. Thompson

Acute Glucocorticoid Deficiency and Diabetes Insipidus Are Common After Acute Traumatic Brain Injury and Predict Mortality

J Clin Endocrinol Metab, August 2013, 98(8):3229–3237

	ECT		TBI	
No. of subjects	41		80	
Age, yrs	25	(21, 45)	29	(21, 49)
Male sex, n (%)	35	(85)	65	(81)
ISS	24	(16, 25)	26	(24, 34)
GCS, mean (%)				
14–15	41	(100)	0	
9–13	0		23	(29)
3–8	0		57	(71)
Days in ICU	4.0	(3, 7)	6.0	(4, 9)
Cortisol, μg/dL				
Daily mean	17.9	(15.3, 22.6)	21.7	(18.6, 26.2)
Morning mean	17.1	(15.1, 22.3)	21.8	(17.4, 26.4)
Afternoon mean	17.7	(14.2, 24.4)	20.5	(17.0, 26.0)
Afternoon–morning[a]	0.77	(−3.0, 5.5)	0.19	(−3.7, 4.0)

Cortisol levels at 6am and 4pm



Pejman Cohan, MD; Christina Wang, MD; David L. McArthur, PhD, MPH; Shon W. Cook, MD; Joshua R. Dusick, MD; Bob Armin, BS; Ronald Swerdloff, MD; Paul Vespa, MD; Jan Paul Muizelaar, MD, PhD; Henry Gill Cryer, MD; Peter D. Christenson, PhD; Daniel F. Kelly, MD

Acute secondary adrenal insufficiency after traumatic brain injury: A prospective study*

Crit Care Med 2005 Vol. 33, No. 10

Table 2. Traumatic brain injury (TBI) subject characteristics according to adrenal insufficiency status

	Non-Adrenal Insufficiency		Adrenal Insufficiency		p Value
No. of subjects	38		42		
At Time of Injury					
Age	40	(25, 56)	26	(19, 35)	.010
Male sex (%)	33/38	(86.8)	32/42	(76.2)	.26
GCS (postresuscitation)	7.0	(6, 10)	6.5	(3, 8)	.10
ISS	25	(17, 29)	28	(25, 36)	.022
Early ischemia factors (%)					
Hypotension[a]	16/38	(42.1)	27/42	(64.3)	.072
Hypoxia[b]	7/38	(18.4)	14/41	(34.2)	.13
Hematocrit <25%[c]	7/38	(18.4)	12/42	(28.6)	.31
Ischemia score (%)[d]					.021
0	19/38	(50.0)	11/41	(26.8)	
1	8/38	(21.1)	12/41	(29.3)	
2	11/38	(29.0)	13/41	(31.7)	
3	0/38	(0.0)	5/41	(12.2)	
CT Findings					
Abnormal cisterns on CT (%)	23/38	(60.5)	22/42	(52.4)	.50
CT composite score[e]	2.0	(0, 4)	2.0	(0, 3)	.37
Medications					
Received etomidate (%)	22/38	(57.9)	33/41	(80.5)	.049
Received metabolic suppressive agents (%)[f]	5/38	(13.1)	11/42	(26.2)	.17
Vasopressor score[g]					
Mean	0.21	(0.03–0.39)	1.04	(0.62–1.47)	.001
50th/75th/90th percentiles	0.0/0.13/0.91		0.10/1.83/2.83		.007
>0 (%)	13/38	(34.2)	24/42	(57.1)	.047
Blood Pressure, ICP, CPP					
Mean arterial pressure					
Lowest	63.4	(60.5–66.3)	56.2	(52.8–59.5)	.001
Ever <60 (%)	10/38	(26.3)	26/42	(61.9)	.002
Mean	90.1	(87.0–93.1)	86.8	(84.2–89.5)	.11
Mean ICP[h]	16.1	(11.3–20.9)	17.3	(15.0–19.5)	.66
Mean CPP[h]	74.4	(68.3–80.4)	70.9	(67.2–74.7)	.32

two consecutive cortisol levels <415nmol/l
one cortisol level < 138nmol/l (n = 13)

Pejman Cohan, MD; Christina Wang, MD; David L. McArthur, PhD, MPH; Shon W. Cook, MD; Joshua R. Dusick, MD; Bob Armin, BS; Ronald Swerdloff, MD; Paul Vespa, MD; Jan Paul Muizelaar, MD, PhD; Henry Gill Cryer, MD; Peter D. Christenson, PhD; Daniel F. Kelly, MD

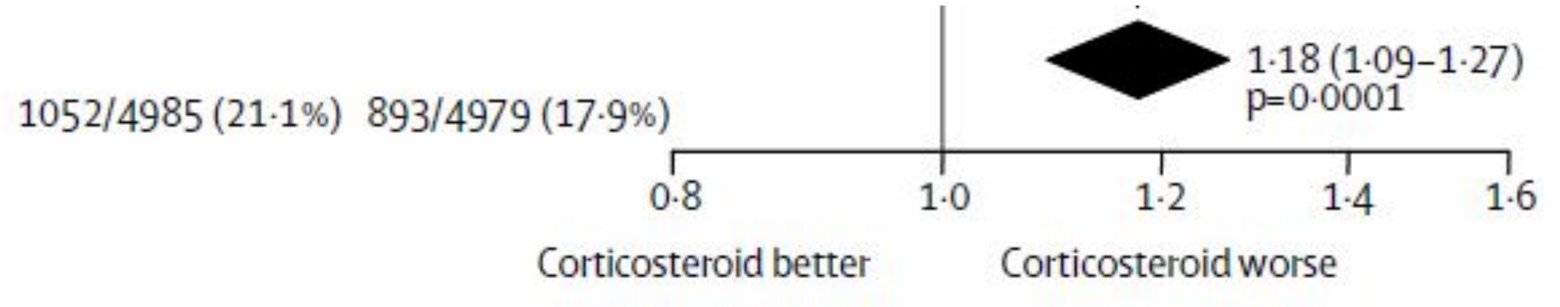
Acute secondary adrenal insufficiency after traumatic brain injury: A prospective study*

Crit Care Med 2005 Vol. 33, No. 10

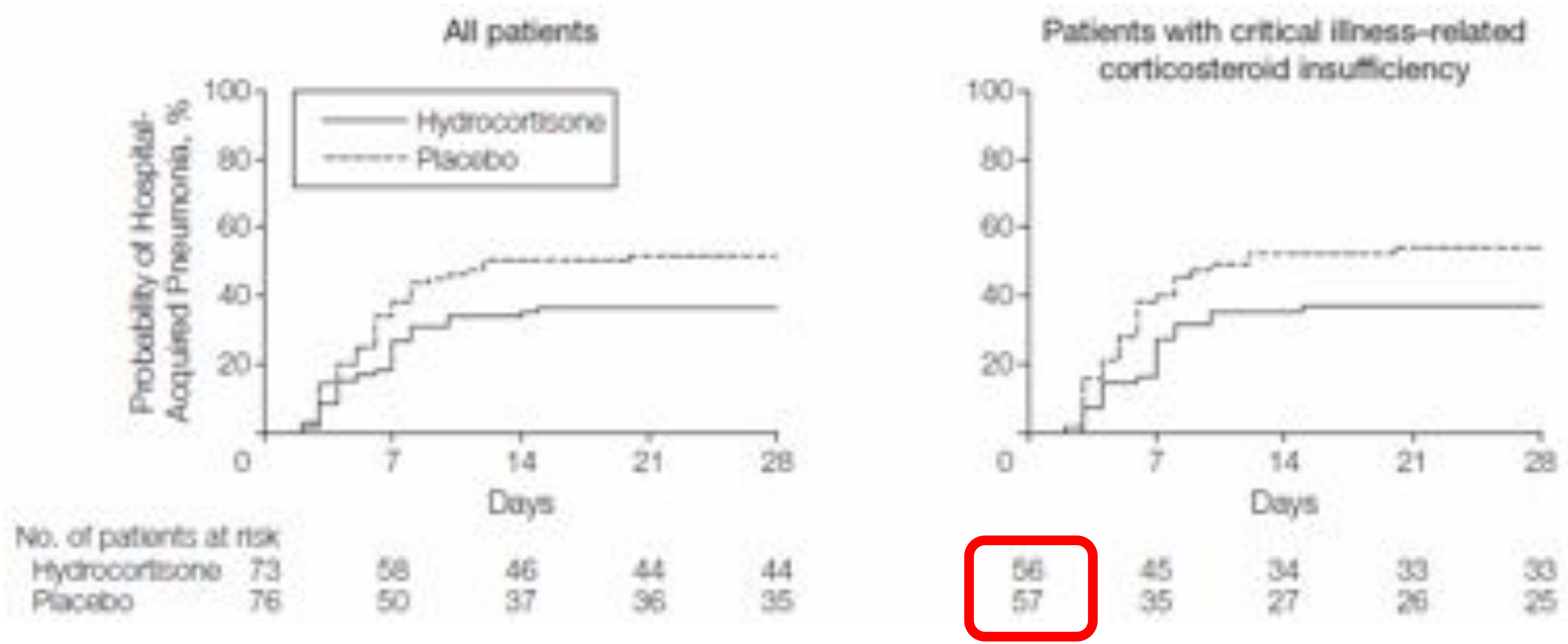
Effect of intravenous corticosteroids on death within 14 days in 10 008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial

*CRASH trial collaborators**

Lancet 2004; 364: 1321–28



- Methylprednisolon:
  - 1g during the first hour
  - 0.4g/h for 48 h
- cumulative 50 000 mg hydrocortisone equivalent per day
  - about 2500 times the endogenous hydrocortisone production in healthy persons



- 149 trauma patients, 84 (56%) with traumatic brain injury
- definition adrenal insufficiency
  - cortisol < 415nmol/l OR
  - cortisol increase 60’ after ACTH stimulation < 250nmol/l
- hydrocortisone treatment (started within 36 hours)
  - 200mg/d continously for 5d, 100mg/d on d6, 50mg/d on d7
  - started in all patients, stopped within 48h if no adrenal insufficiency
- definition pneumonia
  - Temp > 38°C, Lc >12 G/l, Lc <4 G/l, purulent pulmonary secretions (2 out of 3) AND
  - cxr with new or changing infiltrate AND
  - culture of BAL >10^4 CFU/ml

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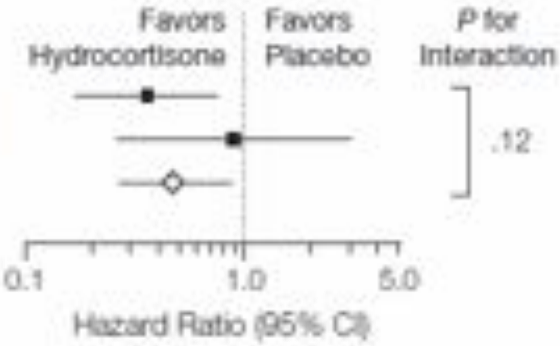
Hydrocortisone Therapy for Patients With Multiple Trauma
The Randomized Controlled HYPOLYTE Study

JAMA. 2011;305(12):1201-1209

Figure 3. Patients With Critical Illness–Related Corticosteroid Insufficiency Presenting With Traumatic Brain Injury

	No. With Hospital-Acquired Pneumonia/Total No. (%)				
	Hydrocortisone	Placebo	Hazard Ratio (95% CI)	Favors Hydrocortisone / Favors Placebo	*P* for Interaction
Trauma brain injury	13/32 (40.6)	25/35 (71.4)	0.36 (0.17-0.74)		.12
No trauma brain injury	7/24 (29.2)	6/22 (27.3)	0.89 (0.26-3.03)		
Whole population	20/56 (35.7)	31/57 (54.4)	0.36 (0.17-0.74)		



Sixty-seven patients had a traumatic brain injury (32 in the hydrocortisone group and 35 in the placebo group); 46 did not have traumatic brain injury (24 in the hydrocortisone group and 22 in the placebo group).

Table 2. Secondary Outcomes[a]

	All Patients				Patients With Corticosteroid Insufficiency			
Outcomes	Hydrocortisone (n = 73)	Placebo (n = 76)	Absolute Difference (95% CI)[c]	*P* Value	Hydrocortisone (n = 56)	Placebo (n = 57)	Absolute Difference (95% CI)[c]	*P* Value
Hyponatremia ≤130 mmol/L	0	7 (9.2)	−9 (−16 to −3)	.01	0	7 (12.3)	−12 (−18 to −4)	.008
Mechanical ventilation–free days, mean (SD)	16 (8)	12 (8.5)	4 (2 to 7)	.001[b]	16 (10)	10 (12)	6 (2 to 11)	<.001[b]
Length of ICU stay, mean (SD), d	18 (15)	24 (16)	−6 (−11 to −1)	.03[b]	17 (13)	25 (17)	−8 (−13 to −3)	.002[b]
Vasoactive drugs								
Duration, median (IQR), d	2.0 (1.0 to 4.0)	3.0 (0.0 to 5.0)	−1 (−2 to 0)	.64	2.5 (1.0 to 4.0)	3.0 (1.0 to 5.0)	−2.0 (−4.1 to 0.00)	.04
Death, No. (%)	6 (8.2)	4 (5.3)	3 (−5 to 11)	.44	6 (10.7)	3 (5.3)	5 (−5 to 15)	.23

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Asehnoune et al. Trials 2011, 12:228
http://www.trialsjournal.com/content/12/1/228

TRIALS

STUDY PROTOCOL **Open Access**

Corticotherapy for traumatic brain-injured Patients - The Corti-TC trial: study protocol for a randomized controlled trial

Karim Asehnoune[1,4*], Antoine Roquilly[2,4], Véronique Sebille[3,4] and The Corti-TC trial group[2,4*]

- 326 patients with traumatic brain injury (GCS < 8)
- Hydro- and fludrocortisone treatment (started within 36 hours)
  - 200mg/d continously for 7d, 100mg/d on d8, 50mg/d on d9 + 50µg Fludrocortison/d for 10d
  - started in all patients, stopped within 48h if no adrenal insufficiency
- Results (unpublished, in review)
  - 86 episodes of HAP were recorded in the steroid group, and 110 episodes in the placebo group (respectively 0.5±0.6 and 0.7±0.7 HAP per patient; P=0.04).
  - no differences in other outcomes including mortality
  - results were not dependent on the adrenal status

Take home

- definition of hormone deficiency in ICU patients is difficult
- hydrocortisone replacement therapy may be beneficial in patients with TBI regarding the incidence of HAP and hyponatremia
- assessment of complete pituitary function in follow up of patients with TBI is senseful