NEURO UPDATE TORINO

# IPOTERMIA


## Anselmo Caricato

*Reparto di Rianimazione*

*Fondazione Policlinico Universitario «A. Gemelli»*

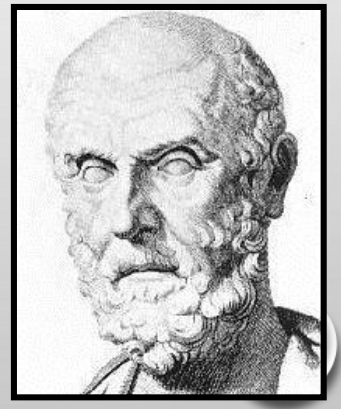
NEURO UPDATE TORINO

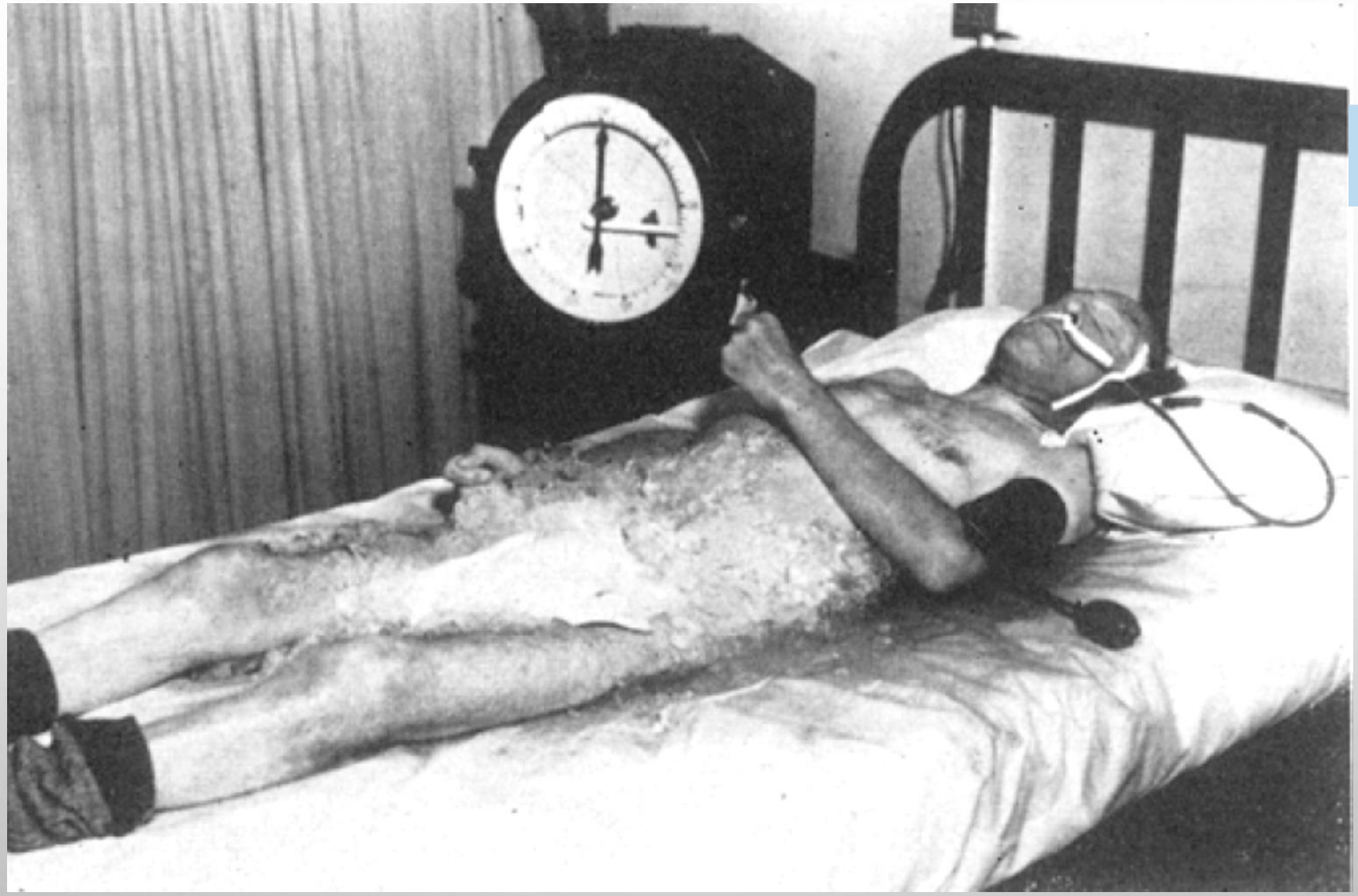
"…SOPRAVVIVERA' DI PIÙ IN INVERNO CHE IN ESTATE, QUALUNQUE SIA LA PARTE DEL CAPO IN CUI SIA STATO COLPITO"

Aristotele

- *De Capitis Vulneribus*

  400 A.C





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# IPOTERMIA E NEUROPROTEZIONE

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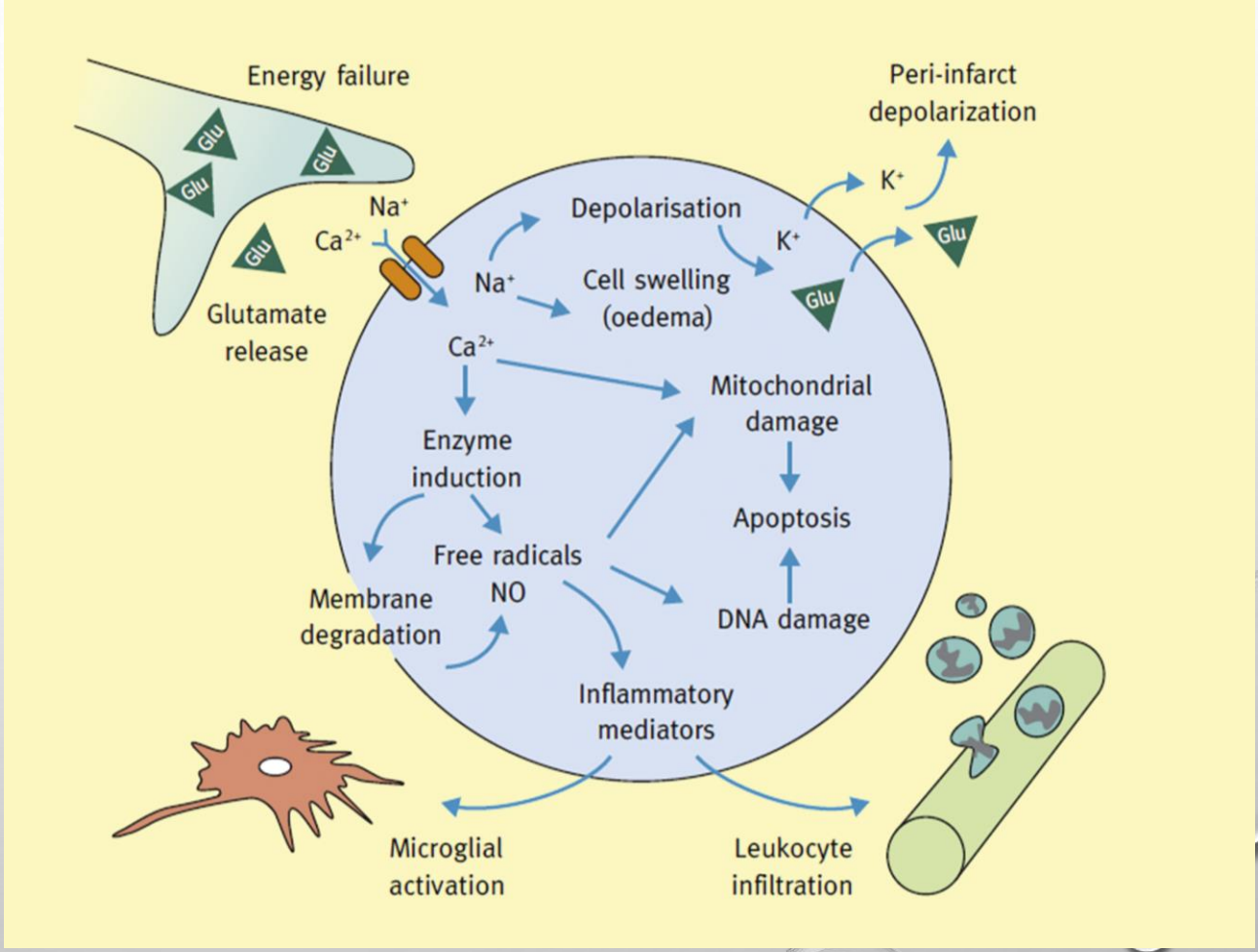
## *Inflammation*

- Decreases the concentrations of excitatory amino acids and lactate
- Reduced the microvessel expression of intercellular adhesion molecule-1 protein and the number of neutrophils migrating into tissue
- Decreased interleukin-10 concentrations in CSF
- Reduced BBB leakage



# IPOTERMIA E NEUROPROTEZIONE

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*CBF and metabolism*

- Hypothermia under 36°C decreases CBF and $CMRO_2$ 6-7%/°C
- Fever above 37°C increases CBF and $CMRO_2$ 10-13%/°C
- ICP reduction

# ARRESTO CARDIACO

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*Guidelines*

## Targeted Temperature Management

**2015 (Updated):** All comatose (ie, lacking meaningful response to verbal commands) adult patients with ROSC after cardiac arrest should have TTM, with a target temperature between 32°C and 36°C selected and achieved, then maintained constantly for at least 24 hours.

# IPOTERMIA ED EFFETTI SISTEMICI

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## *Equilibrio idro-elettrolitico*

- Incremento della diuresi
- Shift intracellulare del potassio
- Ipomagnesiemia
- Iperglicemia

## *Alterazioni coagulative*

- Riduzione attività piastrinica
- Inibizione fattori della coagulazione

## *Aumento suscettibilità infezioni*

# IPOTERMIA NEL TRAUMA

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The New England Journal of Medicine

# TREATMENT OF TRAUMATIC BRAIN INJURY WITH MODERATE HYPOTHERMIA

DONALD W. MARION, M.D., LOUIS E. PENROD, M.D., SHERYL F. KELSEY, PH.D., WALTER D. OBRIST, PH.D.,
PATRICK M. KOCHANEK, M.D., ALAN M. PALMER, PH.D., STEPHEN R. WISNIEWSKI, PH.D.,
AND STEVEN T. DEKOSKY, M.D.

N Engl J Med 1997;336:540-6

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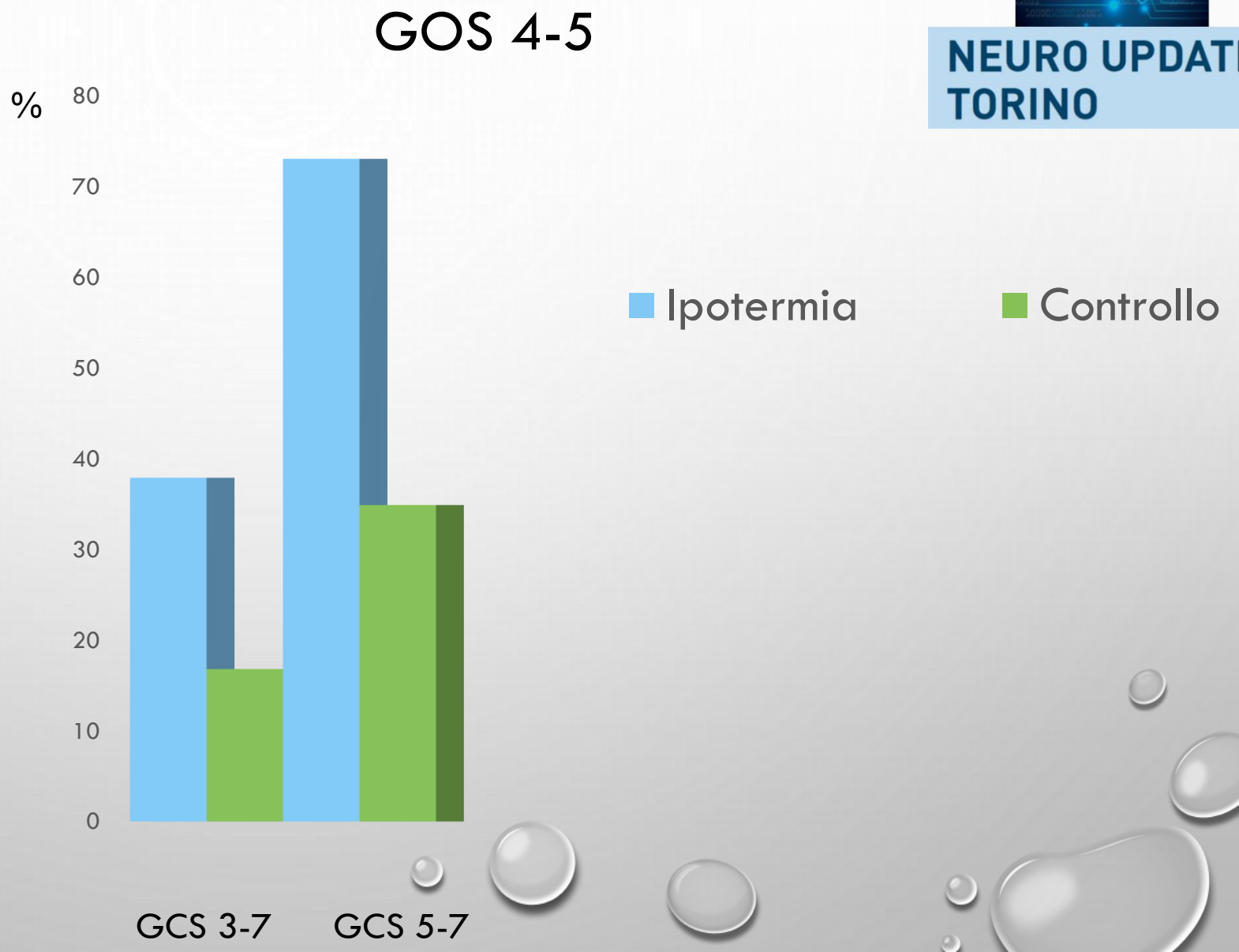
**82 pazienti**

entro 6 h per 24h

32-33°C vs controllo



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The New England Journal of Medicine

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N Engl J Med 1997;336:540-6

***Conclusions***

Treatment with moderate hypothermia for 24 hours in patients with severe traumatic brain injury and coma scores of 5 to 7 on admission may have improved the outcome

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The New England Journal of Medicine

# LACK OF EFFECT OF INDUCTION OF HYPOTHERMIA AFTER ACUTE BRAIN INJURY

GUY L. CLIFTON, M.D., EMMY R. MILLER, PH.D., R.N., SUNG C. CHOI, PH.D., HARVEY S. LEVIN, PH.D., STEPHEN MCCAULEY, PH.D., KENNETH R. SMITH, JR., M.D., J. PAUL MUIZELAAR, M.D., PH.D., FRANKLIN C. WAGNER, JR., M.D., DONALD W. MARION, M.D., THOMAS G. LUERSSEN, M.D., RANDALL M. CHESNUT, M.D., AND MICHAEL SCHWARTZ, M.D.

N Engl J Med 2001; 344:556-63

**NABIS:H I**

# GOS 4-5

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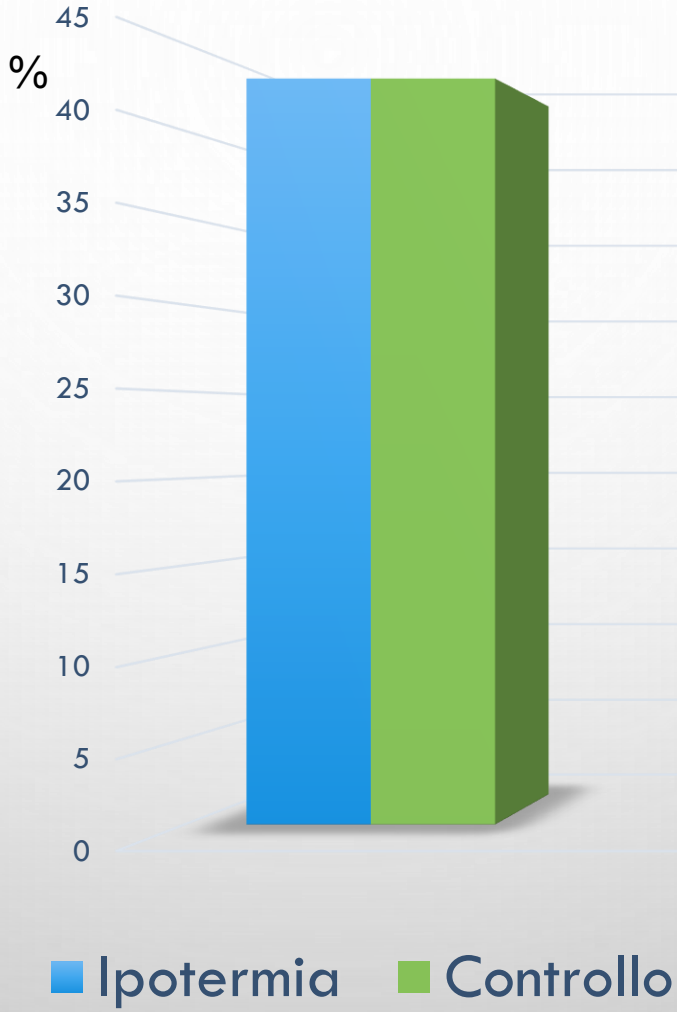
entro 6 h per 48 h
33°C vs controllo




**392 pazienti**

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| VARIABLE | HYPOTHERMIA | NORMOTHERMIA | P VALUE |
|---|---|---|---|
| Morphine (mg)† | 8.2±4.3 | 8.3±4.8 | 0.82 |
| Vecuronium (mg)† | 6.9±2.8 | 8.3±3.8 | 0.003 |
| Mannitol (g) | 43.1±27.3 | 47.3±32.9 | 0.21 |
| Phenytoin (mg) | 273±203 | 279±175 | 0.51 |
| Potassium (mmol) | 25.0±12.6 | 28.0±32.5 | 0.61 |
| Patients receiving vasopressors (%) | 80 | 69 | 0.01 |
| Hours of vasopressor therapy‡ | 48.5±33.9 | 41.0±37.8 | 0.05 |
| Patients receiving two or more vasopressors (%) | 51 | 39 | 0.43 |
| Food intake by day 6 (kcal/day) | 1569±840 | 1480±831 | 0.37 |
| Daily mean TISS score in the ICU§ | 48.4±7.1 | 46.8±8.3 | 0.05 |
| TISS score at hospital discharge§ | 17.4±12.6 | 16.1±11.9 | 0.41 |
| Cumulative fluid balance during first 96 hours (ml) | 3061±5946 | 1947±4586 | 0.04 |
| Hospital days with complications per patient (%)¶ | 78±22 | 70±29 | 0.005 |

# Pz ipotermici all'arrivo

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## GOS 4-5

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# Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial

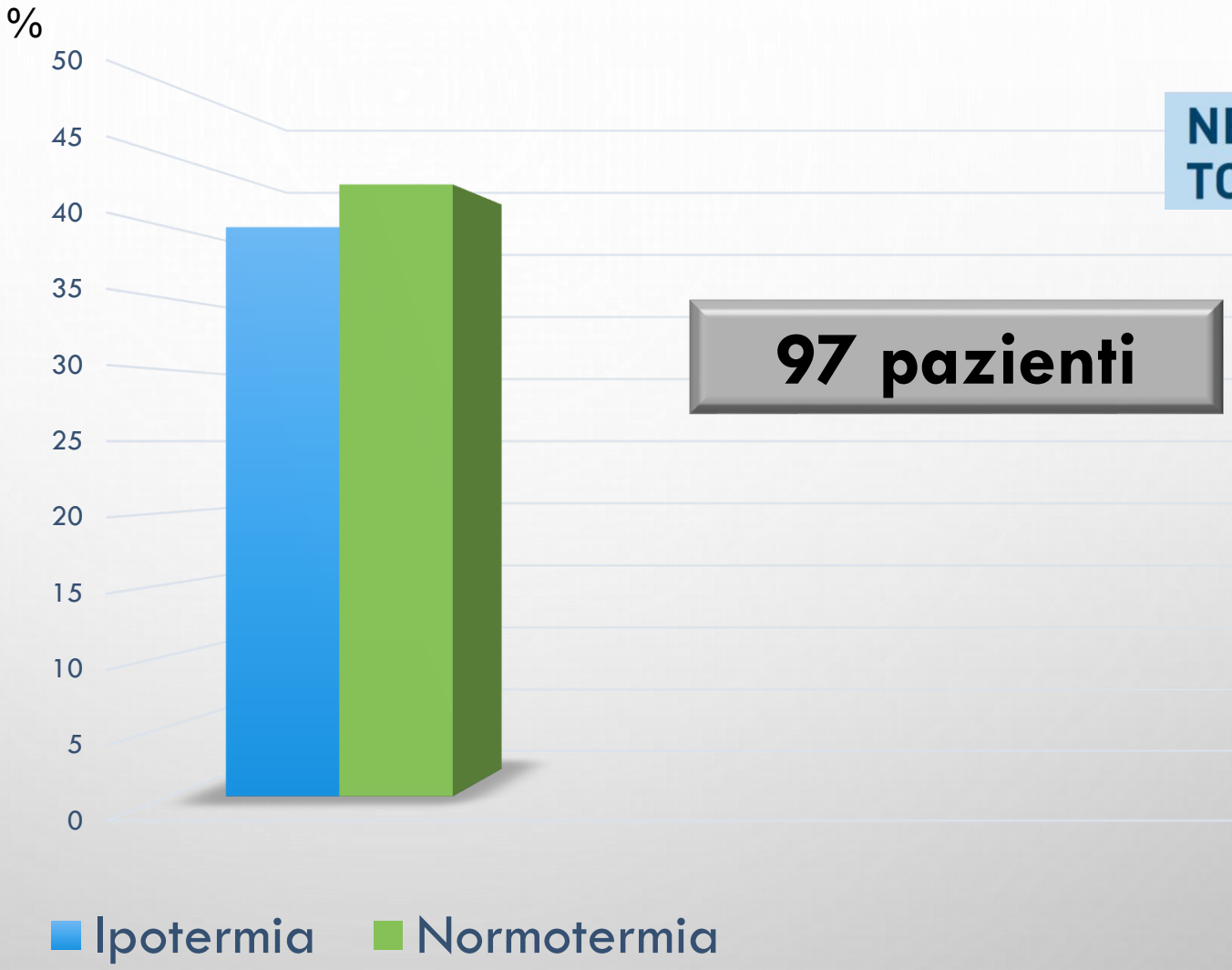
*Guy L Clifton, Alex Valadka, David Zygun, Christopher S Coffey, Pamala Drever, Sierra Fourwinds, L Scott Janis, Elizabeth Wilde, Pauline Taylor, Kathy Harshman, Adam Conley, Ava Puccio, Harvey S Levin, Stephen R McCauley, Richard D Bucholz, Kenneth R Smith, John H Schmidt, James N Scott, Howard Yonas, David O Okonkwo*

*Lancet Neurol* 2011; 10: 131–39

**NABIS: H 2**

entro 2.5 h per 48h
33°C vs controllo

# GOS 4-5

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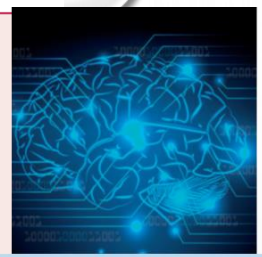
**97 pazienti**



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| | Hypothermia (n=52) | Normothermia (n=45) | p value |
|---|---|---|---|
| Received morphine | 49 (94%) | 39 (87%) | 0·30 |
| Morphine dose (mg/h)* | 6·5 (2·4) | 6·6 (3·0) | 0·88 |
| Received any paralytic | 51 (98%) | 37 (82%) | 0·01 |
| Received pancuronium bromide | 39 (75%) | 26 (58%) | 0·07 |
| Pancuronium bromide dose (mg/h) | 4·9 (2·7) | 6·8 (9·0) | 0·30 |
| Received mannitol | 39 (75%) | 27 (60%) | 0·11 |
| Mannitol dose (g/day)* | 59 (3) | 51 (60) | 0·27 |
| Received phenytoin | 47 (90%) | 42 (93%) | 0·72 |
| Phenytoin dose (mg/day)* | 224 (251) | 283 (311) | 0·33 |
| Administered vasopressors* | 42 (81%) | 32 (71%) | 0·26 |
| Daily therapeutic intervention score in ICU* | 46 (8) | 40 (7) | 0·0006 |
| Daily therapeutic intervention score after ICU discharge | 17 (18) | 15 (15) | 0·46 |
| Daily therapeutic intensity level *† | 5·4 (2·3) | 4·0 (2·0) | 0·002 |
| Fluids administered (mL) | 2375 (1240) | 1159 (999) | <0·0001 |
| Cumulative fluid balance (mL)* | 5285 (4285) | 3099 (4080) | 0·01 |
| Negative fluid balance* | 4 (8%) | 9 (20%) | 0·08 |
| Caloric intake on day 5 (kcal) | 761 (732) | 704 (800) | 0·71 |

NEURO UPDATE TORINO

| | Hypothermia (n=52) | | Normothermia (n=45) | | p value | | Number of episodes | | p value |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Critical | Total | Critical | Total | Critical | Hypothermia | Normothermia | |
| Neurological complications* | 43 (83%) | 26 (50%) | 31 (69%) | 18 (40%) | 0·11 | 0·32 | 428 | 208 | 0·01 |
| Increased ICP | 37 (71%) | 14 (27%) | 27 (60%) | 9 (20%) | 0·25 | 0·42 | 335 | 148 | 0·003 |
| Decreased CPP | 24 (46%) | 21 (40%) | 16 (36%) | 13 (29%) | 0·29 | 0·24 | 82 | 54 | 0·27 |
| Hydrocephalus | 4 (8%) | 0 (0%) | 2 (4%) | 0 (0%) | 0·68 | 0·99 | 4 | 2 | 0·13 |
| New subdural haemorrhage | 2 (4%) | 1 (2%) | 2 (4%) | 1 (2%) | 0·99 | 0·99 | 2 | 2 | 0·97 |
| New epidural haemorrhage | 2 (4%) | 0 (0%) | 0 (0%) | 0 (0%) | 0·50 | .. | 2 | 0 | .. |
| New intraparenchymal haemorrhage | 1 (2%) | 1 (2%) | 1 (2%) | 0 (0%) | 0·99 | .. | 1 | 1 | .. |
| New intraventricular haemorrhage | 1 (2%) | 0 (0%) | 0 (0%) | 0 (0%) | 0·99 | .. | 1 | 0 | .. |
| Seizures | 1 (2%) | 0 (0%) | 0 (0%) | 0 (0%) | 0·99 | .. | 1 | 0 | .. |
| Infectious complications | 29 (56%) | 0 (0%) | 31 (69%) | 2 (4%) | 0·18 | 0·21 | 38 | 48 | 0·28 |
| Miscellaneous complications | 21 (40%) | 7 (13%) | 14 (31%) | 3 (7%) | 0·34 | 0·33 | 30 | 20 | 0·21 |
| Cardiovascular complications | 9 (17%) | 2 (4%) | 3 (7%) | 1 (2%) | 0·11 | 1·00 | 15 | 8 | 0·20 |
| Bleeding complications | 2 (0%) | 1 (0%) | 1 (0%) | 0 (0%) | 1·00 | 1·00 | 2 | 1 | 0·26 |
| All complications | 50 (96%) | 30 (58%) | 40 (89%) | 20 (44%) | 0·24 | 0·19 | 513 | 285 | 0·01 |

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| | Poor outcome | | | Died | | |
|---|---|---|---|---|---|---|
| | n (%) | RR (95% CI) | p value | n (%) | RR (95% CI) | p value |
| **Primary analysis** | | | | | | |
| All patients (n=97) | 56 (58%) | .. | .. | 20 (21%) | .. | .. |
| Hypothermia (n=52) | 31 (60%) | 1·08 (0·76–1·53) | 0·67 | 12 (23%) | 1·30 (0·58–2·89) | 0·52 |
| Normothermia (n=45) | 25 (56%) | .. | .. | 8 (18%) | .. | .. |
| **Subgroup analysis** | | | | | | |
| Diffuse brain injury (n=69) | 42 (61%) | .. | .. | 13 (19%) | .. | .. |
| Hypothermia (n=37) | 26 (70%) | 1·44 (0·95–2·17) | 0·09 | 10 (27%) | 2·88 (0·87–9·57) | 0·08 |
| Normothermia (n=32) | 16 (50%) | .. | .. | 3 (9%) | .. | .. |
| Surgically removed haematomas (n=28) | 14 (50%) | .. | .. | 7 (25%) | .. | .. |
| Hypothermia (n=15) | 5 (33%) | 0·44 (0·22–0·88) | 0·02 | 2 (13%) | 0·35 (0·08–1·50) | 0·16 |
| Normothermia (n=13) | 9 (69%) | .. | .. | 5 (39%) | .. | .. |

Data are number (%). RR=relative risk.

***Table 2:*** **Outcome and mortality rates**

# Early induction of hypothermia for evacuated intracranial hematomas: a post hoc analysis of two clinical trials

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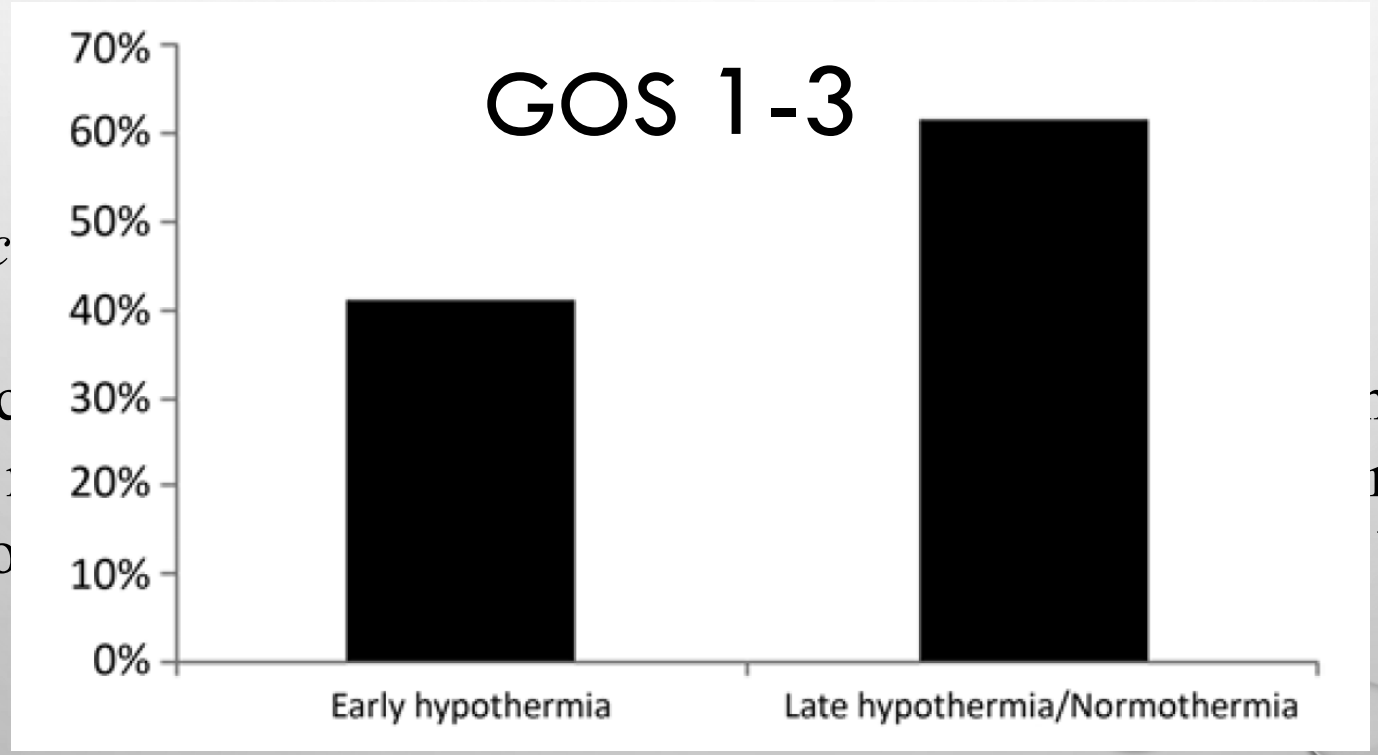
Clinical article

GUY L. CLIFTON, M.D.,[1] CHRISTOPHER S. COFFEY, PH.D.,[2] SIERRA FOURWINDS,[3] DAVID ZYGUN, M.D., PH.D.,[4] ALEX VALADKA, M.D.,[1] KENNETH R. SMITH JR., M.D.,[5] MELISA L. FRISBY, M.S.N., R.N.,[6] RICHARD D. BUCHOLZ, M.D.,[5] ELISABETH A. WILDE, PH.D.,[6] HARVEY S. LEVIN, PH.D.,[6] AND DAVID O. OKONKWO, M.D., PH.D.[7]

J Neurosurg 117:714–720, 2012

*Conc*

Induc niotomy
with rove
outco brain injury



# METODOLOGIA DEGLI STUDI

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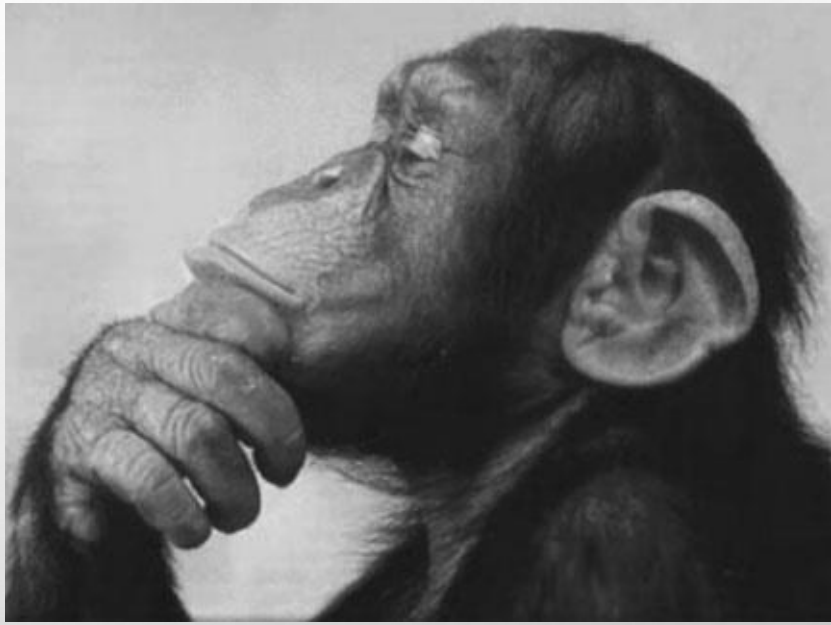
Mancanza di un vero gruppo di controllo

Tecniche di ipotermia differenti

Riscaldamento troppo precoce

Tempi di riscaldamento troppo rapidi



# Effect of long-term mild hypothermia therapy in patients with severe traumatic brain injury: 1-year follow-up review of 87 cases

**Ji-yao Jiang, M.D., Ph.D., Ming-kun Yu, M.D., Ph.D., and Cheng Zhu, M.D.**

*Department of Neurosurgery, Chang Zheng Hospital, Shanghai Neurosurgical Institute, Shanghai, People's Republic of China*

**J Neurosurg 93**:546–549, 2000

justment of the blanket thermostat. In the 44 patients assigned to the normothermia group, body temperature was maintained between 37°C and 38°C throughout the entire 14-day monitoring period.

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The New England Journal of Medicine

## TREATMENT OF TRAUMATIC BRAIN INJURY WITH MODERATE HYPOTHERMIA

Donald W. Marion, M.D., Louis E. Penrod, M.D., Sheryl F. Kelsey, Ph.D., Walter D. Obrist, Ph.D., Patrick M. Kochanek, M.D., Alan M. Palmer, Ph.D., Stephen R. Wisniewski, Ph.D., and Steven T. DeKosky, M.D.

N Engl J Med 1997;336:540-6

per hour, by a gradual adjustment of the blanket thermostat. In the 42 patients in the normothermia group, the temperature was kept between 37 and 38.5°C during the entire five-day monitoring period. The patients in the normothermia group who had

# METODOLOGIA DEGLI STUDI

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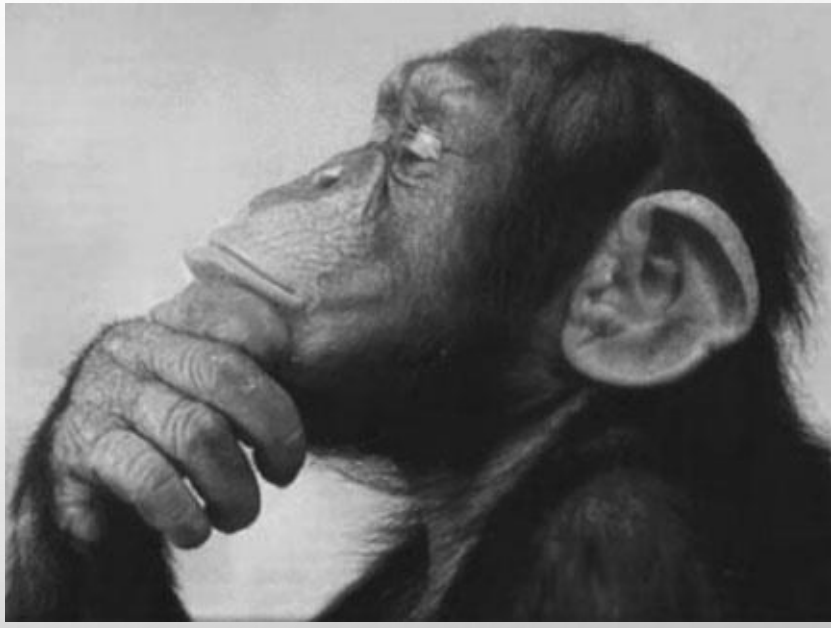
Mancanza di un vero gruppo di controllo

Tecniche di ipotermia differenti

Riscaldamento troppo precoce

Tempi di riscaldamento troppo rapidi



JOURNAL OF NEUROTRAUMA 32:422–429 (April 1, 2015)
© Mary Ann Liebert, Inc.
DOI: 10.1089/neu.2013.3197

Original Articles

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# Prolonged Mild Therapeutic Hypothermia versus Fever Control with Tight Hemodynamic Monitoring and Slow Rewarming in Patients with Severe Traumatic Brain Injury: A Randomized Controlled Trial

B-HYPO Trial

Tsuyoshi Maekawa,[1,2,*] Susumu Yamashita,[2,*] Seigo Nagao,[3] Nariyuki Hayashi,[4] and Yasuo Ohashi[5] on behalf of the Brain-Hypothermia (B-HYPO) Study Group[†]

# Target temperature within 6 h

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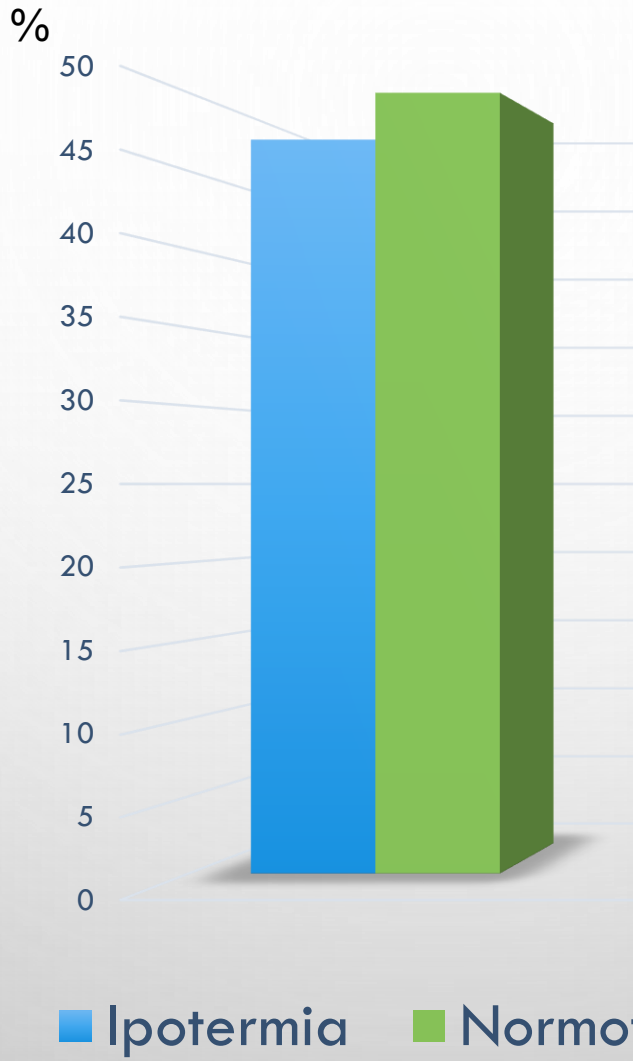
**Ipotermia**
32-34°C

**Normotermia**
35.5- 37°C

when cooling was allowed to be 35.5 °C before the randomization in both groups, to prolong duration of hypothermia (>72 h), to reduce rewarming speed (<1.0°C/day) and to randomize for two parameters (Glasgow Coma Scale [GCS] scores 4–5 and 6–8; ages

# GOS 4-5

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**148 pazienti**

# IPOTERMIA PROFILATTICA

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Brain Trauma FOUNDATION

**RECOMMENDATIONS**

***Level I and II A***

- There was insufficient evidence to support a Level I or II A recommendation for this topic.

***Level II B***

- Early (within 2.5 hours), short-term (48 hours post-injury) prophylactic hypothermia is not recommended to improve outcomes in patients with diffuse injury.

# IPOTERMIA TERAPEUTICA

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L'ipotermia è efficace per ridurre la pressione intracranica

Controllo dell'ipertensione intracranica

EUROTHERM

35°
34°
33°
32°

EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Hypothermia for Intracranial Hypertension after Traumatic Brain Injury

Peter J.D. Andrews, M.D., M.B., Ch.B., H. Louise Sinclair, R.G.N., M.Sc., Aryelly Rodriguez, M.Sc., Bridget A. Harris, R.G.N., Ph.D., Claire G. Battison, R.G.N., B.A., Jonathan K.J. Rhodes, Ph.D., M.B., Ch.B., and Gordon D. Murray, Ph.D., for the Eurotherm3235 Trial Collaborators*

N Engl J Med 2015;373:2403-12.

ICP > 20 mmHg
for 5 min after sedation
and analgesia

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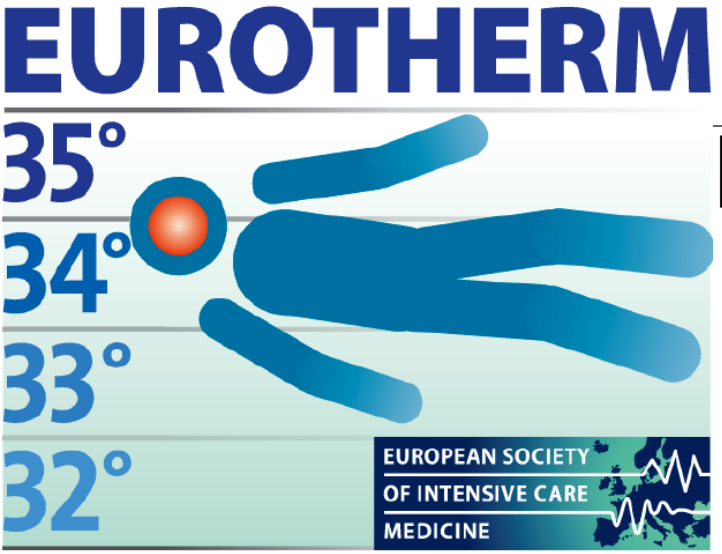
**Ipotermia**
32-35°C

**Standard care**




The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

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Peter J.D. Andrews, M.D., M.B., Ch.B., H. Louise Sinclair, R.G.N., M.Sc., Aryelly Rodriguez, M.Sc., Bridget A. Harris, R.G.N., Ph.D., Claire G. Battison, R.G.N., B.A., Jonathan K.J. Rhodes, Ph.D., M.B., Ch.B., and Gordon D. Murray, Ph.D., for the Eurotherm3235 Trial Collaborators*

## Table S7. ICP reduction therapy failure; first occurrence after randomization

| Parameter | Category | Hypothermia (N=195) | Control (N=192) |
|---|---|---|---|
| First occurrence (n(%)) | at Day 1 | 15 ( 7.8) | 31 (16.4) |
| | at Day 2 | 15 ( 7.8) | 22 (11.6) |
| | at Day 3 | 14 ( 7.3) | 17 ( 9.0) |
| | at Day 4 | 13 ( 6.8) | 14 ( 7.4) |
| | at Day 5 | 7 ( 3.6) | 7 ( 3.7) |
| | at Day 6 | 11 ( 5.7) | 4 ( 2.1) |
| | at Day 7 | 9 ( 4.7) | 7 ( 3.7) |
| | Never occurred (Days 1- 7) | 108 (56.3) | 87 (46.0) |
| | Missing | 3 | 3 |

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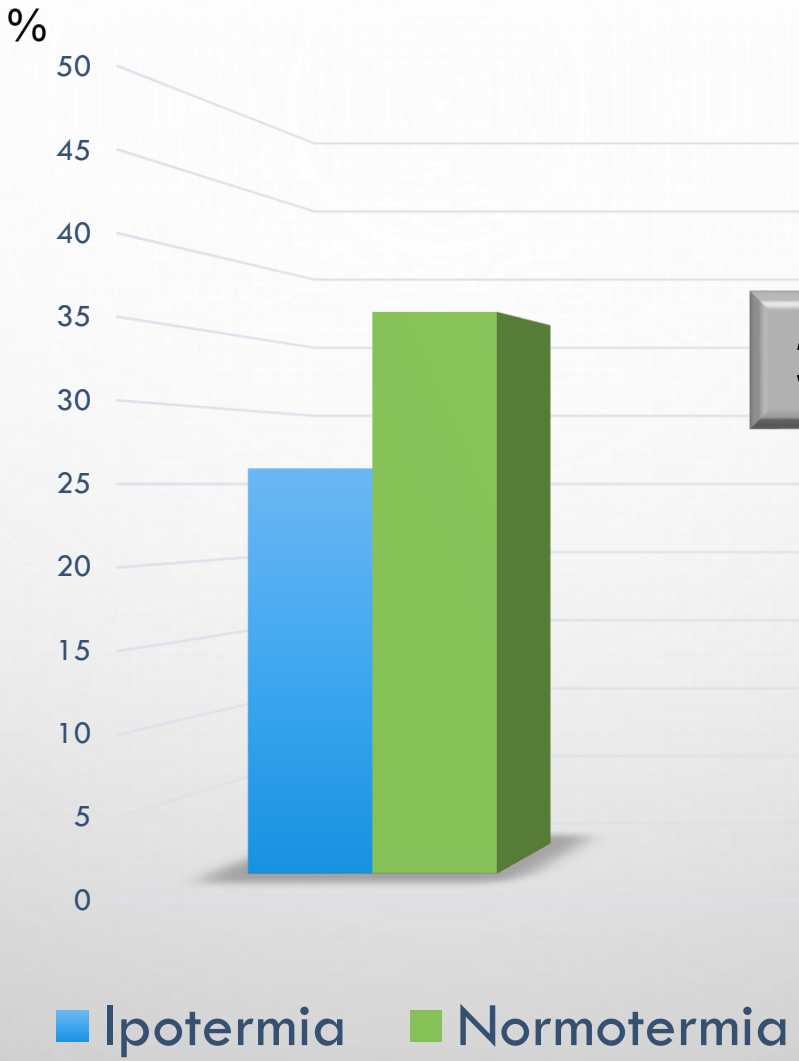
# GOS-E 5-8




**387 pazienti**

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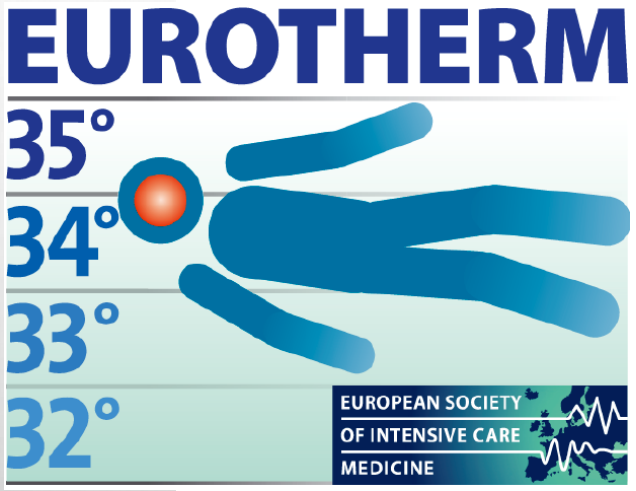


**Stage 1**

**Traumatic Brain Injury**

Stage 1 treatment:
- Admission to ICU
- Mechanical ventilation
- Sedation
- Analgesia with or without paralysis
- Head of bed elevated to 30 degrees
- Intravenous fluids with or without inotropes to maintain mean arterial pressure ≥80 mm Hg

Stage 1 options:
- Ventriculostomy with or without CSF drainage
- Surgical removal of space-occupying lesions

↓

Intracranial pressure >20 mm Hg within 10 days after injury
for at least 5 minutes

↓

**Stage 2**

**Control Group**

Continue stage 1 treatments and add stage 2 treatments without therapeutic hypothermia

Stage 2 treatment:
- Mannitol (maintain serum osmolarity <315 mOsm per kilogram of water)
- Hypertonic saline (avoid in hyponatremia, caution with cardiac or pulmonary problems)
- Inotropes to maintain cerebral perfusion pressure ≥60 mm Hg

Barbiturates not permitted

**Hypothermia Group**

Continue stage 1 treatments and initiate hypothermia

Add stage 2 treatments only if needed

Barbiturates not permitted


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# EFFETTI COLLATERALI

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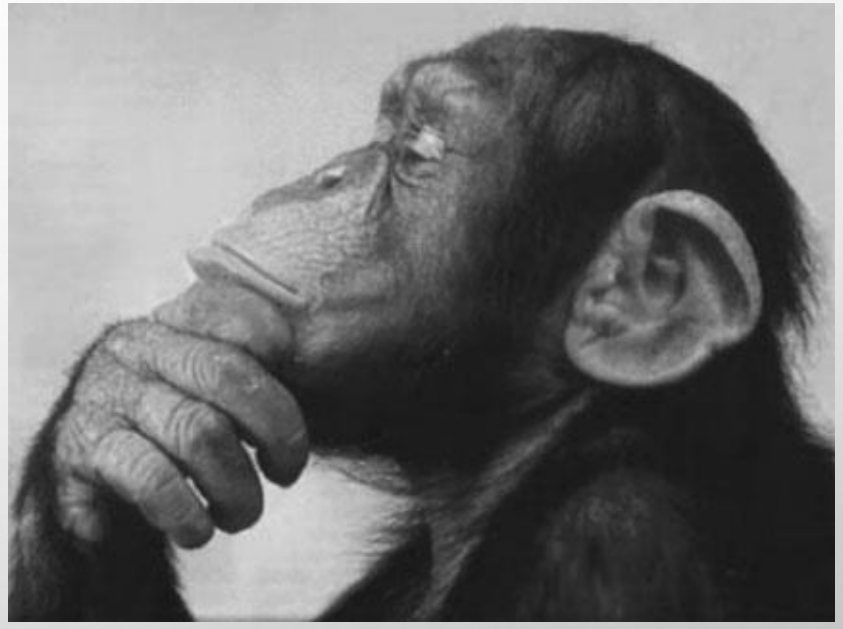

- Infezioni
- Ipovolemia
- Brivido
- Necessità di curarizzazione
- Riscaldamento

# Prevenibili ?

# INFEZIONI ED IPOTERMIA

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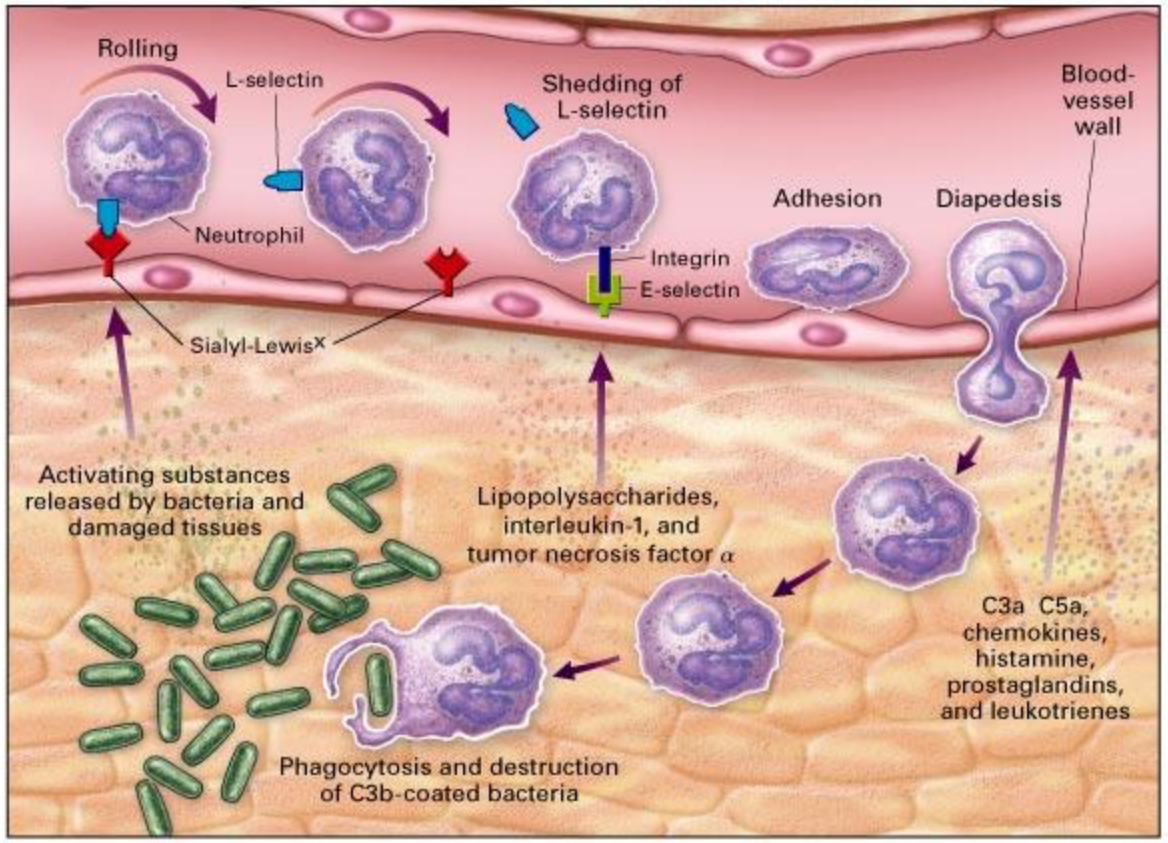
- Inibizione della secrezione delle citochine proinfiammatorie
- Sopprime la migrazione leucocitaria e la fagocitosi
- Aumenta la resistenza periferica tissutale all'insulina



# POLMONITI

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| Study or Subgroup | Hypothermia group Events | Total | Normothermia group Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Clifton 1993 | 11 | 24 | 9 | 22 | 9.0% | 1.12 [0.58, 2.18] |
| Clifton 2011 | 29 | 52 | 31 | 45 | 13.9% | 0.81 [0.59, 1.11] |
| Gal 2002 | 5 | 15 | 4 | 15 | 5.0% | 1.25 [0.41, 3.77] |
| Hashiguchi 2003 | 8 | 9 | 2 | 8 | 4.3% | 3.56 [1.05, 12.07] |
| Jiang 2000 | 16 | 43 | 14 | 44 | 10.0% | 1.17 [0.65, 2.09] |
| Lee 2010 | 8 | 15 | 9 | 16 | 9.3% | 0.95 [0.50, 1.80] |
| Maekawa 2015 | 3 | 98 | 1 | 50 | 1.6% | 1.53 [0.16, 14.34] |
| Qiu 2005 | 26 | 43 | 14 | 43 | 11.3% | 1.86 [1.13, 3.04] |
| Qiu 2006 | 15 | 45 | 7 | 45 | 7.5% | 2.14 [0.97, 4.75] |
| Qiu 2007 | 23 | 40 | 13 | 40 | 10.9% | 1.77 [1.05, 2.98] |
| Shiozaki 1993 | 9 | 16 | 6 | 17 | 7.7% | 1.59 [0.73, 3.46] |
| Shiozaki 1999 | 5 | 8 | 1 | 8 | 2.1% | 5.00 [0.74, 33.78] |
| Shiozaki 2001 | 21 | 43 | 6 | 40 | 7.5% | 3.26 [1.46, 7.24] |
| **Total (95% CI)** | | **451** | | **393** | **100.0%** | **1.51 [1.12, 2.03]** |
| Total events | 179 | | 117 | | | |

Heterogeneity: Tau² = 0.14; Chi² = 26.67, df = 12 (P = 0.009); I² = 55%

Test for overall effect: Z = 2.72 (P = 0.006)

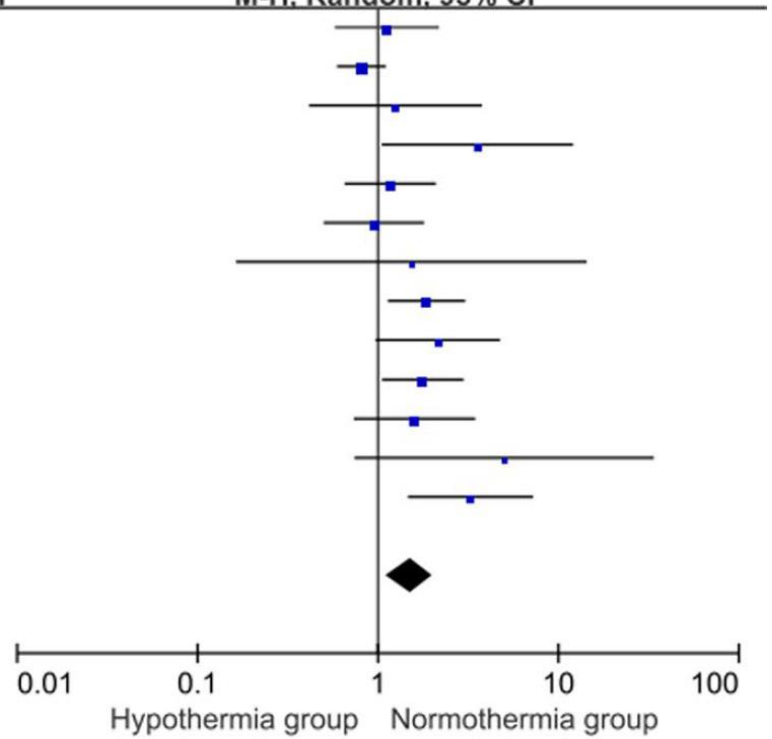


**Fig. 9** Pneumonia complications between the TH and NT groups

Zhu *et al. SpringerPlus (2016) 5:801*
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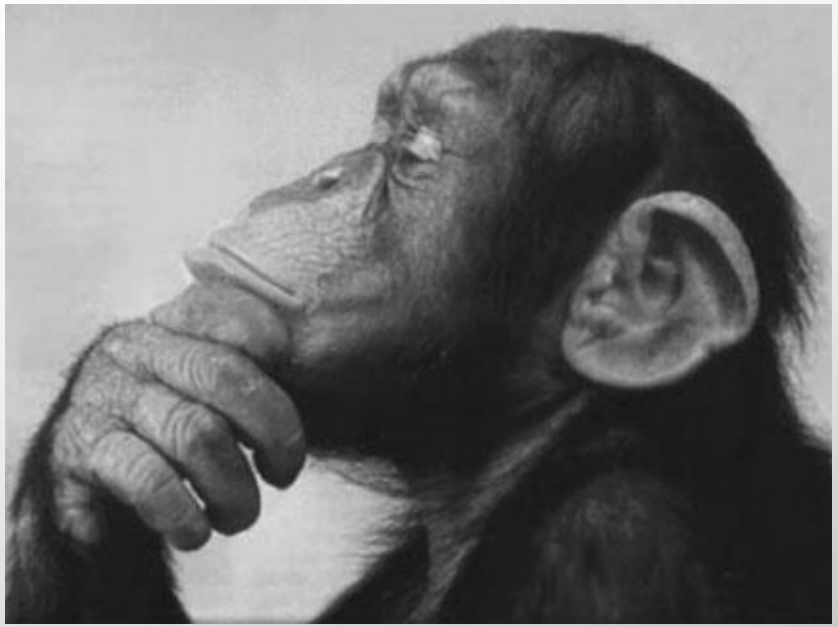
# EFFETTI COLLATERALI

NEURO UPDATE TORINO



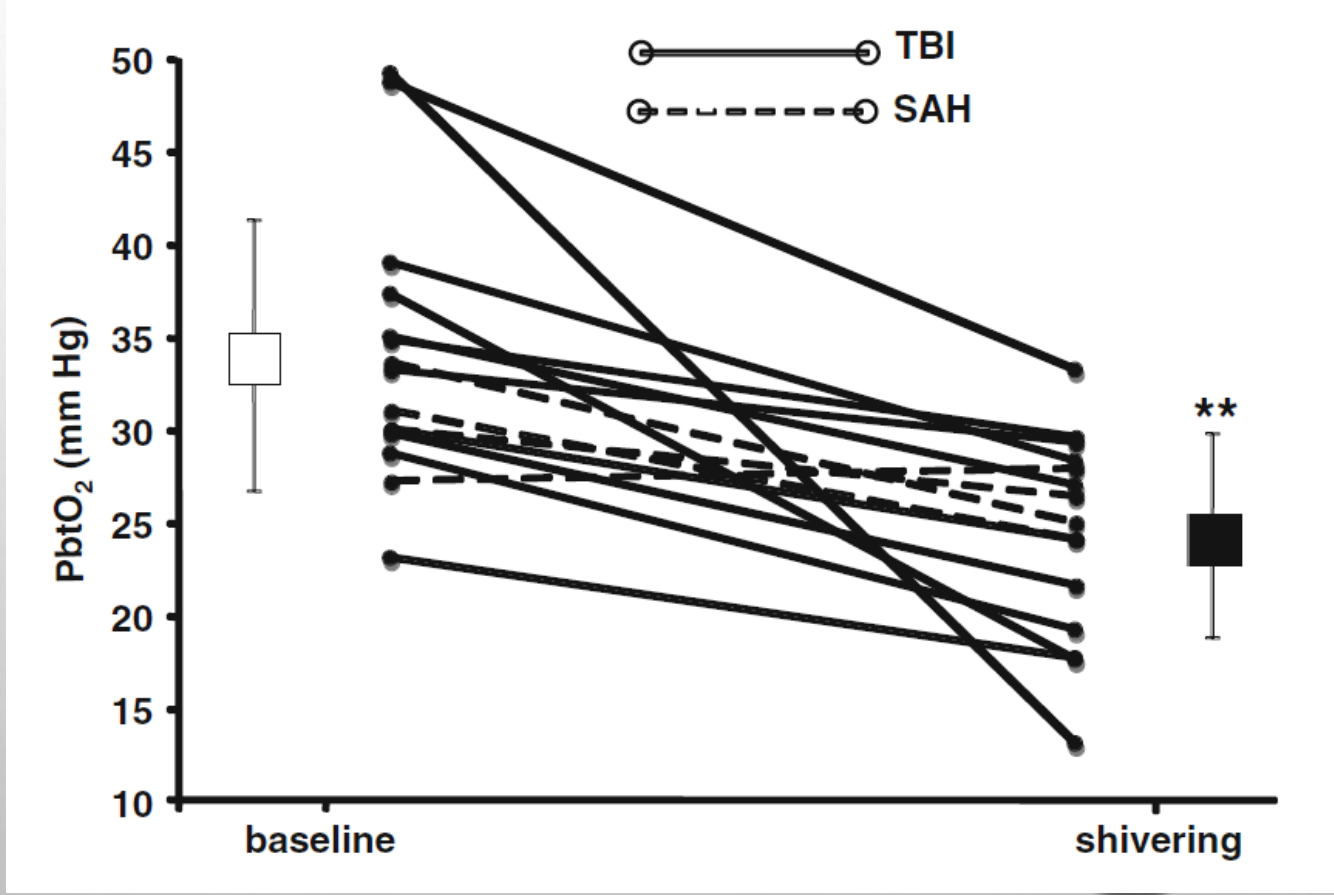
- Infezioni
- Ipovolemia
- Brivido
- Necessità di curarizzazione
- Riscaldamento

# Prevenibili ?

# EFFETTI DEL BRIVIDO SULL'OSSIGENAZIONE CEREBRALE

NEURO UPDATE TORINO

Neurocrit Care (2010) 12:10–1610–16



# TAKE HOME MESSAGE

NEURO UPDATE TORINO

- Assenza di raccomandazioni favorevoli all'impiego dell'ipotermia nel trauma cranico

- Ridurre gli effetti collaterali prevenibili
  - Impiego di sistemi di raffreddamento commerciali ?
  - Ipotermia selettiva ?

- Terapia straordinaria