



**ACTUALITÉS EN RÉANIMATION**  
**Réanimation, Surveillance Continue**  
**et Urgences Graves**

**14 et 15 novembre 2013**

**Cité Centre de Congrès de Lyon**

# **Gestion de la température dans le choc septique**

**Frédérique Schortgen**  
**GH Mondor-APHP-Créteil**

Alexandre le Grand  
mort à Babylone en 323 av. J.-C.



# Éphémérides Royales

Eumène de Cardia

(archigrammate : « premier secrétaire ») d'Alexandre le Grand

Détail des derniers jours du roi  
entre le 15 et le 28 du mois de Dæsius (27 mai au 10  
juin)

## 1<sup>er</sup> Juin

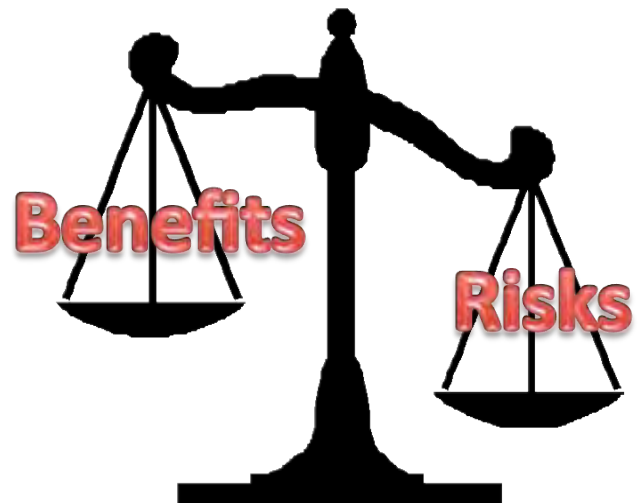
*il prit **un bain** ; après le **bain**, il mangea un peu et dormit dans le lieu même, parce qu'il avait déjà la fièvre. .... Le lendemain, il prit de nouveau **un bain** et fit le sacrifice ordonné. ....il eut la fièvre toute la nuit sans interruption. Le jour suivant, il prit **un bain**, et après ce bain il fit le sacrifice. Couché dans la salle de bains, il passa le temps avec les officiers de Néarque, écoutant ce qu'ils disaient de la navigation et de la grande mer.*

*Le jour suivant, il prit un nouveau **bain**, il fit les sacrifices ordonnés. **Il ne cessa plus d'avoir la fièvre**, et la chaleur fébrile fut plus grande. ...la nuit fut pénible. Le jour suivant, il fut transporté dans la maison située près du grand bassin ; il fit, il est vrai, le sacrifice ordinaire, mais **il avait beaucoup de fièvre**. Il resta couché ;*

## 18 Juin

*même état, et le lendemain **le roi mourut vers le soir**.*

# Fever control



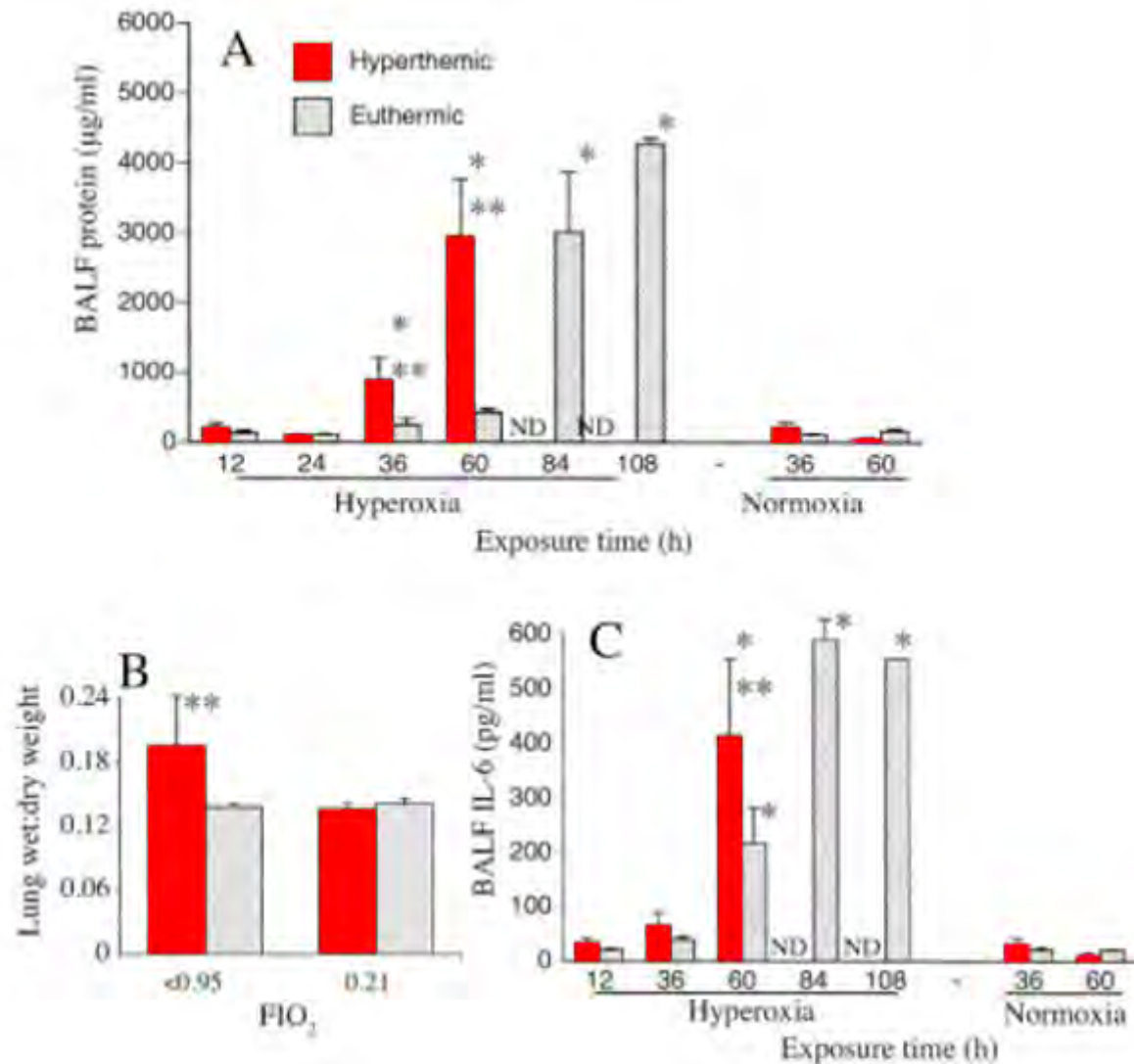
# Rôle de la fièvre dans le control de l'infection: Les risques

➤ La fièvre est pro inflammatoire

# Febrile-Range Hyperthermia Augments Pulmonary Neutrophil Recruitment and Amplifies Pulmonary Oxygen Toxicity

Jeffrey D. Hasday

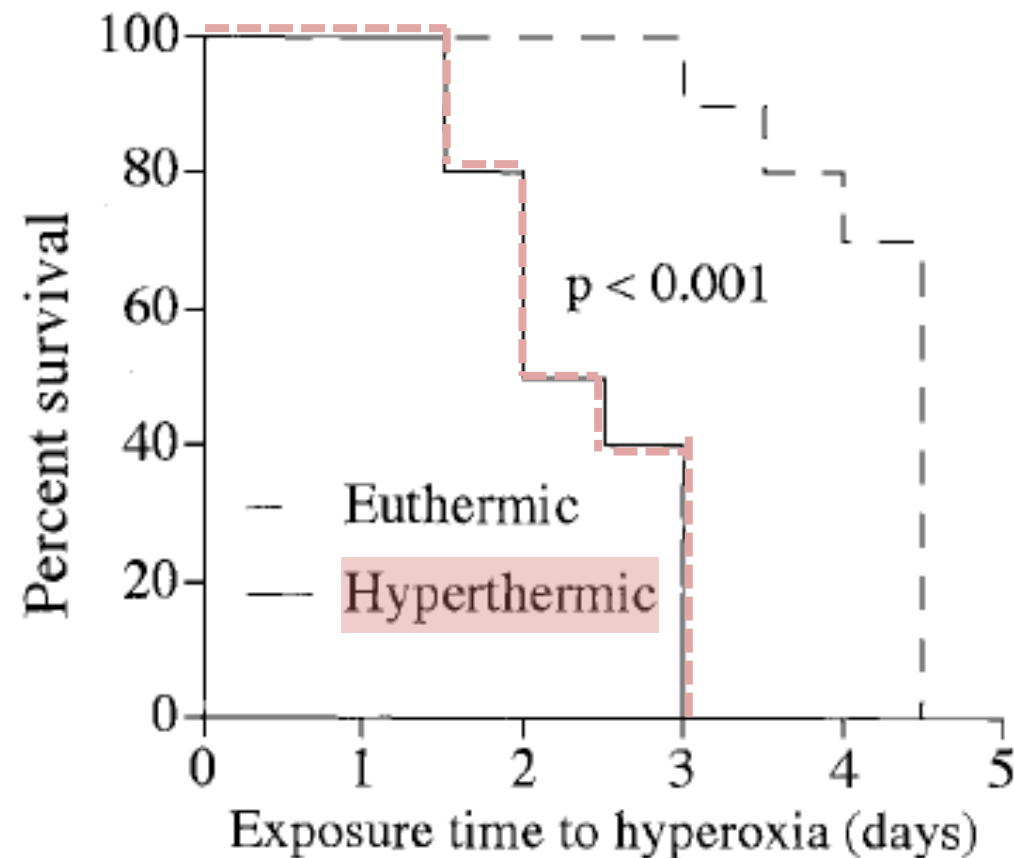
*American Journal of Pathology, Vol. 162, No. 6, June 2003*



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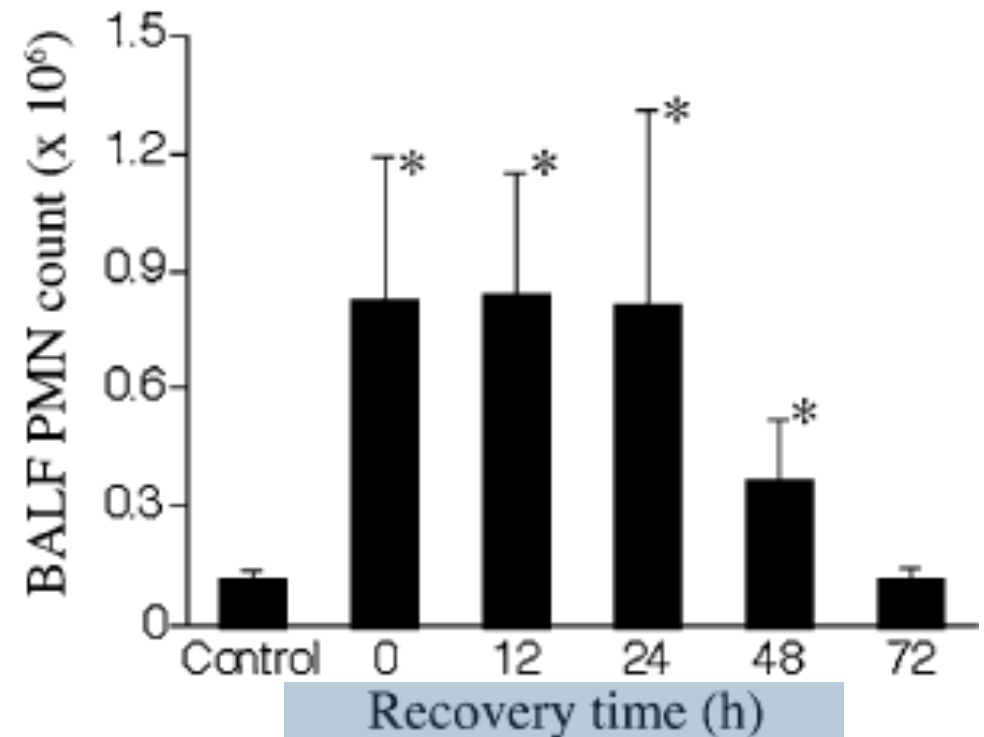
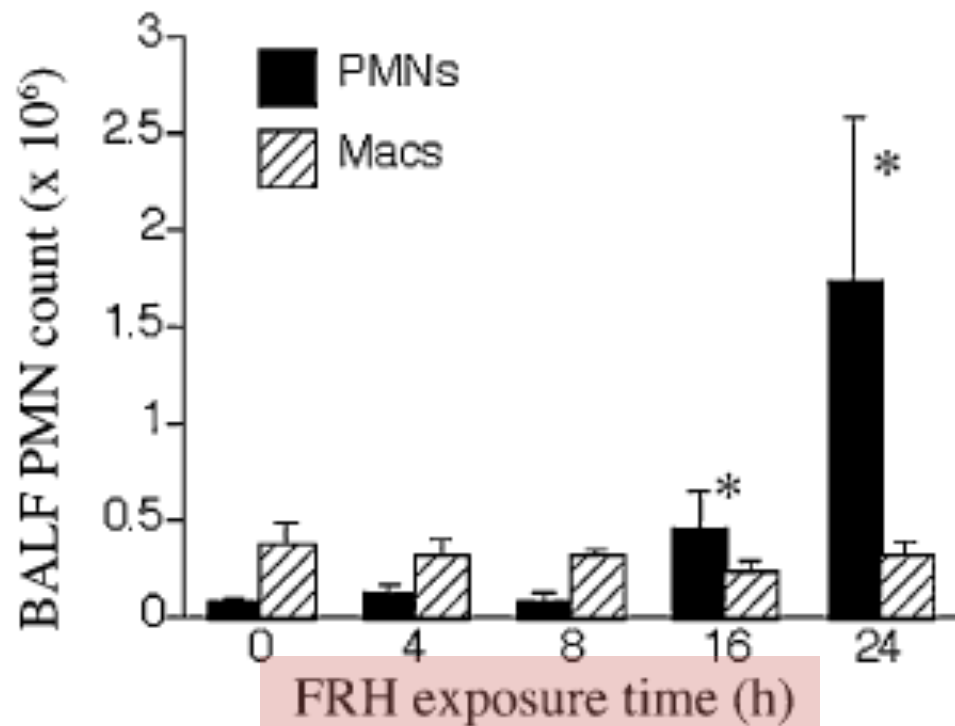
*American Journal of Pathology, Vol. 162, No. 6, June 2003*



# Febrile-Range Hyperthermia Modifies Endothelial and Neutrophilic Functions to Promote Extravasation

Mohan E. Tulapurkar<sup>1,2\*</sup>, Eid A. Almutairy<sup>1\*</sup>, Nirav G. Shah<sup>1</sup>, Ju-ren He<sup>1,5</sup>, Adam C. Puche<sup>4</sup>, Paul Shapiro<sup>3</sup>, Ishwar S. Singh<sup>1,2,5</sup>, and Jeffrey D. Hasday<sup>1,2,5</sup>

## More body temperature more lung inflammation



Core temperature was maintained at approximately 39.5°C

# Rôle de la fièvre dans le control de l'infection: Les bénéfiques

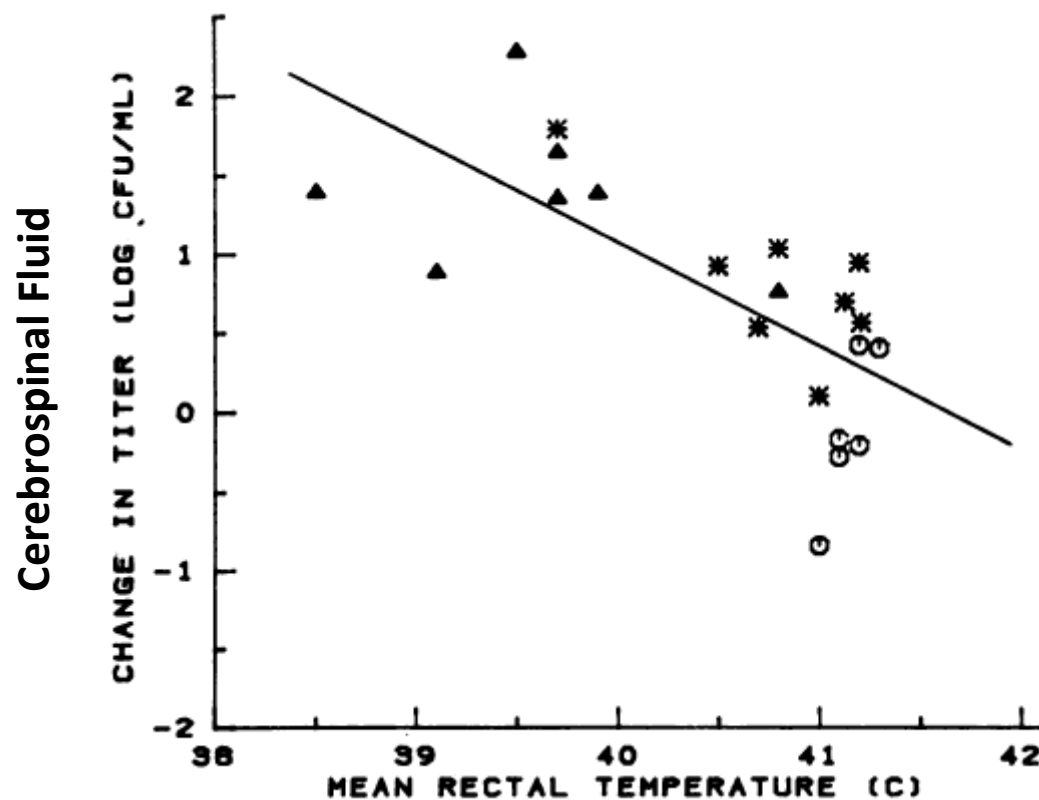
- La fièvre inhibe la replication virale et la croissance bacterienne
- La fièvre stimule les défenses immunitaires



## Influence of Body Temperature on Bacterial Growth Rates in Experimental Pneumococcal Meningitis in Rabbits

P. M. SMALL, M. G. TÄUBER,† C. J. HACKBARTH, AND M. A. SANDE\*

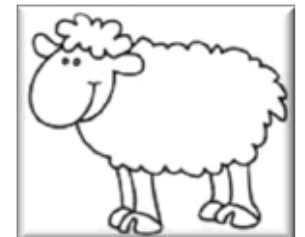
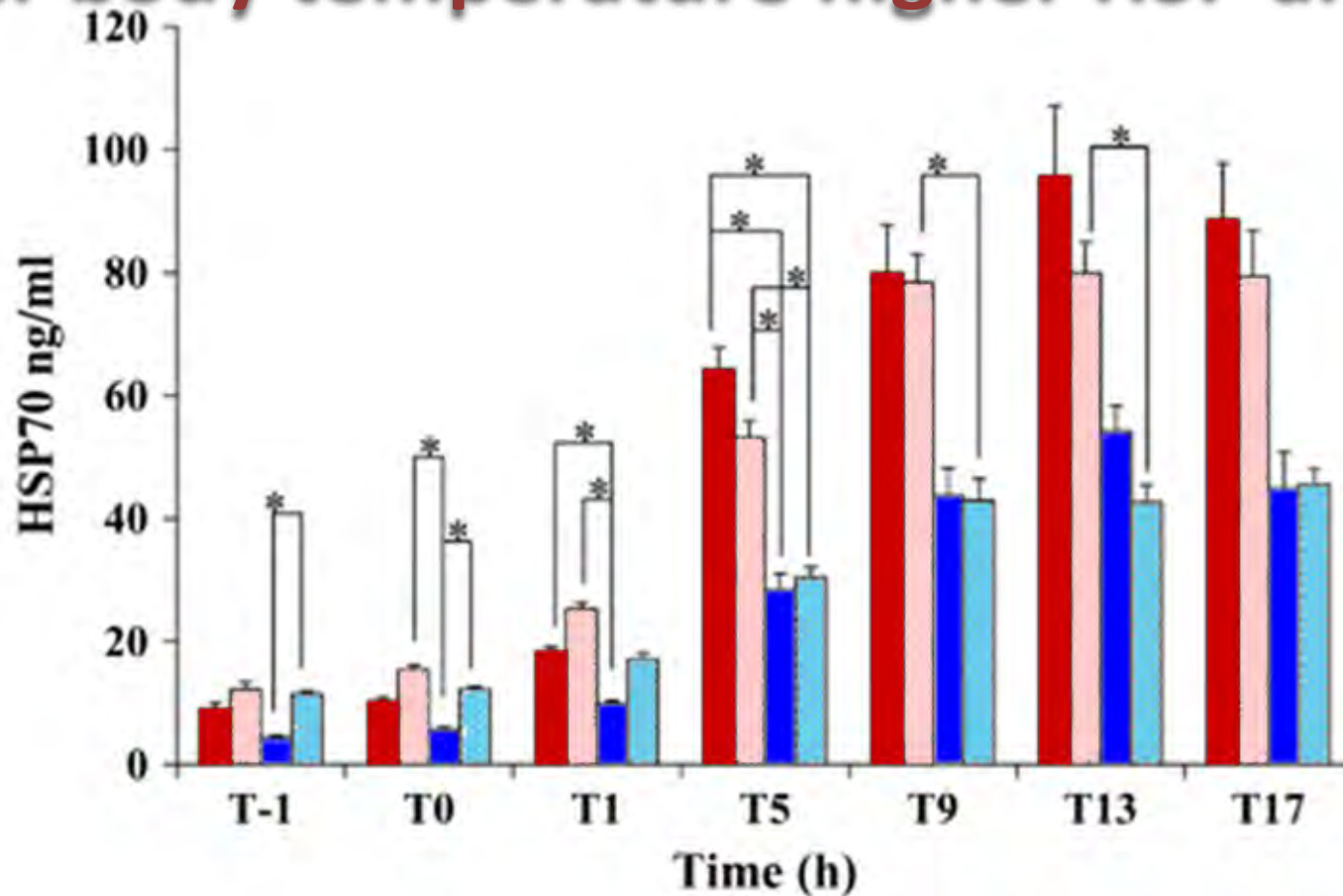
**Higher body temperature lower bacterial load**



## FEVER CONTROL IN SEPTIC SHOCK: BENEFICIAL OR HARMFUL?

Fuhong Su,<sup>\*</sup> Nam Duc Nguyen,<sup>†</sup> Zhen Wang,<sup>\*</sup> Ying Cai,<sup>‡</sup> Peter Rogiers,<sup>§</sup>  
and Jean-Louis Vincent<sup>\*</sup>

# Higher body temperature higher HSP and survival



# Fievre et inflammation bon ou mauvais?

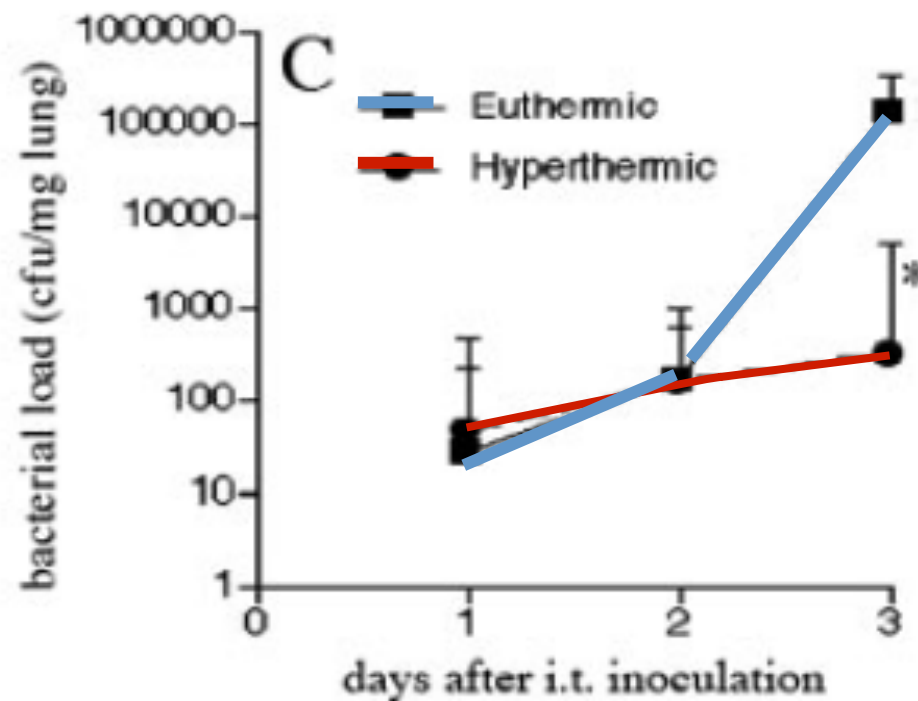


# Fever & inflammation good or bad?

## Febrile-Range Hyperthermia Augments Neutrophil Accumulation and Enhances Lung Injury in Experimental Gram-Negative Bacterial Pneumonia<sup>1</sup>

Penelope Rice,\* Erica Martin,\* Ju-Ren He,\* Mariah Frank,\* Louis DeTolla,† Lisa Hester,\*‡ Timothy O'Neill,† Cheu Manka,\* Ivor Benjamin,|| Ashish Nagarsekar,\* Ishwar Singh,\*‡|| and Jeffrey D. Hasday<sup>2,\*†‡§||</sup>

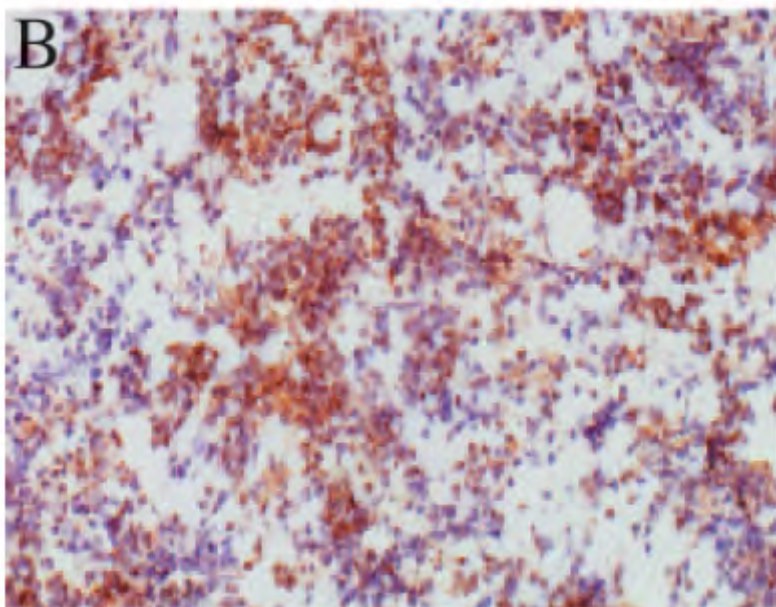
*Journal of Immunology*, 2005, 174: 3676–3685.



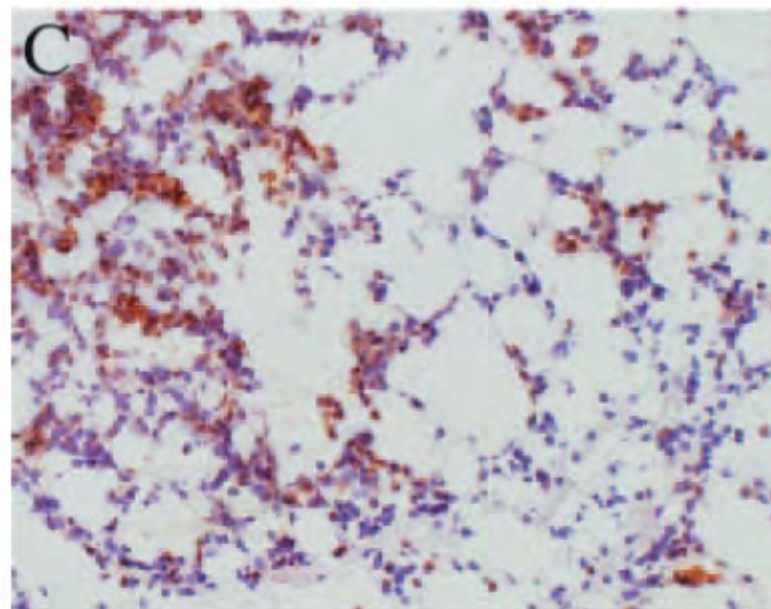
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## Lung histology



Hyperthermic

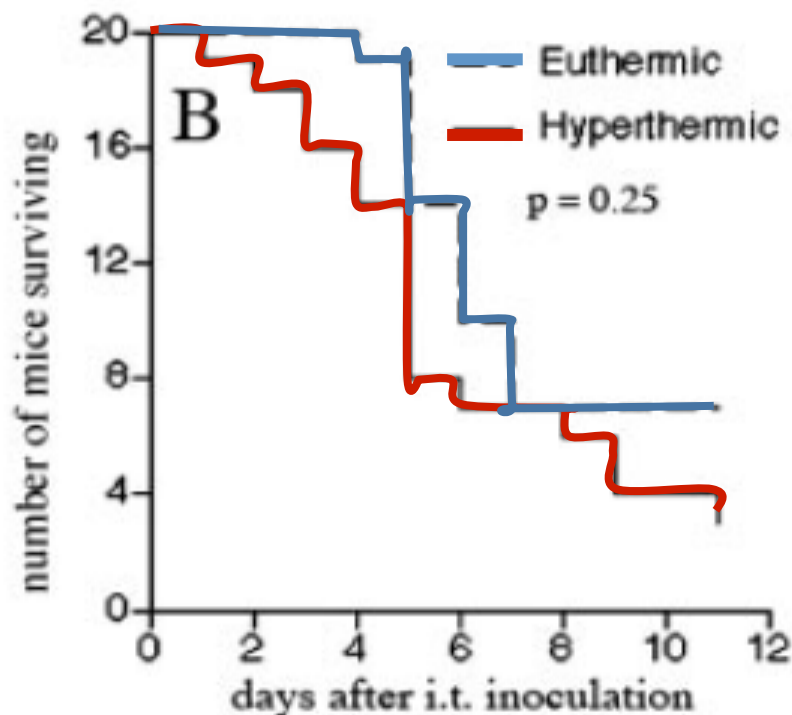


Euhermic

More bacterial load  
but less inflammation

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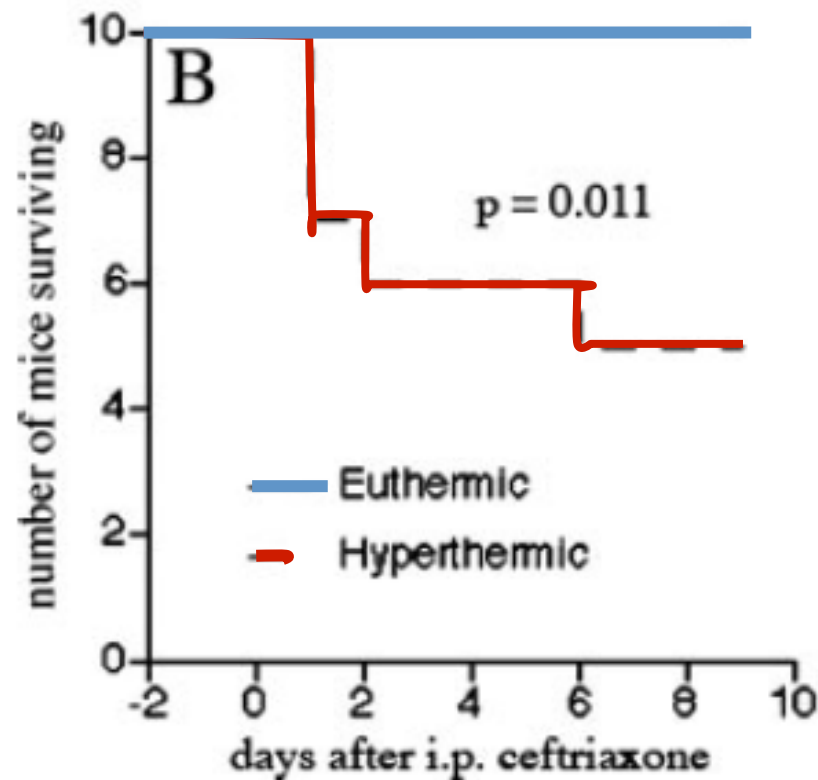


More bacterial load/less inflammation

Less bacterial load/more inflammation

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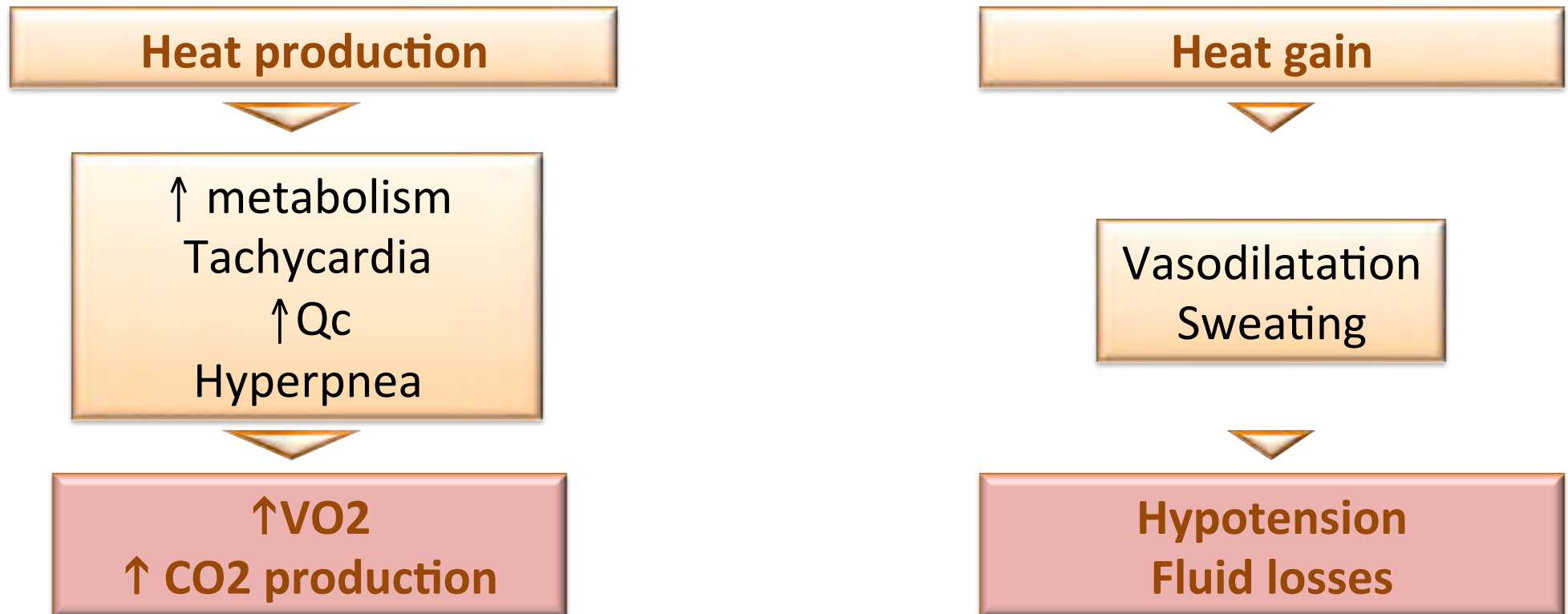
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Fever control is beneficial when bacterial load is controlled by antibiotics



# Les risques de la fièvre sur l'hémodynamique:



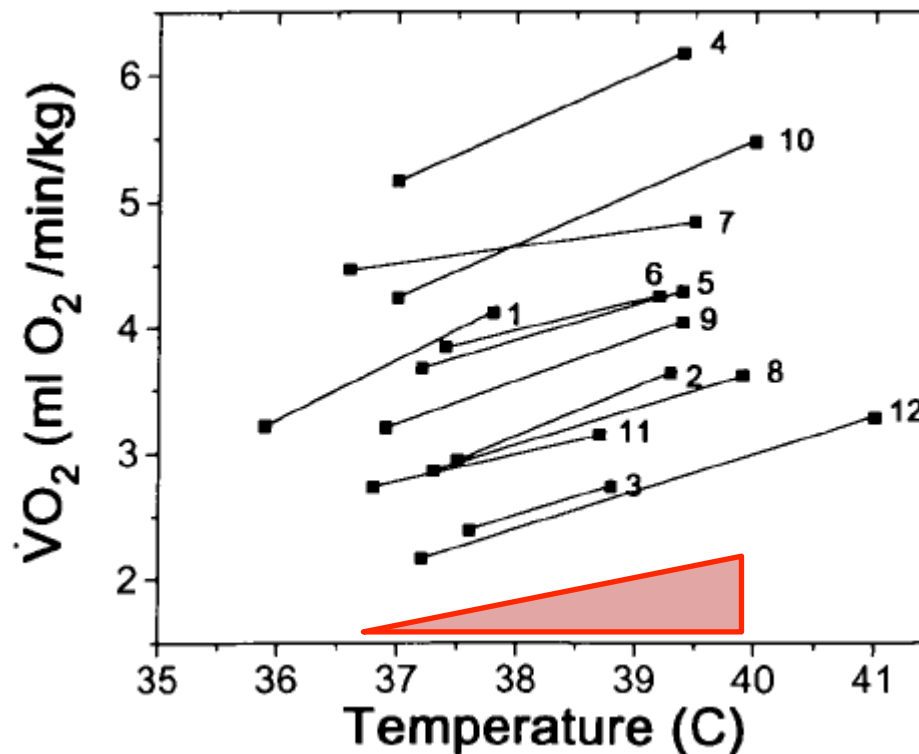


# Effect of Cooling on Oxygen Consumption in Febrile Critically Ill Patients

Am J Respir Crit Care Med Vol 151. pp 10-14, 1995

CONSTANTINE A. MANTHOUS, JESSE B. HALL, DAVID OLSON, M. SINGH, WISAM CHATILA, ANNE POHLMAN, ROBERT KUSHNER, GREGORY A. SCHMIDT, and LAWRENCE D. H. WOOD

In the absence of shivering!



Mean ± SD    %  $\Delta\dot{V}O_2/^\circ\text{C}$     9.7 ± 3.4

**Contrôle de la température dans le  
choc septique:  
Par quelle méthode?**

## Metabolic effects of i.v. propacetamol, metamizol or external cooling in critically ill febrile sedated patients

*British Journal of Anaesthesia* 1997; 78: 123–127

B. POBLETE, J.-A. ROMAND, C. PICHARD, P. KÖNIG AND P. M. SUTER

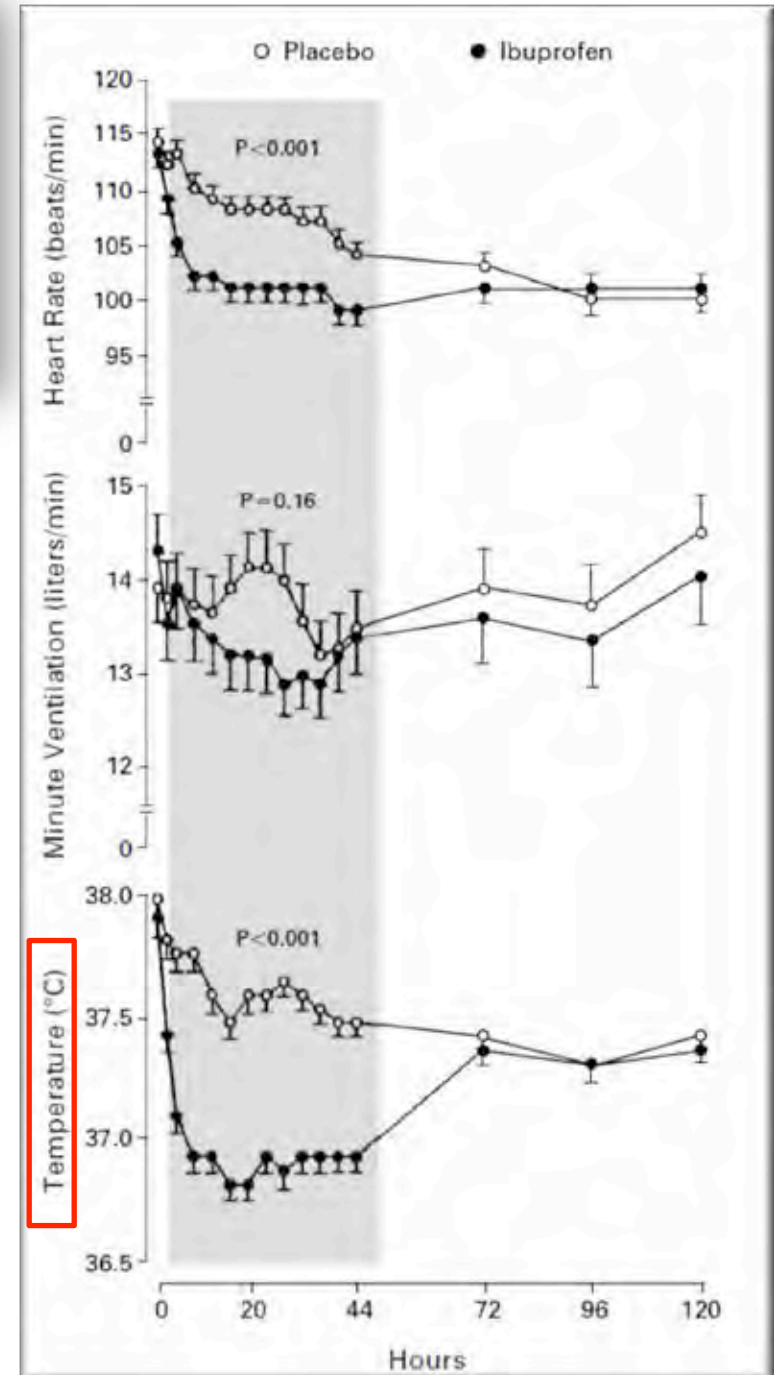
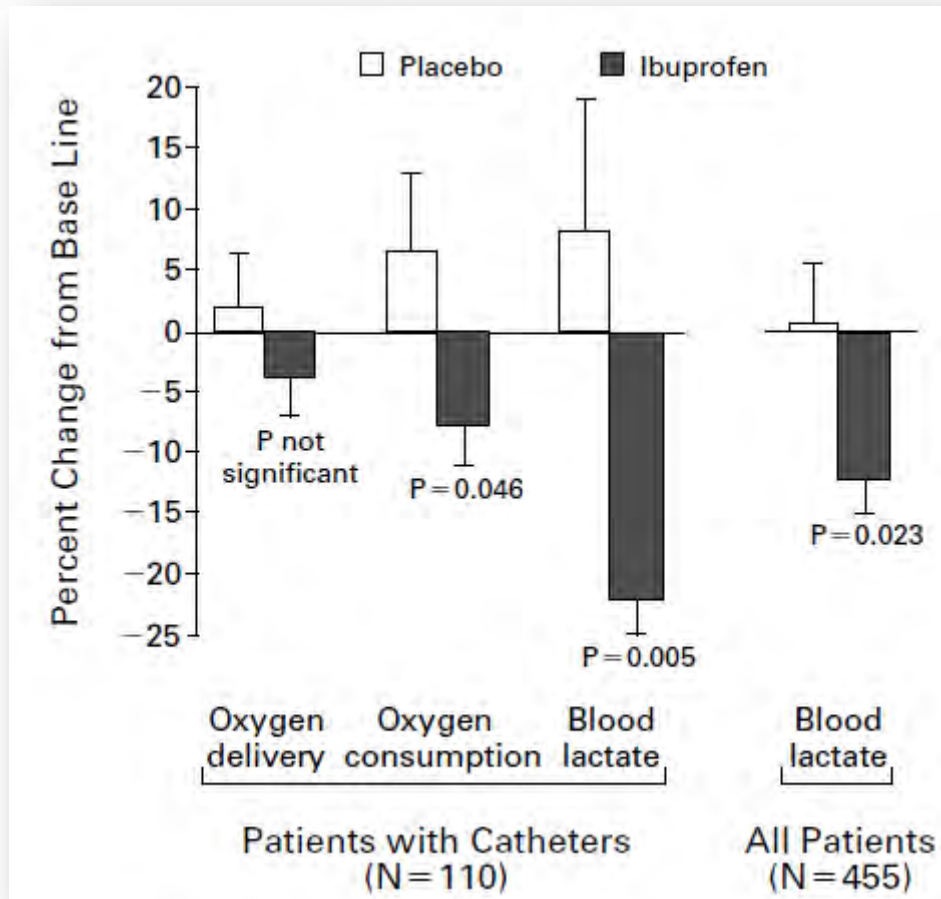
### Before/After fever treatment (1h)

Method		T (°C)	HR (beat min <sup>-1</sup> )	MAP (mm Hg)	EE (kcal day <sup>-1</sup> )	$\dot{V}O_2$ (ml min <sup>-1</sup> )	$\dot{V}CO_2$ (ml min <sup>-1</sup> )
Propacetamol (n = 11)	Baseline	39.2 (0.2)	117 (5)	79 (5)	1974 (76)	286 (13)	258 (14)
	After treatment	39.2 (0.2)	114 (5)	79 (5)	2009 (85)	287 (12)	260 (16)
	% Baseline				1.8 (1.8)	0.6 (2.1)	0.6 (1.8)
Metamizol (n = 12)	Baseline	38.9 (0.2)	118 (4)	79 (4)	2006 (90)	285 (13)	262 (14)
	After treatment	38.5 (0.3)*	112 (4)*	79 (5)	1946 (109)	282 (17)	254 (14)
	% Baseline				-2.9 (4.0)	-1.2 (4.5)	3.0 (1.7)
External cooling (n = 16)	Baseline	39.1 (0.2)	110 (4)	84 (4)	2034 (73)	297 (11)	252 (10)
	After treatment	37.1 (0.2)***	96 (5)***	85 (4)	1791 (88)*	259 (12)*	226 (15)*
	% Baseline				-11.9 (3.5)	-12.6 (3.3)	-10.9 (4.3)

**Under light sedation**  
**No neuromuscular blockers**

### THE EFFECTS OF IBUPROFEN ON THE PHYSIOLOGY AND SURVIVAL OF PATIENTS WITH SEPSIS

GORDON R. BERNARD, M.D., ARTHUR P. WHEELER, M.D., JAMES A. RUSSELL, M.D., ROLAND SCHEIN, M.D., WARREN R. SUMMER, M.D., KENNETH P. STEINBERG, M.D., WILLIAM J. FULKERSON, M.D., PATRICK E. WRIGHT, M.D., BRIAN W. CHRISTMAN, M.D., WILLIAM D. DUPONT, PH.D., STANLEY B. HIGGINS, PH.D., AND BRIDGET B. SWINDELL, R.N., FOR THE IBUPROFEN IN SEPSIS STUDY GROUP\*





**Nonsteroidal Antiinflammatory Drugs May  
Affect the Presentation and Course of  
Community-Acquired Pneumonia**

*Guillaume Voiriot, MD; Sandra Dury, MD; Antoine Parrot, MD; Charles Mayaud, MD;  
and Muriel Fartoukh, MD*

## NSAIDs before hospital admission:

- More pleural effusion
- More cavitations
- More AB days
- Longer LOS

# Paracetamol

## **Does therapeutic use of acetaminophen cause acute liver failure?**

*Dart RC, Bailey E. Pharmacotherapy 2007;27(9):1219-1230.*

## **Paracetamol in therapeutic dosages and acute liver injury: causality assessment in a prospective case series.**

*Sabate M, Ibanez L, Perez E, et al. BMC Gastroenterol 2011;11:80.*

## **Effect of intravenous propacetamol on blood pressure in febrile critically ill patients**

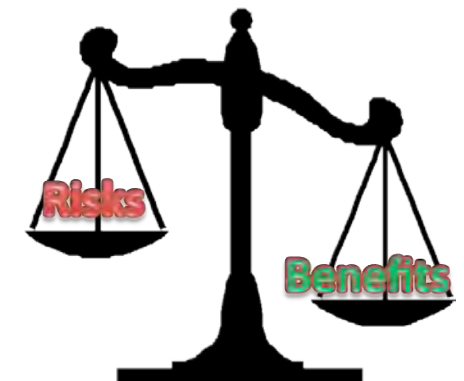
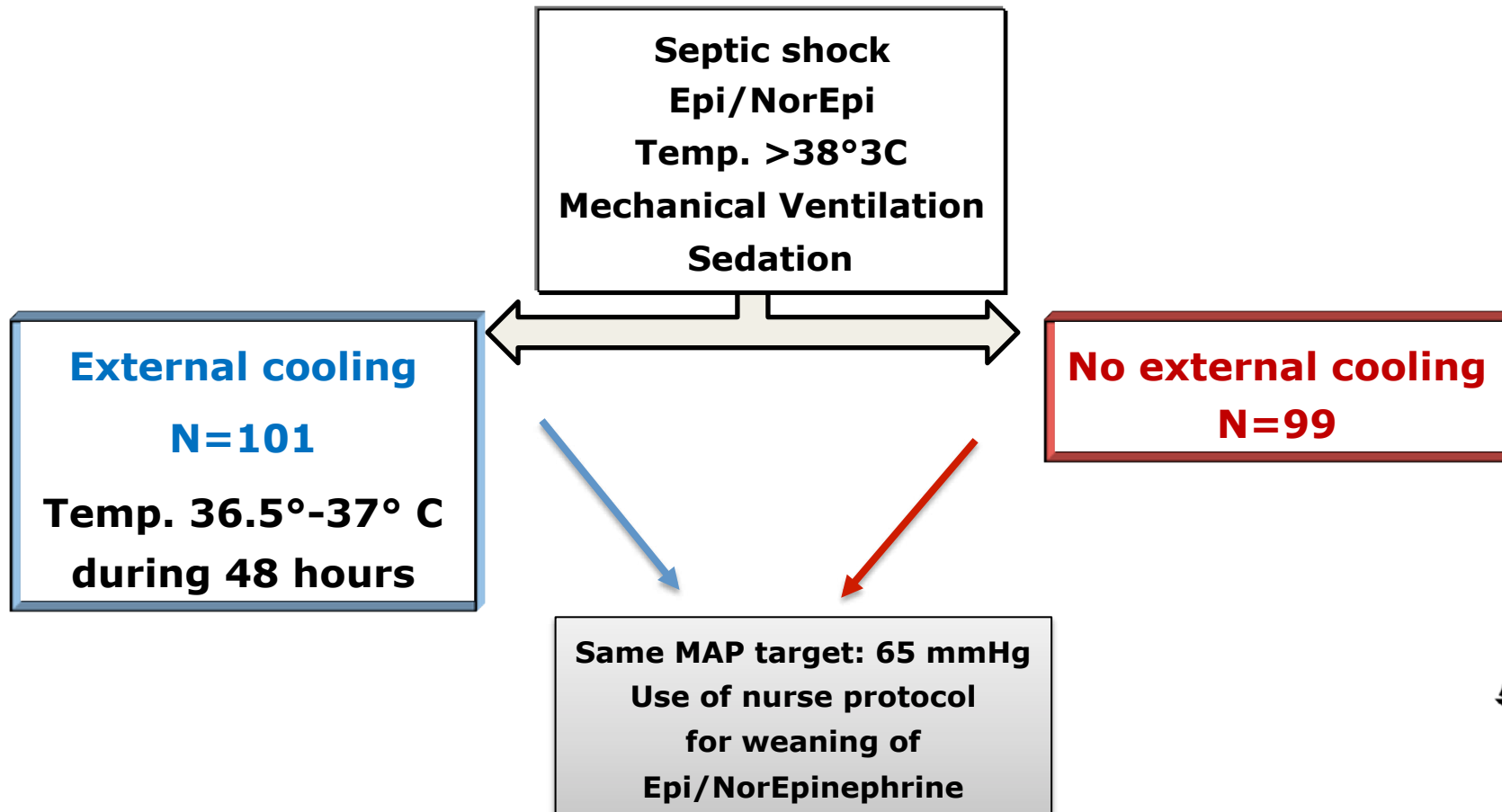
*Hersch M, Raveh D, Izbicki G. Pharmacotherapy 2008;28(10):1205-1210.*

# Fever Control Using External Cooling in Septic Shock

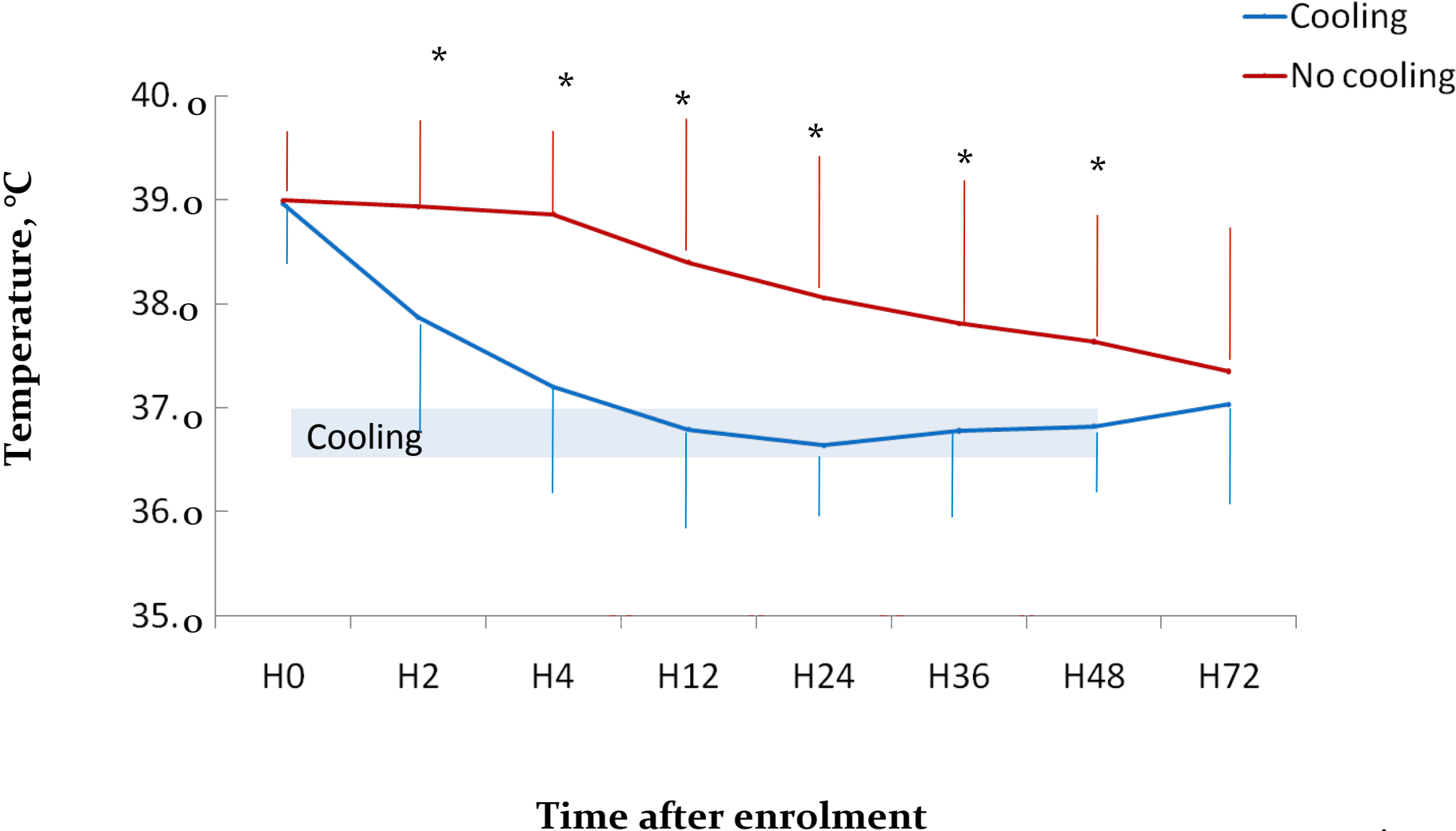
## A Randomized Controlled Trial

Am J Respir Crit Care Med Vol 185, Iss. 10, pp 1088-1095, May 15, 2012

Frédérique Schortgen<sup>1,2</sup>, Karine Clabault<sup>3</sup>, Sandrine Katsahian<sup>4</sup>, Jerome Devaquet<sup>5</sup>,  
Alain Mercat<sup>6</sup>, Nicolas Deye<sup>7</sup>, Jean Dellamonica<sup>8</sup>, Lila Bouadma<sup>9</sup>, Fabrice Cook<sup>10</sup>, Olfa Beji<sup>1</sup>,  
Christian Brun-Buisson<sup>1</sup>, François Lemaire<sup>1</sup>, and Laurent Brochard<sup>1,2,11</sup>



# Body core temperature evolution after inclusion



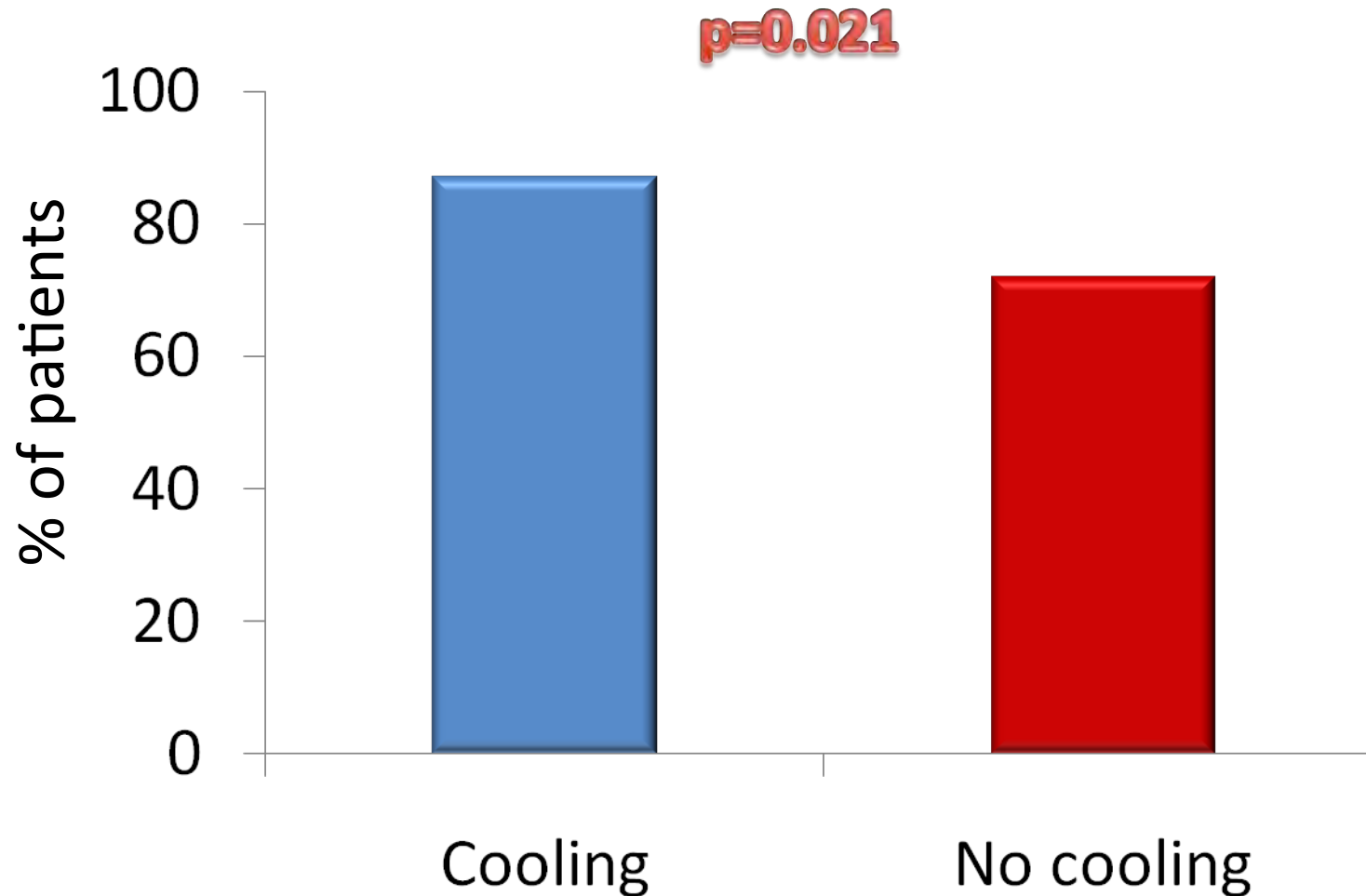
\*  $p < 0.00001$



# Fever Control Using External Cooling in Septic Shock

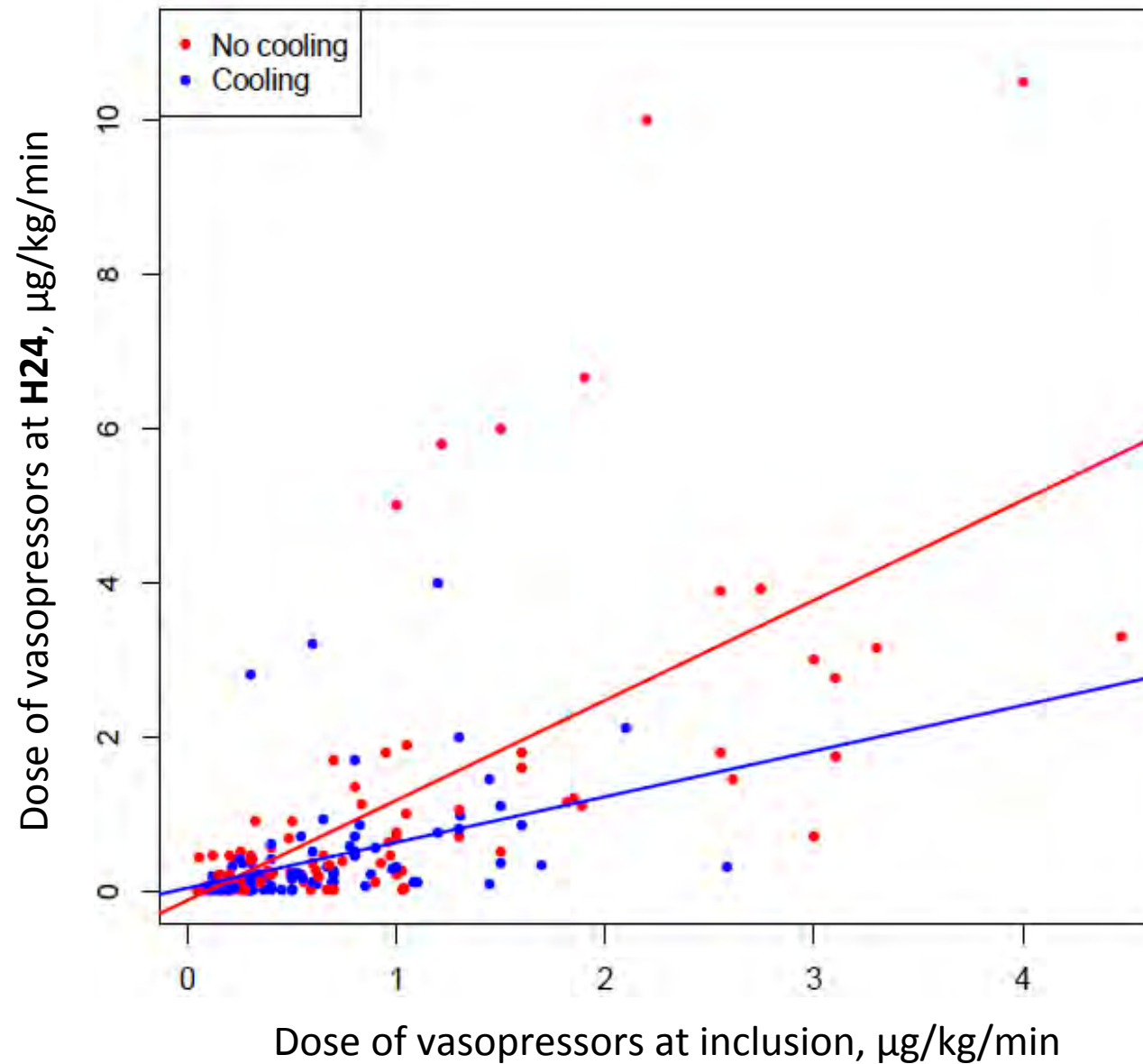
A Randomized Controlled Trial

## Shock reversal in the ICU



# Fever Control Using External Cooling in Septic Shock

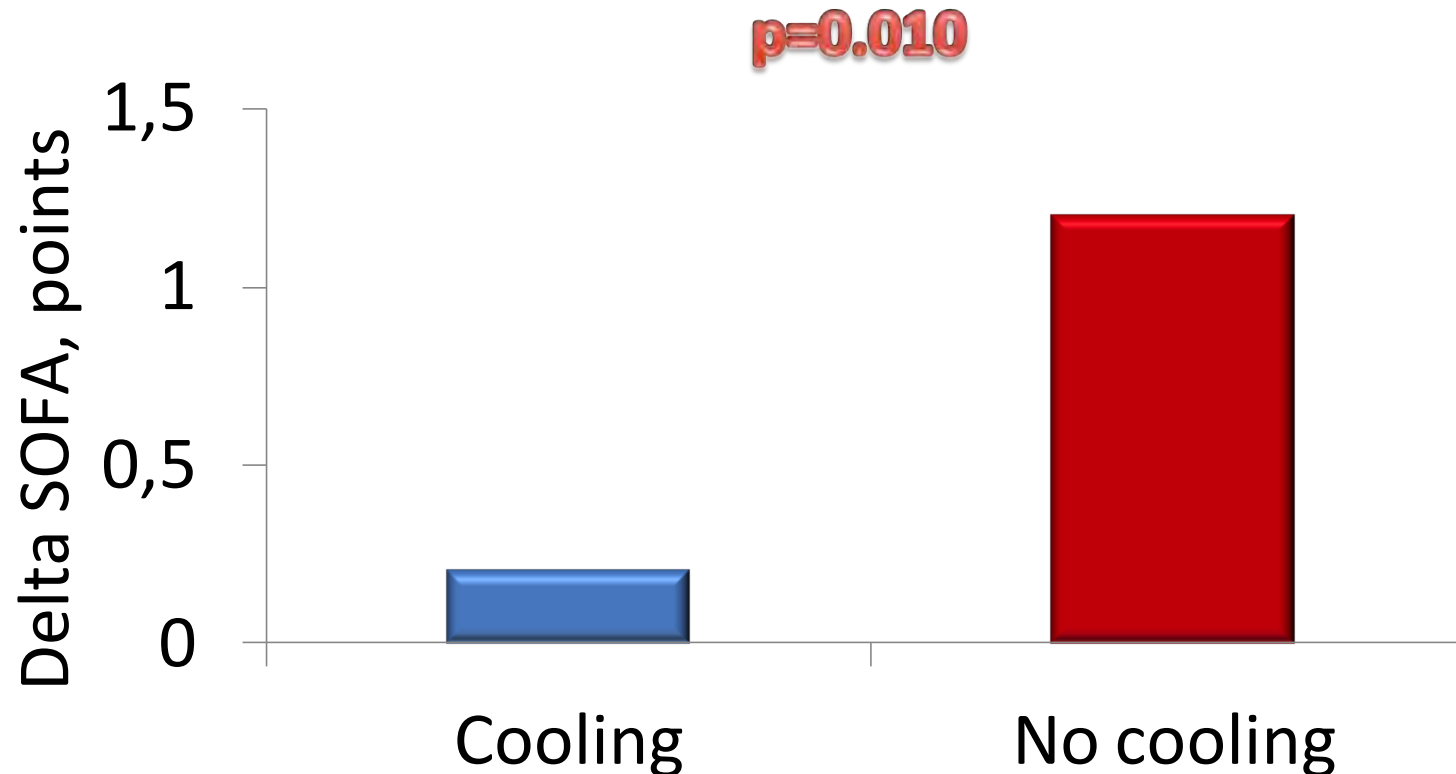
A Randomized Controlled Trial



# Fever Control Using External Cooling in Septic Shock

A Randomized Controlled Trial

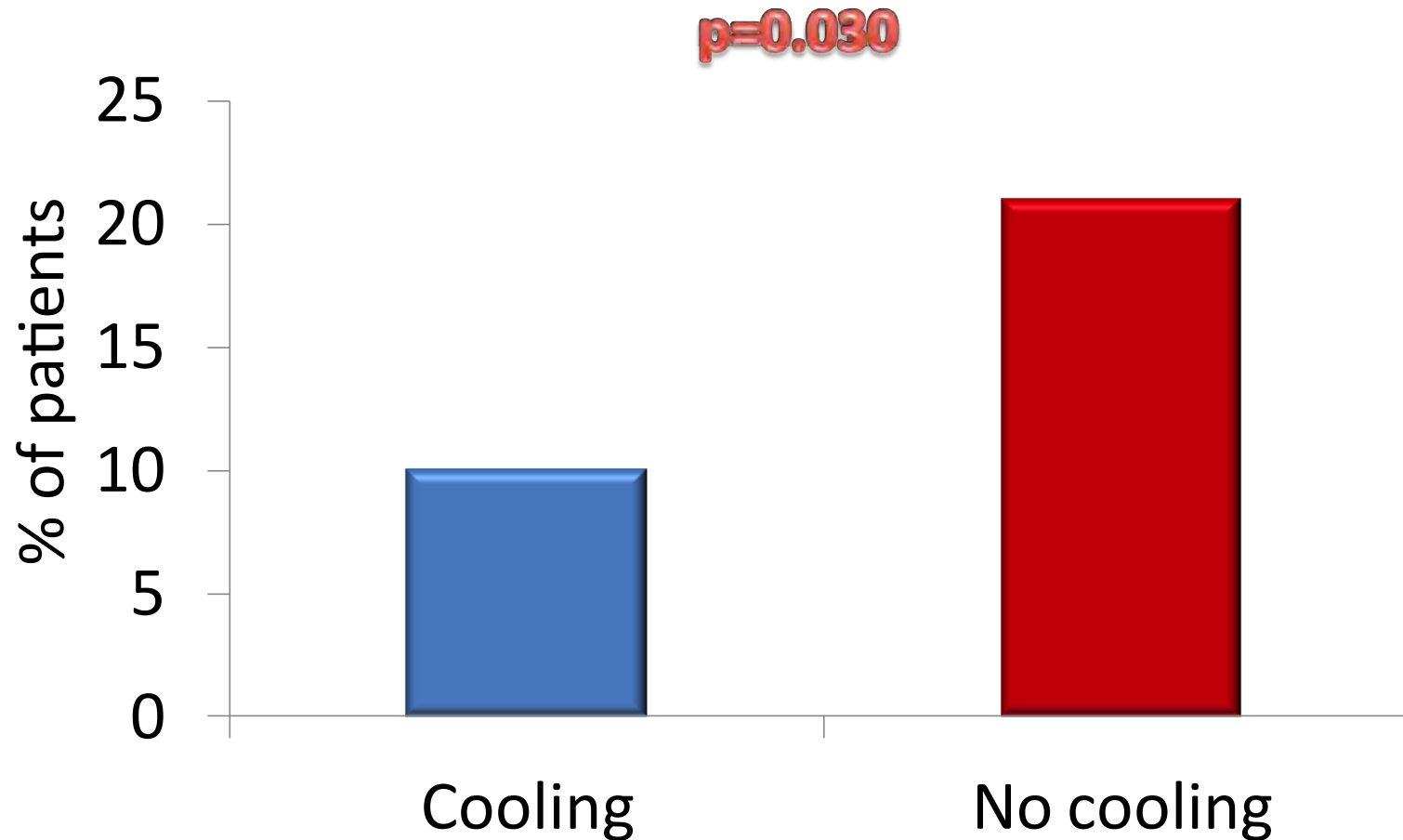
## Evolution of organ failures



# Fever Control Using External Cooling in Septic Shock

A Randomized Controlled Trial

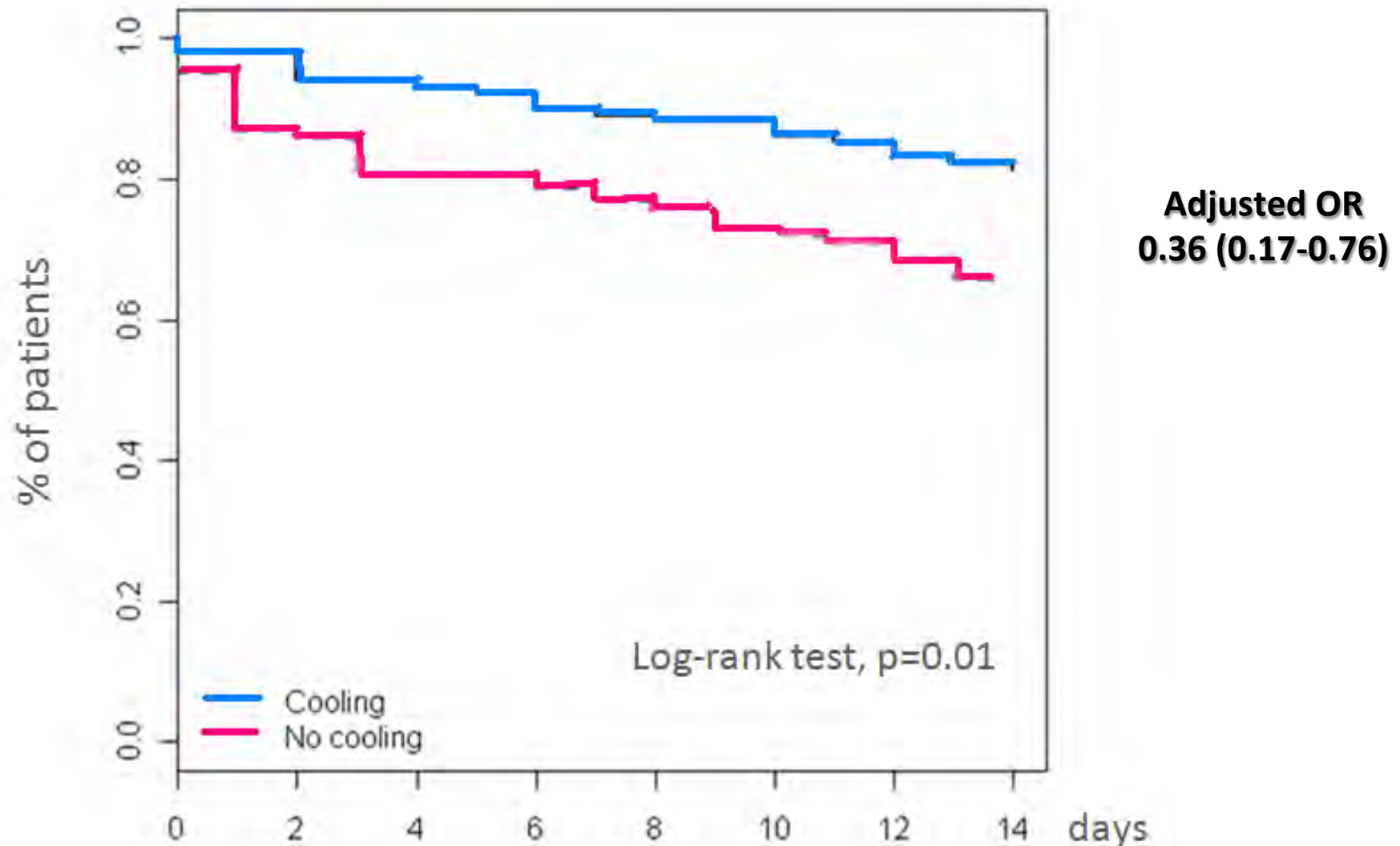
## Need for RRT start



# Fever Control Using External Cooling in Septic Shock

## A Randomized Controlled Trial

### Kaplan-Meier survival curve for mortality until day 14



## Favorable effect of cooling in which type of patients?

Characteristics at inclusion	Cooling N=101	No Cooling N=99
Age, y	62 (51-70)	61 (49-70)
PaO <sub>2</sub> /FIO <sub>2</sub> , mm Hg	165 (106–230)	153 (104–206)
SOFA score, points	11 (9.0-14.0)	11 (9.0-14.0)
ARDS, n	54	45
Source of infection, n		
Pulmonary	71	67
Abdominal	5	8
Uro-genital	4	8
Others	15	13
Not known	5	3
Appropriate antimicrobial therapy, n		
Yes	83	84
No	13	11
Unknown	5	4
Blood lactate level, mmol/l	2.2 (1.3-3.4)	2.4 (1.3-3.5)
Epi and/or nor epinephrine*		
Dose, µg/kg/min	0.50 (0.28-0.80)	0.63 (0.27-1.22)

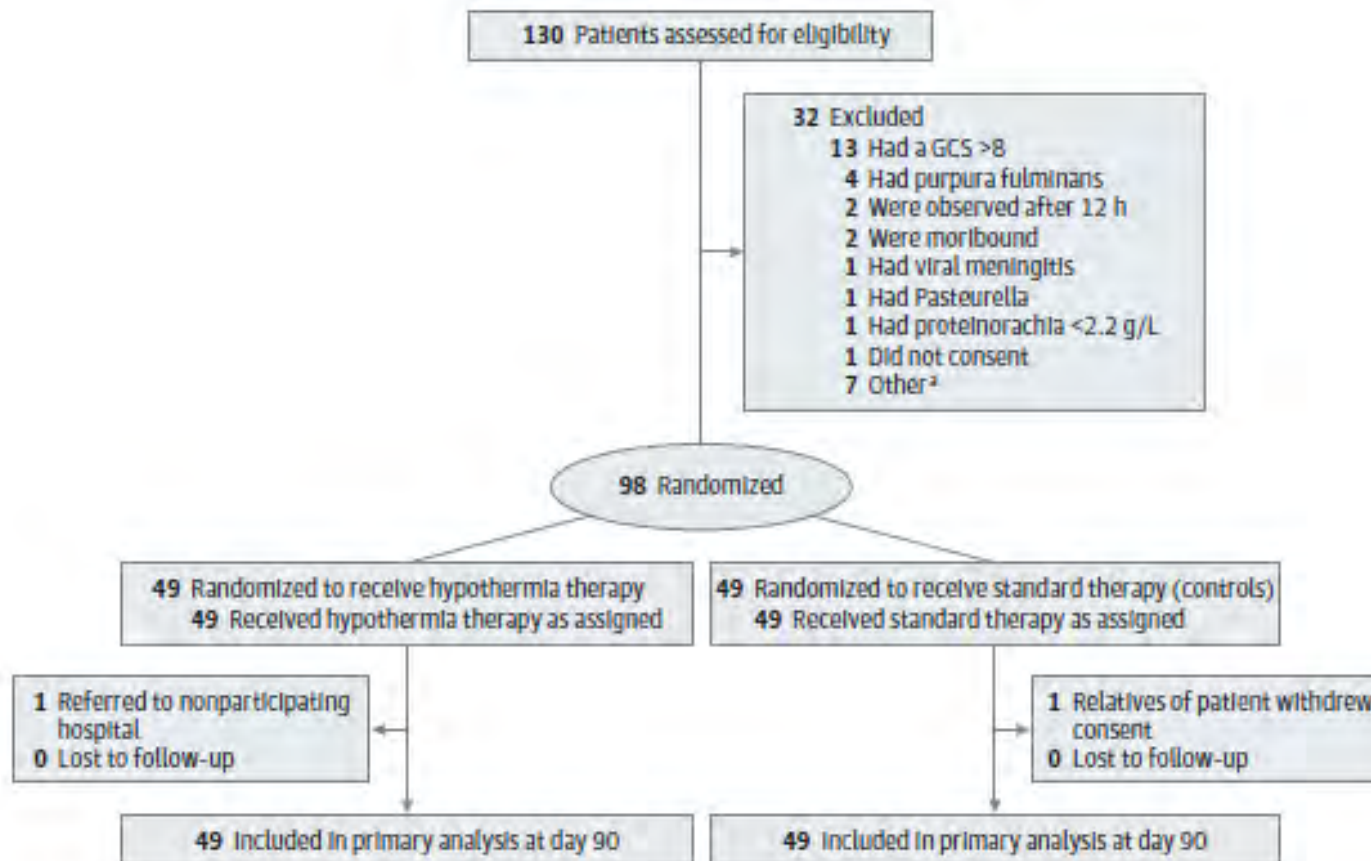
\* p=0.03

# Induced Hypothermia in Severe Bacterial Meningitis

## A Randomized Clinical Trial

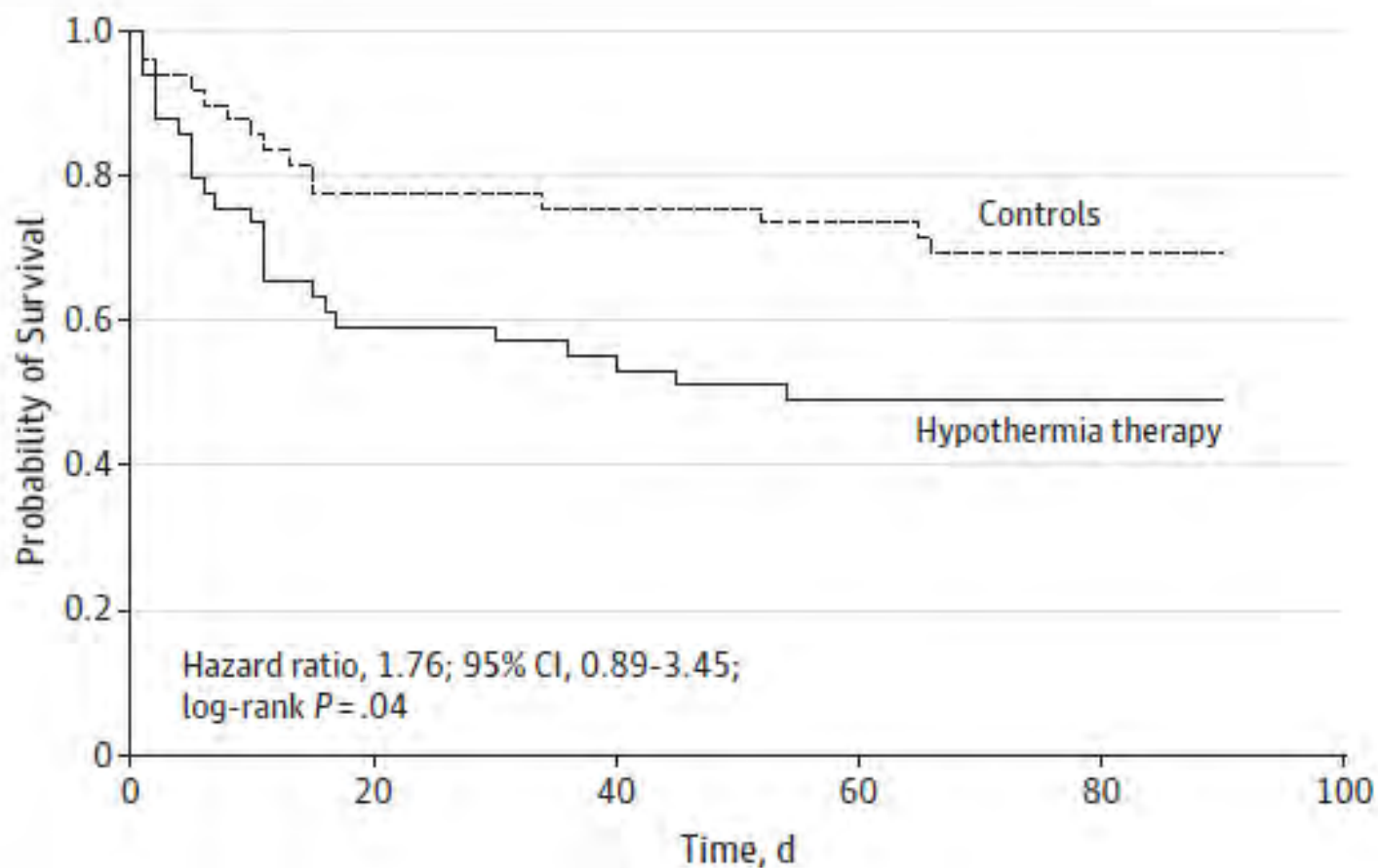
JAMA. doi:10.1001/jama.2013.280506  
Published online October 8, 2013.

Bruno Mourvillier, MD; Florence Tubach, MD, PhD; Diederik van de Beek, MD, PhD; Denis Garot, MD; Nicolas Pichon, MD; Hugues Georges, MD; Laurent Martin Lefevre, MD; Pierre-Edouard Bollaert, MD; Thierry Boulain, MD; David Luis, MD; Alain Cariou, MD; Patrick Girardie, MD; Riad Chelha, MD; Bruno Megarbane, MD, PhD; Arnaud Delahaye, MD; Ludivine Chalumeau-Lemoine, MD; Stéphane Legriel, MD; Pascal Beuret, MD; François Brivet, MD; Cédric Bruel, MD; Fabrice Camou, MD; Delphine Chatellier, MD; Patrick Chillet, MD; Bernard Clair, MD; Jean-Michel Constantin, MD; Alexandre Duguet, MD; Richard Galliot, MD; Frédérique Bayle, MD; Hervé Hyvernat, MD; Kader Ouchenir, MD; Gaetan Plantefevre, MD; Jean-Pierre Quenot, MD; Jack Richecoeur, MD; Carole Schwebel, MD; Michel Sirodot, MD; Marina Esposito-Farèse, PhD; Yves Le Tulzo, MD, PhD; Michel Wolff, MD



# Induced Hypothermia in Severe Bacterial Meningitis A Randomized Clinical Trial

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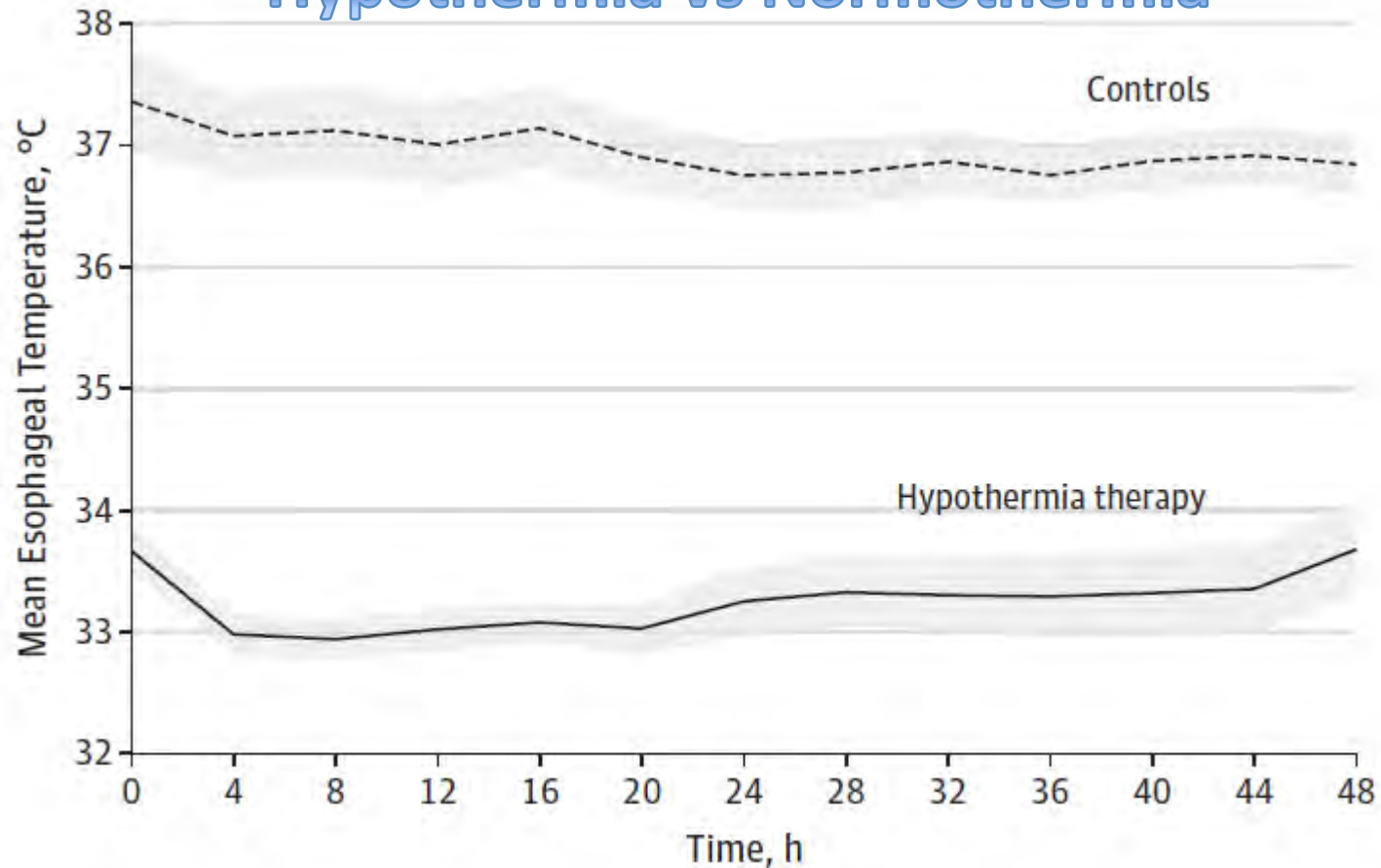


Characteristics	Hypothermia Group (n = 49)	Control Group (n = 49)
Male sex, No. (%)	28 (57)	31 (63)
GCS score on ICU admission, median (IQR), n <sup>a</sup>	7 (4-8)	7 (6-8)
SAPS II score, mean (SD) <sup>b</sup>	57 (16)	53 (17)
SOFA score, mean (SD) <sup>c</sup>	9 (3)	8 (4)
CSF leukocyte count, / $\mu$ L		
Mean (SD)	4747 (9601)	2678 (5457)
Septic shock, No. (%)	18 (37)	10 (20)
Lactate, mean (SD), mg/dL	139.64 (90.09)	144.14 (54.05)
CSF culture results, No. (%)		
<i>Streptococcus pneumoniae</i>	37 (76)	38 (78)
<i>Streptococcus bovis</i>	1 (2)	0
<i>Neisseria meningitidis</i>	2 (4)	6 (12)
<i>Listeria monocytogenes</i>	1 (2)	2 (4)
Enterobacteriaceae	3 (6)	0
<i>Mycobacterium tuberculosis</i>	1 (2)	0
None	5 (10)	3 (6)
Positive soluble antigen, No. (%) <sup>d</sup>	19 (40)	24 (50)
Positive culture, No. (%) <sup>d</sup>	23 (48)	20 (42)
Positive PCR, No. (%) <sup>d</sup>	6 (13)	4 (8)
Corticosteroids, No. (%)	43 (88)	42 (87)
Hospital admission to first antibiotic dose	3.0 (1.1-4.8)	2.6 (1.4-4.9)
Hospital admission to first dose of corticosteroid <sup>e</sup>	5.8 (2.5-8.8)	4.3 (2.3-7.9)
Sedative drugs, No. (%)	14 (29)	13 (27)

# Induced Hypothermia in Severe Bacterial Meningitis A Randomized Clinical Trial

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## Hypothermia vs Normothermia



# Conclusion

- **Le control de la fièvre:**
  - n'empêche pas la guérison de l'infection
  - permet une évolution plus favorable des défaillances
  - diminue la mortalité précoce
  
- **Quand la fièvre est contrôlée:**
  - chez des patients chez qui l'infection est traitée
  - par un refroidissement externe chez des patients déjà sédatisés
  - sans induire d'hypothermie

# Conclusion

## **Beaucoup de questions restent à résoudre**

- Quel bénéfice sur la mortalité à plus long terme?
- Le bénéfice/risque dépend-t-il:
  - De l'origine de l'infection
  - De la sévérité
  - De la méthode utilisée, de la rapidité du contrôle thermique, d'un seuil de baisse de la température?
- L'hypothermie thérapeutique serait elle encore plus bénéfique?