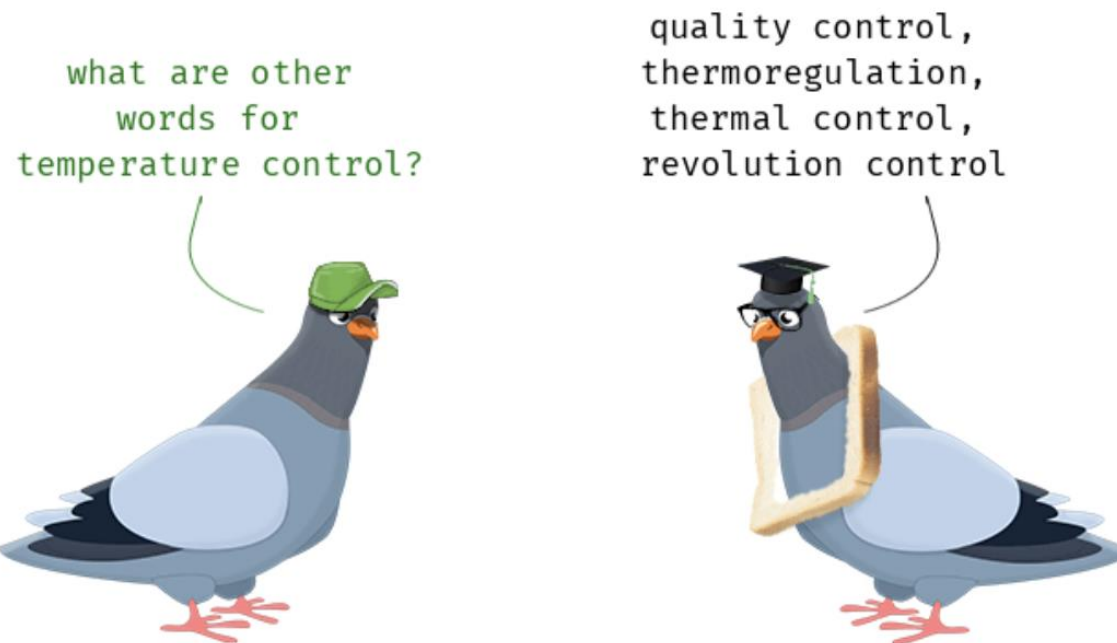


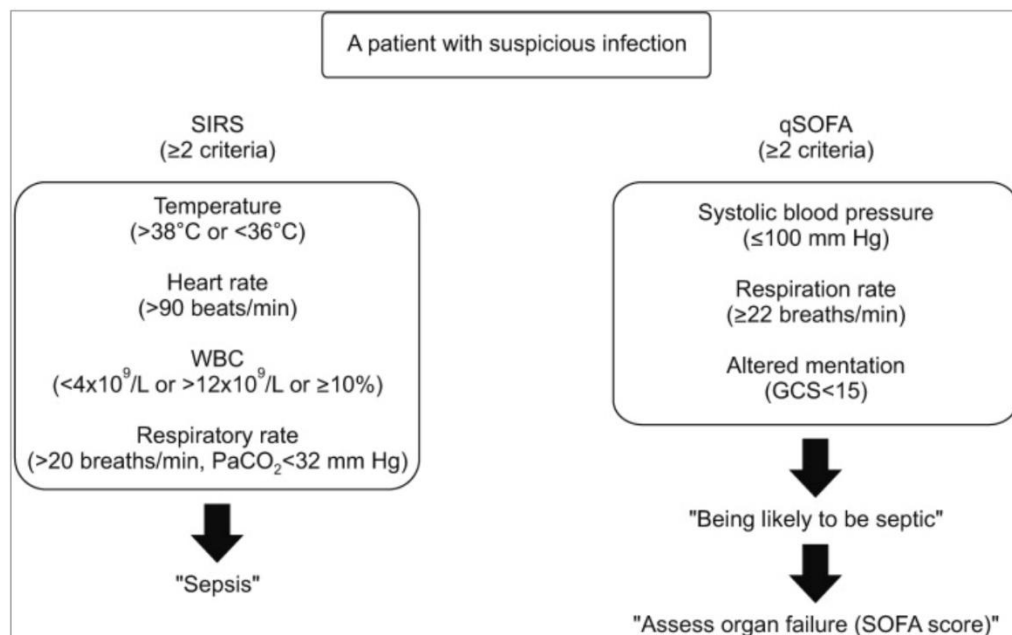
TERMOREGULACIJA IN SEPSA



Klinika za infekcijske bolezni in vročinska stanja, UKCL
Medicinska fakulteta Univerze v Ljubljani

Ljubljana, 12.9.2024

DEFINICIJE SEPSE SKOZI ČAS



	Traditional definition	Sepsis-3 definition
Sepsis	Suspicious/known infection + ≥ 2 SIRS	Suspicious/known infection + increase of ≥ 2 SOFA
Severe sepsis	Sepsis + organ failure	Not a category
Septic shock	Sepsis + refractory hypotension after adequate fluid or need of vasopressors	Sepsis + vasopressors and lactate > 2 mmol/L

TERMOREGULACIJA

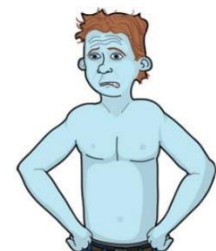
- Termoregulacija - sposobnost organizma za ohranjanje telesne temperature v določenih mejah (36,5 in 37,5 °C), tudi ob znatno drugačni temperaturi okolja.
- “Termoregulacijski organi”: možgani, koža, skeletne mišice, znojnice, endokrini in živčni sistem, črevesje?
- HIPOTERMIJA: pod 35°C
- HIPERTERMIJA
 - **Low grade:** 37.3 to 38.0°C (99.1 to 100.4°F)
 - **Moderate grade:** 38.1 to 39.0°C (100.6 to 102.2°F)
 - **High grade:** 39.1 to 41°C (102.4 to 105.8°F)
 - **Hyperthermia:** Greater than 41 C (105.8°F)

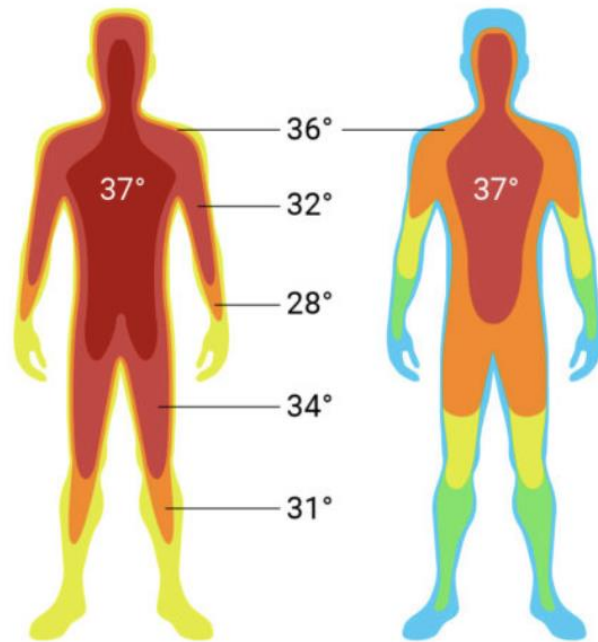
Hyperthermia and hypothermia

Prolonged exposure to high temperatures can lead to **hyperthermia**. The body's core temperature rises above 41°C causing its thermoregulatory mechanisms to break down.

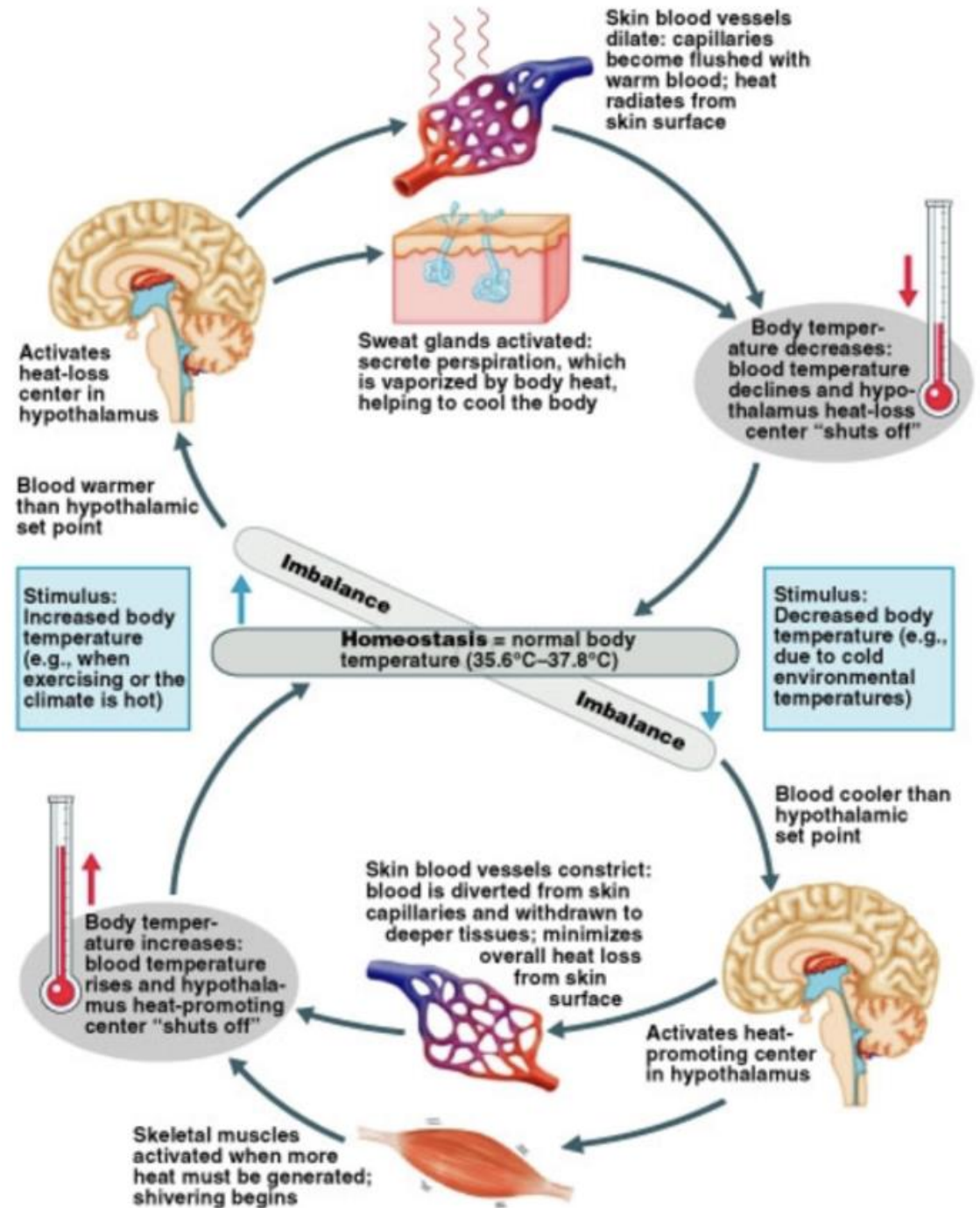
When this happens, positive feedback occurs and the person's body temperature can spiral out of control. A core body temperature of 43°C and higher usually causes death.

If the body's core temperature falls below 35°C a person may suffer from **hypothermia**. Again the body's thermoregulatory mechanisms fail and positive feedback occurs leading to a further decrease in temperature.





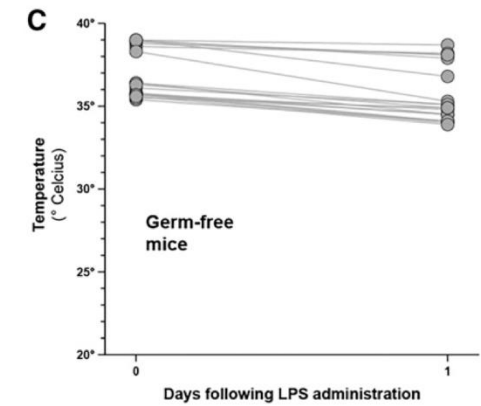
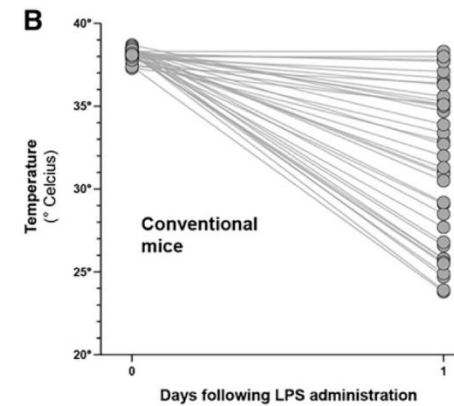
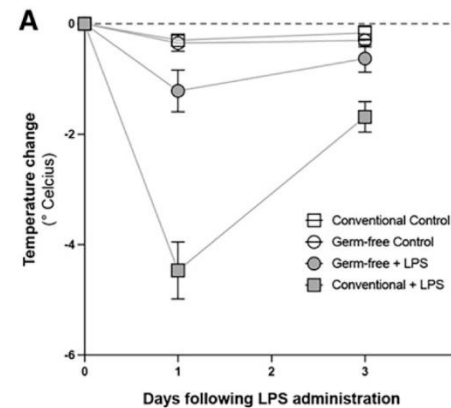
30°C — Ambient temperature — 20°C



TERMOREGULACIJA IN ČREVESNA MIKROBIOTA

Table 1. Clinical Characteristics across Temperature Subphenotypes in Study Cohort

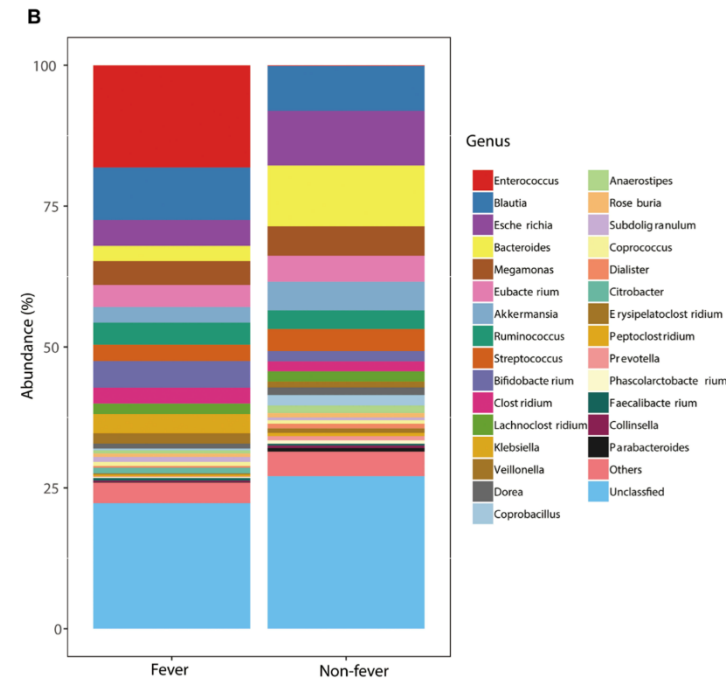
	Hyperthermic, Slow Resolvers	Hyperthermic, Fast Resolvers	Normothermic	Hypothermic
<i>n</i> (%)	852 (6.39)	3,690 (28.27)	8,343 (63.93)	166 (1.27)
Age, yr, median (IQR)	53 (38–66)	60 (45–70)	63 (51–73)	63 (53–74)
Male, <i>n</i> (%)	502 (58.92)	1,901 (51.52)	4,461 (53.47)	106 (63.86)
Race, <i>n</i> (%)				
White	618 (72.53)	3,002 (81.35)	7,009 (84.01)	129 (78.71)
Black	151 (17.72)	439 (11.89)	867 (10.39)	20 (12.04)
Other	83 (9.74)	249 (6.74)	467 (5.60)	17 (10.24)
Mortality, <i>n</i> (%)	97 (11.38)	194 (5.26)	696 (8.34)	96 (57.83)



Bongers KS, Chanderraj R, Woods RJ, McDonald RA, Adame MD, Falkowski NR, et al.
The gut microbiome modulates body temperature both in Sepsis and health. *Am J Respir Crit Care Med.* (2023) 207:1030–41. doi: 10.1164/rccm.202201-0161OC

TERMOREGULACIJA IN ČREVESNA MIKROBIOTA

- 187 Covid --19 bolnikov, 127 z vročino – pri tistih z vročino spremenjena mikrobiota (oportunistični patogeni - *Enterococcus faecalis* in *Saccharomyces cerevisiae*)



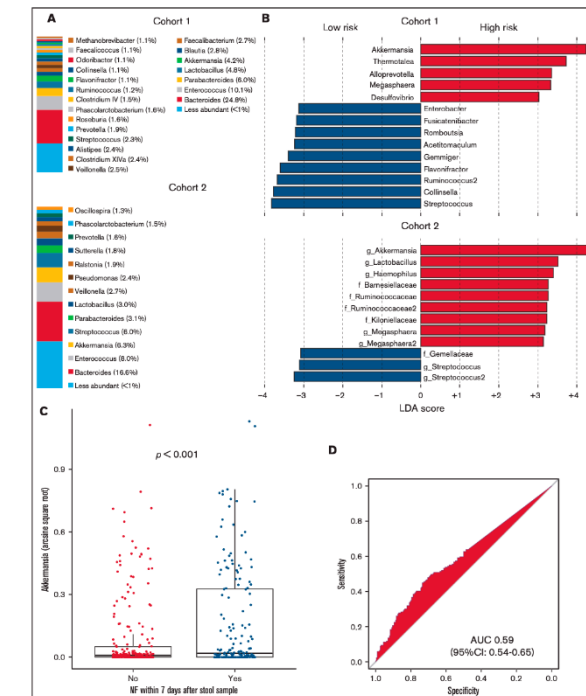
TERMOREGULACIJA IN ČREVESNA MIKROBIOTA

- FEBRILNA NEVTROPENIJA – verjetno gre za “izgubo” zaščitnih metabolitov normalne mikrobiote
- Pri 2 kohortah bolnikov z akutno levkemijo (AML, ALL) je širjenje *Akkermansie* v črevesju napovedovalo večje tveganje za febrilno nevtropenijo

Altered microbiota-host metabolic cross talk preceding neutropenic fever in patients with acute leukemia

Armin Rashidi,^{1,*} Maryam Ebadi,¹ Tauseef Ur Rehman,¹ Heba Elhusseini,¹ Harika Nalluri,² Thomas Kaiser,² Sivapriya Ramamoorthy,³ Shernan G. Holtan,¹ Alexander Khoruts,⁴ Daniel J. Weisdorf,¹ and Christopher Staley²

¹Department of Medicine, Division of Hematology, Oncology, and Transplantation and, ²Department of Surgery, University of Minnesota, Minneapolis, MN, ³Metabolon, Inc., Morrisville, NC and ⁴Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, University of Minnesota, Minneapolis, MN



POJAVNOST VROČINE V EIT

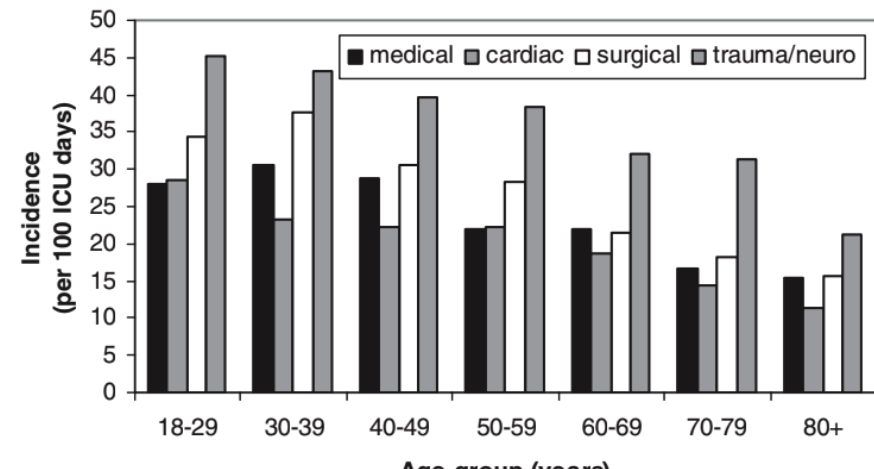
ncidenca pri 60 % septičnih bolnikih v EIT; 10-30 % septičnih je ob sprejemu hipotermičnih

Pojavnost 22-88 %; “samo” v 50 % pozitivne kulture !!!

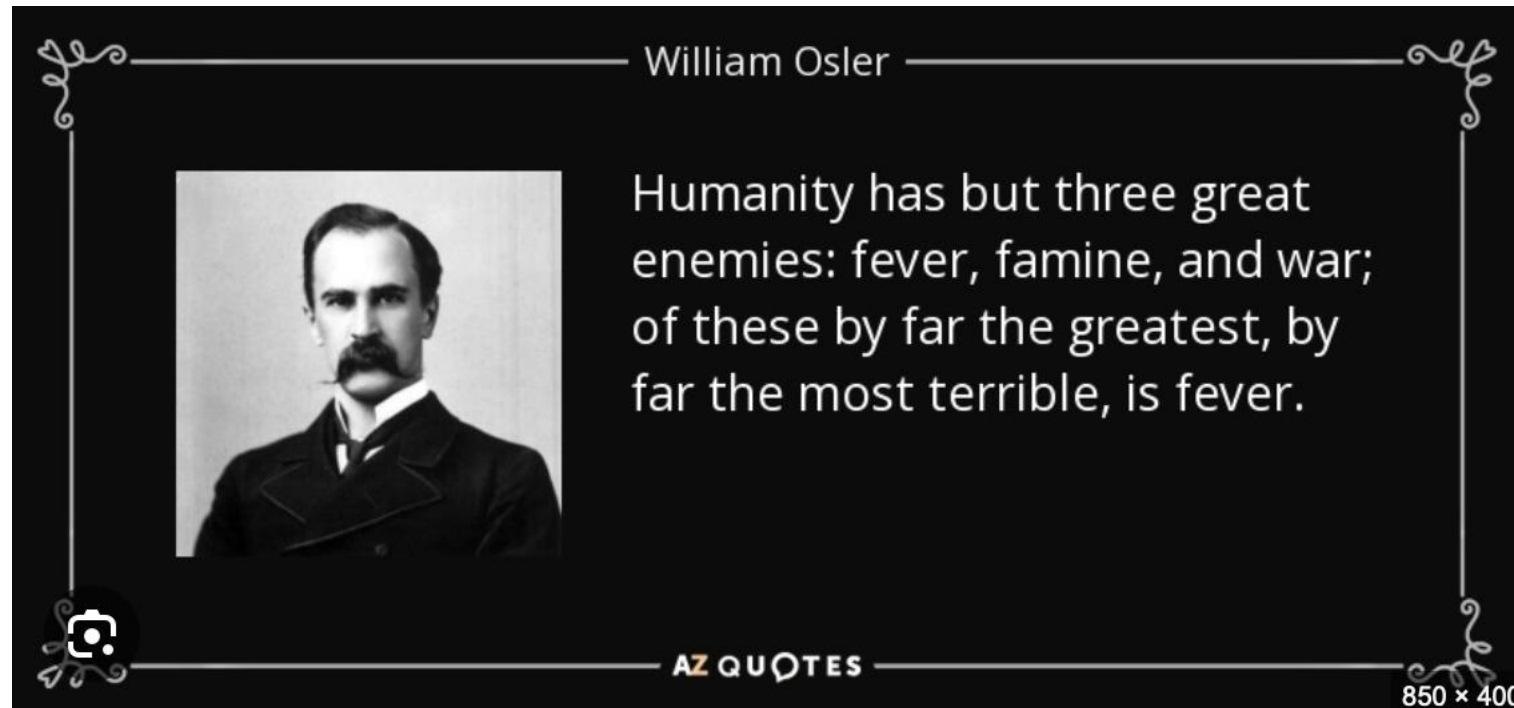
Occurrence and outcome of fever in critically ill adults*

Kevin B. Laupland, MD, MSc, FRCPC; Reza Shahpori, BSc; Andrew W. Kirkpatrick, MD, MSc, FRCSC;
Terry Ross, MLT; Daniel B. Gregson, MD, FRCPC; H. Thomas Stelfox, MD, PhD, FRCPC

- 24.000 bolnikov
- Definicija: vročina 38.3 C/visoka vročina 39.5 C
- 44 % vročina, 8 % visoka vročina – primerjava skupin
- Travma/nevro, moški, mlajši
- Nižja temp. ob APACHE nad 25
- 17 %/31 % - pozitivne kulture
- Ni bilo razlike v smrtnosti ($p=0,08$)

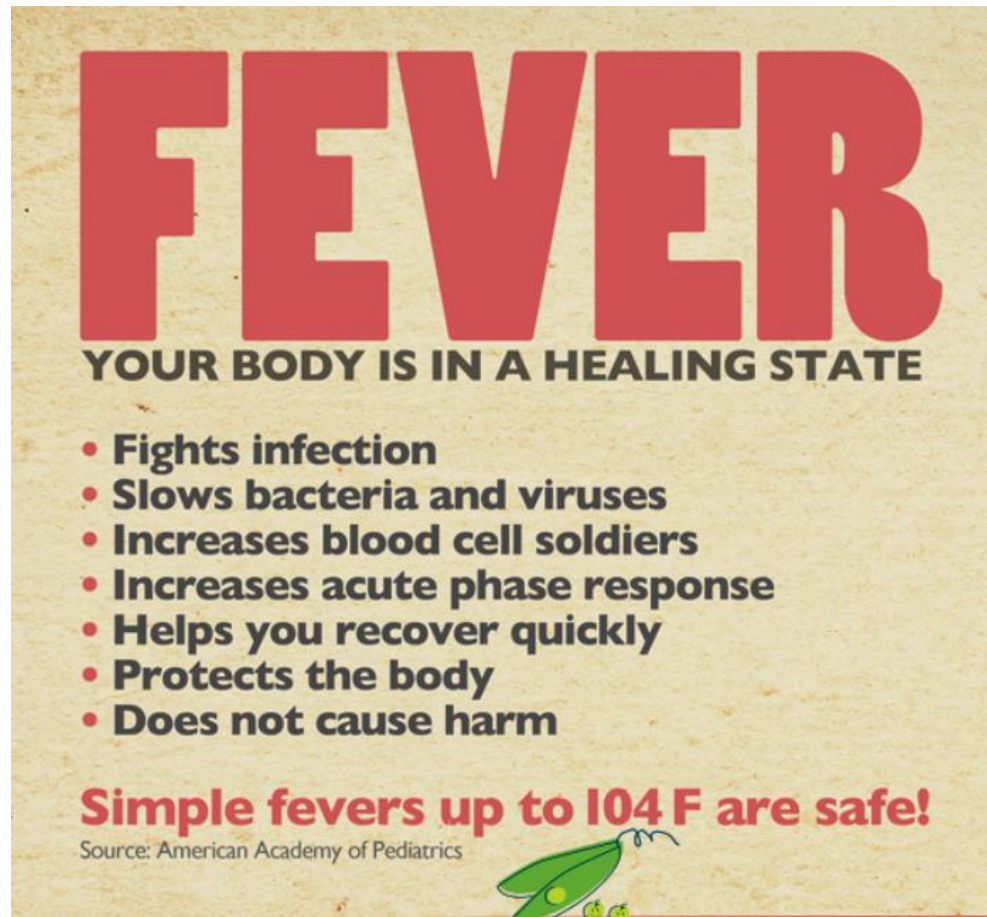


VROČINA



- Prilagoditveni mehanizem na okužbo (upočasnjeno razmnoževanje bakterij pri višjih temperaturah)
- Previsoka temperatura je škodljiva (tahikardija, vazodilatacija, izguba tekočine in elektrolitov)

UČINKI VROČINE



FEVER
YOUR BODY IS IN A HEALING STATE

- Fights infection
- Slows bacteria and viruses
- Increases blood cell soldiers
- Increases acute phase response
- Helps you recover quickly
- Protects the body
- Does not cause harm

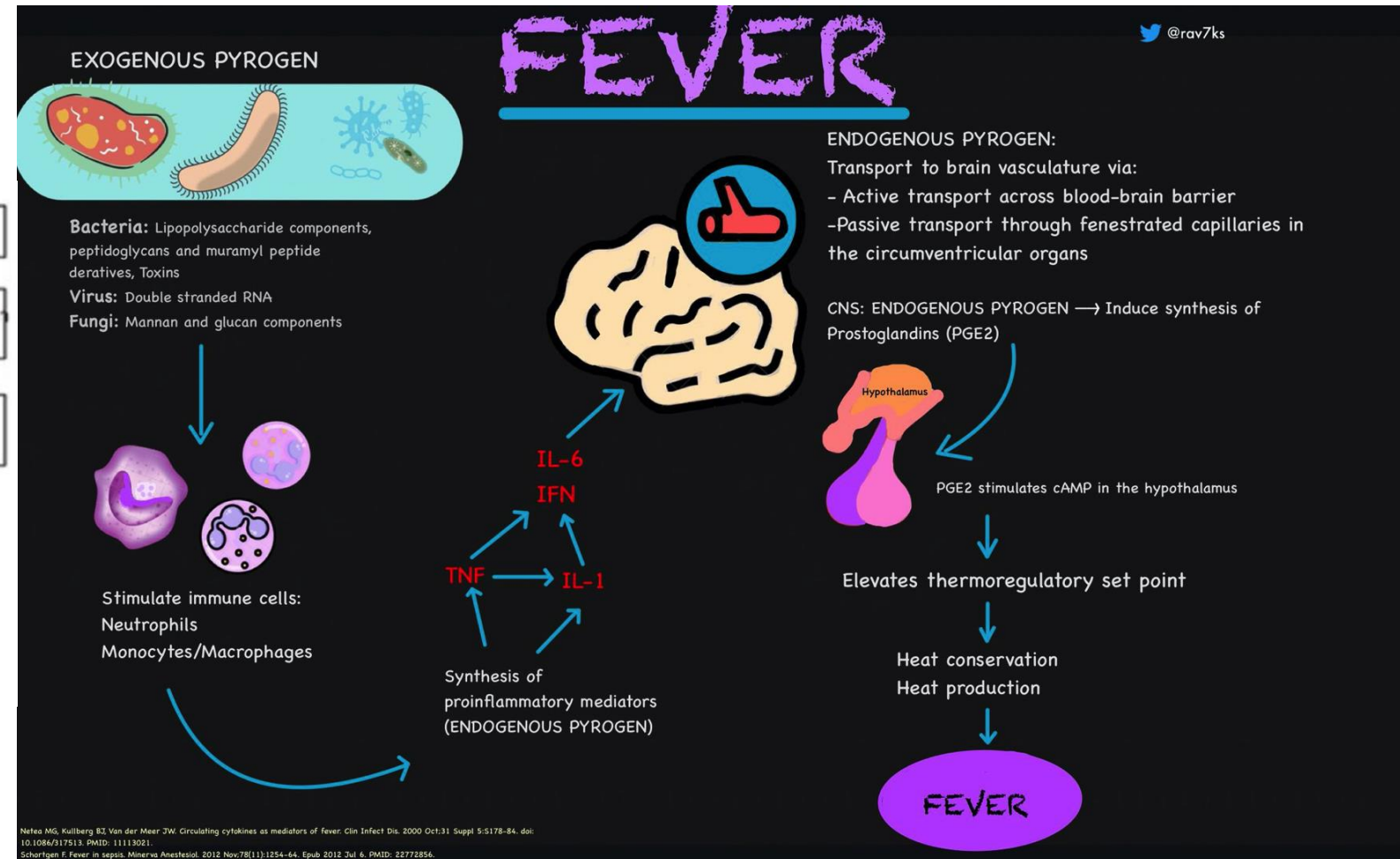
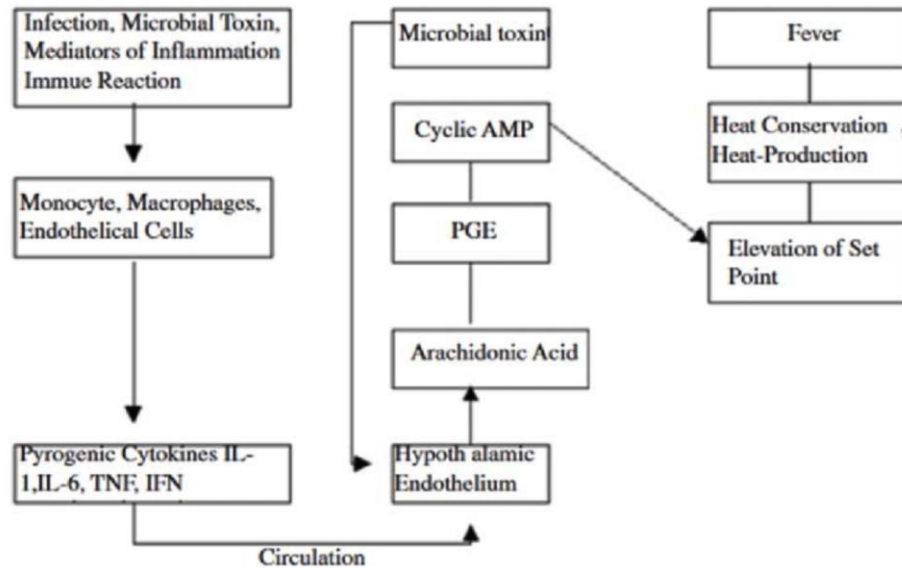
Simple fevers up to 104 F are safe!
Source: American Academy of Pediatrics



BENEFIT/ HARM

- **Potential benefits** of fever include
 - retardation of the growth and reproduction of some bacteria and viruses
 - enhanced immunologic function at moderately elevated temperatures
- **Potential harms**
 - Fever can make patients uncomfortable.
 - increased metabolic rate,
 - Increased oxygen consumption,
 - increased carbon dioxide production,
 - Increased demands on the cardiovascular and pulmonary systems.

PATOFIZIOLOGIJA VROČINE





Defining Fever

Philip A. Mackowiak^{1,✉} Frank A. Chervenak² and Amos Grünebaum²

¹Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA; and ²Department of Obstetrics and Gynecology, Zucker School of Medicine at Hofstra/Northwell, Manhasset, New York, USA

“Measure what is measurable, and
make measurable what is not so.”
— Attributed to Galileo Galilei

- Oralna zjutraj nad 37.2 C/nad 37.8 C kadarkoli oz. nad 38 C merjeno v danki/timpanično
- Carl Reinhold: 38-38.4 C/38.5-39 C/nad 39 C
- Harrison’s Principles of Internal Medicine:
 - rektalno 37.5-38.3 C
 - aksilarno nad 37.2 C
 - oralno zjutraj nad 37.2 C
 - oralno popoldne nad 37.7 C
- Merck Manual: oralno nad 37.8 C

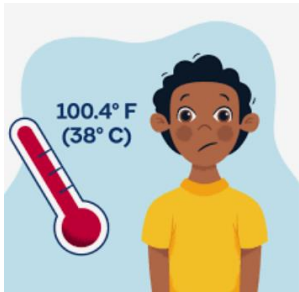


Table 2. Accuracy of methods used for measuring temperature (6, 12–16)

Most accurate
Pulmonary artery thermistor
Urinary bladder catheter thermistor
Esophageal probe
Rectal probe
Other acceptable methods in order of accuracy
Oral probe
Infrared ear thermometry
Other methods less desirable
Temporal artery thermometer
Axillary thermometer
Chemical dot

DEFINICIJA VROČINE V EIT

Special Article

Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America

Naomi P. O'Grady, MD; Philip S. Barie, MD, MBA, FCCM; John G. Bartlett, MD; Thomas Bleck, MD, FCCM; Karen Carroll, RN; Andre C. Kalil, MD; Peter Linden, MD; Dennis G. Maki, MD; David Nierman, MD, FCCM; William Pasculle, MD; Henry Masur, MD, FCCM



The definition of fever in the ICU is different from the usual definition of fever. Fever in an ICU patient is defined as a single temperature of ≥ 101 degrees F or ≥ 38.3 as per the American College of Critical Care Medicine (ACCCM) and Infectious Disease Society of America (IDSA) joint task force.^[1] Also, the ACCCM and IDSA recommend that fever in ICU should be investigated only if the temperature is ≥ 101 degrees F. Hyperpyrexia or hyperthermia is defined as a temperature of more than 105.8 degrees F (or 41 degrees C) and is uncommonly encountered in intensive care settings.

CILJNA TEMPERATURA? DEFINICIJE...

- Niven et al. 2013, EUROBACT
- Protokolizirano le v 22 % EIT
- Nevrološki bolniki, AKS

- Definicija?
- Ciljna temperatura?
- Mesto merjenja?

Table 1 Temperature measurement modalities used in EUROBACT intensive care units

Thermometer type/location	ICUs reporting usage	Primary measure
Axillary	102	58
Pulmonary artery catheter	78	1
Rectal	73	12
Tympanic	64	30
PICCO	59	2
Esophageal	51	4
Urinary bladder	50	16
Temporal	14	9
Oral	12	2
Other	8	1

Niven et al. *Critical Care* 2013, 17:R289
<http://ccforum.com/content/17/6/R289>



RESEARCH

Open Access

Diagnosis and management of temperature abnormality in ICUs: a EUROBACT investigators' survey

Daniel J Niven¹, Kevin B Laupland^{1,2,3*}, Alexis Tabah^{3,4,5}, Aurélien Vesin³, Jordi Rello^{6,7}, Despoina Koulenti⁸, George Dimopoulos⁸, Jan de Waele⁹ and Jean-Francois Timsit^{3,10}, for the EUROBACT Investigators

Table 3 Temperature control practices in selected patient diagnostic subgroups

Item	Never	Rarely	Sometimes	Most of the time	Always	*Median (IQR)
Acute neurological injury (brain or spinal cord)	1 (1%)	3 (2%)	7 (5%)	28 (20%)	100 (72%)	5 (4 to 5)
Septic shock	4 (3%)	8 (6%)	29 (21%)	45 (32%)	53 (38%)	4 (3 to 5)
Severe sepsis without shock	6 (4%)	13 (9%)	28 (20%)	50 (36%)	42 (30%)	4 (3 to 5)
Infection without sepsis	9 (6%)	21 (15%)	32 (23%)	42 (30%)	35 (25%)	4 (3 to 5)
Acute liver failure	9 (6%)	24 (17%)	38 (27%)	38 (27%)	30 (22%)	3 (3 to 4)
Chronic liver failure	11 (8%)	30 (22%)	47 (34%)	31 (22%)	20 (14%)	3 (2 to 4)
Acute coronary syndrome	9 (6%)	12 (9%)	38 (27%)	49 (35%)	31 (22%)	4 (3 to 4)

*Median score (Interquartile range, IQR) of response with 1 = Never, 2 = Rarely, 3 = Sometimes, 4 = Most of the time, and 5 = Always

VZROKI VROČINE

Category	Examples
Hyperthermia syndromes	Environmental (heatstroke) Drug-induced (neuroleptic malignant syndrome, malignant hyperthermia, serotonin syndrome)
Infectious fever	Endocrine (thyrotoxicosis, pheochromocytoma, adrenal crisis) Community- and hospital-acquired infections: bacterial, fungal, viral, and protozoa
Noninfectious fever	Drug hypersensitivity Hematologic (transfusion reactions, hematomas at deep body sites, deep vein thrombosis, pulmonary embolus/infarct, acute hemorrhage) Intra-abdominal (acalculous cholecystitis, pancreatitis, organ transplant rejection) Pulmonary (fibroproliferative phase of acute respiratory distress syndrome, aspiration pneumonitis) Collagen vascular (systemic lupus erythematosus, adult Still's disease, and others) Neoplastic (Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, multiple myeloma, sarcoma, and tumors of the liver, brain, kidney, colon, gallbladder and pancreas) Vascular (stroke, myocardial infarction)

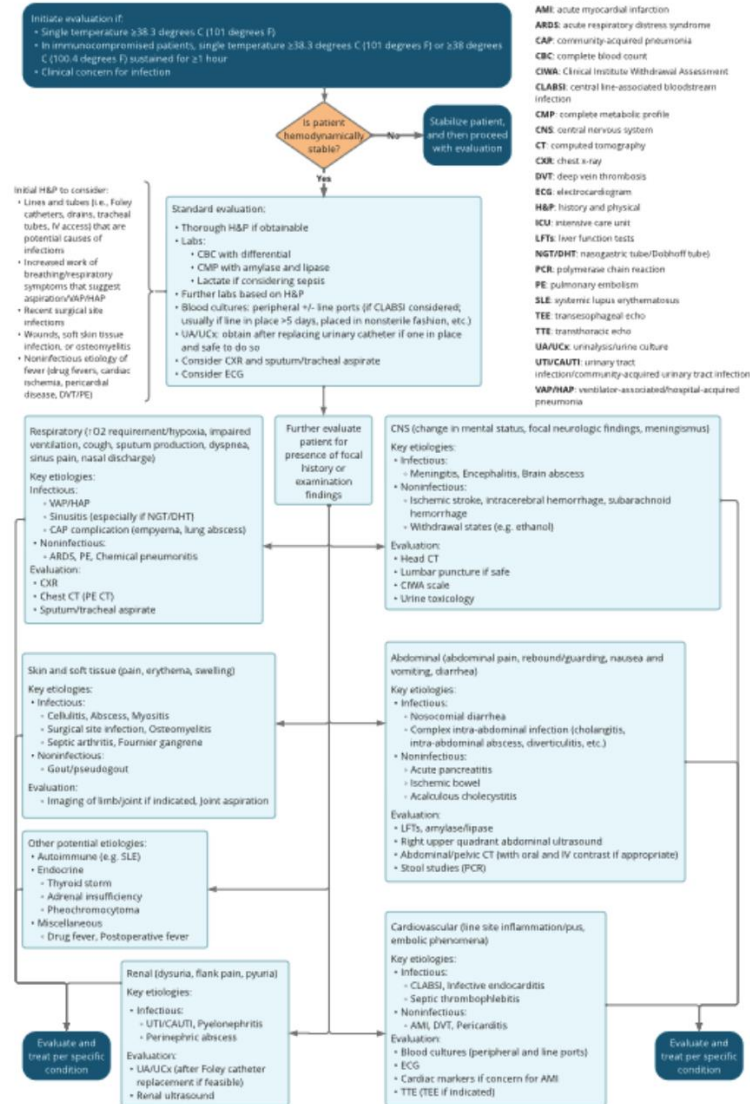
Table 1—Common Causes of Persistent Fever in the ICU: A Head-to-Toe Approach to Differential Diagnosis

Site	Infectious	Noninfectious
Head and neck	Meningitis Otitis media Sinusitis	Cerebrovascular accident Seizure disorder Traumatic brain injury
Chest	CVC-related blood stream infection Infective endocarditis Ventilator-associated tracheobronchitis Ventilator-associated pneumonia Empyema	Myocardial infarction Pericarditis Pulmonary embolism ARDS Pancreatitis
Abdomen and pelvis	Intraabdominal infections (eg, SBP, abscesses) <i>Clostridium difficile</i> infection Pyelonephritis Catheter-related UTI Perineal or perianal abscess	Acalculous cholecystitis Ischemic colitis
Extremities	Femoral line/PICC-related blood stream infection	Gout DVT
Skin and back	Septic arthritis Cellulitis	Drug eruptions
Miscellaneous	Infected pressure ulcer Surgical site infection ...	Drugs Transfusion reactions Endocrine disorders (eg, thyrotoxicosis, adrenal insufficiency) Malignancy Inflammatory disorders (eg, SLE)

CVC = central venous catheter; PICC = peripherally inserted central catheter; SBP = spontaneous bacterial peritonitis; SLE = systemic lupus erythematosus; UTI = urinary tract infection.

PRISTOP K BOLNIKU Z VROČINO

ICU Fever Evaluation



Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America

Naomi P. O'Grady, MD; Philip S. Barie, MD, MBA, FCCM; John G. Bartlett, MD; Thomas Bleck, MD, FCCM; Karen Carroll, RN; Andre C. Kalil, MD; Peter Linden, MD; Dennis G. Maki, MD; David Nierman, MD, FCCM; William Pasculle, MD; Henry Masur, MD, FCCM

opazovanje
osnovne laboratorijske preiskave
odvzem mikrobioloških kužnin
morfološka diagnostika
razširjene laboratorijske preiskave

TIMING UVEDBE ANTIBIOTIKA

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Society of
Critical Care Medicine

The Intensive Care Professionals



The Intensive Connection

Surviving Sepsis
Campaign®

Antibiotic Timing

	 Shock is present	 Shock is absent
Sepsis is definite or probable	☒ Administer antimicrobials immediately , ideally within 1 hour of recognition.	☒ Administer antimicrobials immediately , ideally within 1 hour of recognition.
Sepsis is possible	☒ Administer antimicrobials immediately , ideally within 1 hour of recognition.	☒ Rapid assessment* of infectious vs. noninfectious causes of acute illness. ☒ Administer antimicrobials within 3 hours if concern for infection persists.

*Rapid assessment includes history and clinical examination, tests for both infectious and noninfectious causes of acute illness, and immediate treatment of acute conditions that can mimic sepsis. Whenever possible, this should be completed within 3 hours of presentation so that a decision can be made as to the likelihood of an infectious cause of the patient's presentation and timely antimicrobial therapy provided if the likelihood is thought to be high.

VPLIV VROČINE NA PROGNOZO SEPSE

- Meta-analiza 42 raziskav, 2017

PLOS ONE | DOI:10.1371/journal.pone.0170152 January 12, 2017

RESEARCH ARTICLE

Fever Is Associated with Reduced, Hypothermia with Increased Mortality in Septic Patients: A Meta-Analysis of Clinical Trials

Zoltan Rumbus¹, Robert Matics¹, Peter Hegyi^{1,2,3}, Csaba Zsiborasz¹, Imre Szabo⁴, Anita Illes⁴, Erika Petervari¹, Marta Balasko¹, Katalin Marta^{1,2}, Alexandra Miko¹, Andrea Parniczky^{1,4}, Judit Tenk¹, Ildiko Rostas¹, Margit Solymar¹, Andras Garami^{1*}

SMRTNOST

22,2 % ($T > 38,0^{\circ}\text{C}$),
31,2 % pri normotermičnih bolnikih
47,3 % ($T < 36,0^{\circ}\text{C}$).

Conclusions

Deep T_b shows negative correlation with the clinical outcome in sepsis. Fever predicts lower, while hypothermia higher mortality rates compared with normal T_b . Septic patients with the lowest ($< 25\%$) chance of mortality have higher T_b than those with the highest chance ($> 75\%$).

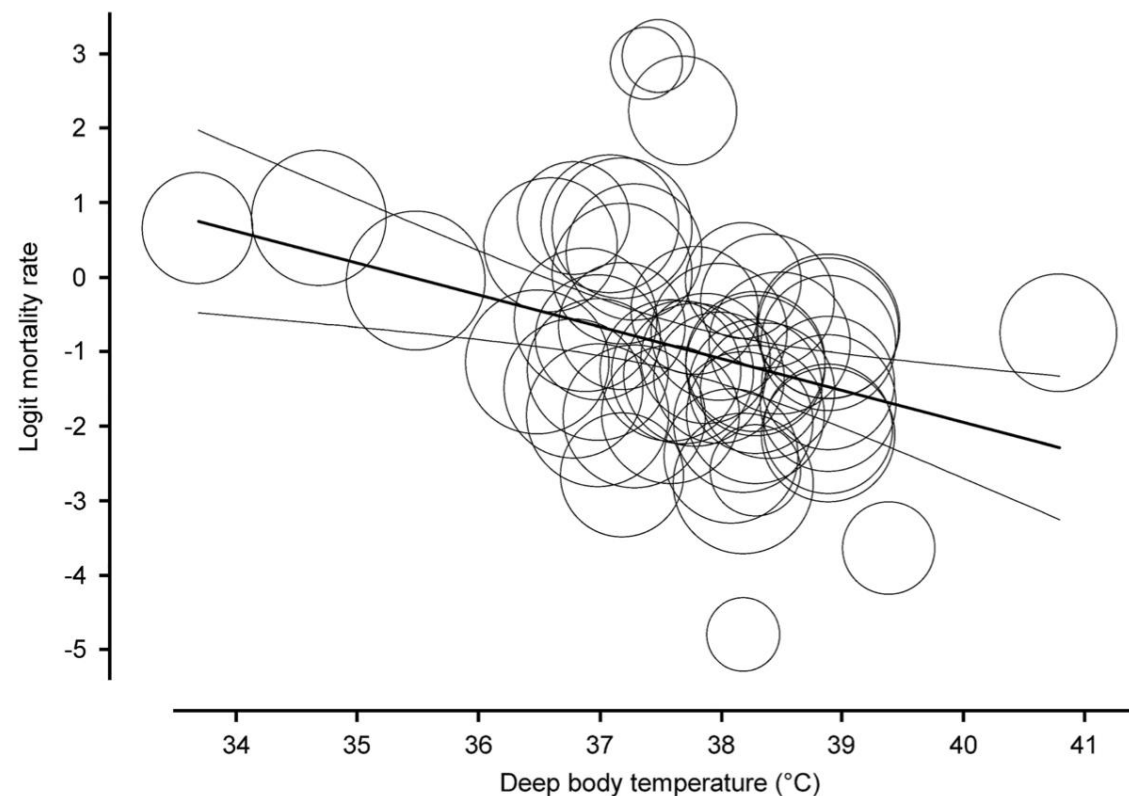


Fig 5. Meta-regression analysis of the association between body temperature and mortality ratio in septic patients ($n = 10,834$).

VPLIV VROČINE NA PROGNOZO SEPSE

Early peak temperature and mortality in critically ill patients with or without infection

Original | Published: 31 January 2012

Conclusions

Elevated peak temperature in the first 24 h in ICU is associated with decreased in-hospital mortality in critically ill patients with an infection; randomised trials are needed to determine whether controlling fever increases mortality in such patients.

VROČINA PRI STAROSTNIKU S SEPSO

- Starejši – večkrat hipotermični – vendar ni povezave s smrtnostjo

Conclusions: In septic patients, we found mortality in non-elderly sepsis patients was increased with hypothermia and decreased with fever. However, mortality in elderly patients was not associated with BT. These results illuminate the difference in the inflammatory response of the elderly compared to non-elderly sepsis patients.

RESEARCH

Open Access

Significance of body temperature in elderly patients with sepsis

Takashi Shimazui¹, Taka-aki Nakada^{1*}, Keith R. Walley², Taku Oshima¹, Toshikazu Abe^{3,4}, Hiroshi Ogura⁵, Atsushi Shiraishi⁶, Shigeki Kushimoto⁷, Daizoh Saitoh⁸, Seitaro Fujishima⁹, Toshihiko Mayumi¹⁰, Yasukazu Shiino¹¹, Takehiko Tarui¹², Toru Hifumi¹³, Yasuhiro Otomo¹⁴, Kohji Okamoto¹⁵, Yutaka Umemura⁵, Joji Kotani¹⁶, Yuichiro Sakamoto¹⁷, Junichi Sasaki¹⁸, Shin-ichiro Shiraishi¹⁹, Kiyotsugu Takuma²⁰, Ryosuke Tsuruta²¹, Akiyoshi Hagiwara²², Kazuma Yamakawa²³, Tomohiko Masuno²⁴, Naoshi Takeyama²⁵, Norio Yamashita²⁶, Hiroto Ikeda²⁷, Masashi Ueyama²⁸, Satoshi Fujimi²³, Satoshi Gando^{29,30}, on behalf of the JAAM FORECAST Group

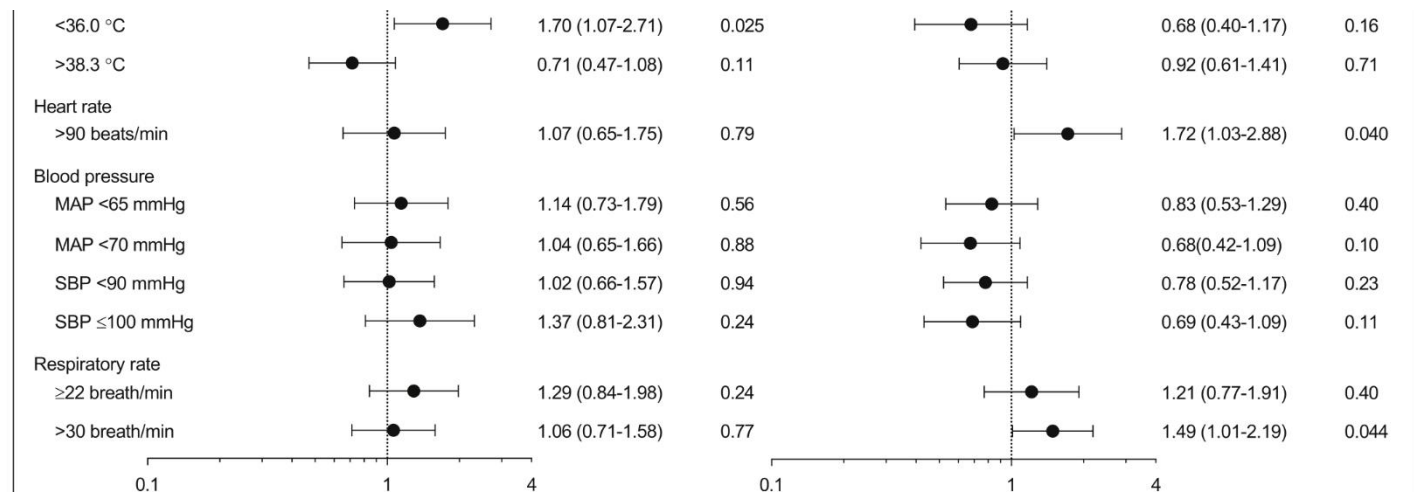


Fig. 1 Associations between the vital signs and 90-day in-hospital mortality in discovery cohort (FORECAST cohort). Non-elderly patients with BT < 36.0 °C showed a significant increase for hazard of death over 90-day period. The hypothermia was not associated with mortality in elderly patients. Heart rate > 90 beats/min and RR > 30 breaths/min had a significant association for increased mortality in elderly patients. CI, confidence interval. The adjusted hazard ratio was calculated using potentially confounding factors such as the age, sex, chronic steroid use, and acute physiology and chronic health evaluation (APACHE) II score

VROČINA PRI NEVTROPENIČNIH S SEPSO

- Vročina NE vpliva na prognozo, ne glede na prisotnost maligne bolezni!

> [Ann Hematol.](#) 2015 May;94(5):857-64. doi: 10.1007/s00277-014-2273-z. Epub 2014 Dec 18.

Association between early peak temperature and mortality in neutropenic sepsis

[Robert Weinkove](#)¹, [Michael Bailey](#), [Rinaldo Bellomo](#), [Manoj K Saxena](#), [Constantine S Tam](#),
[David V Pilcher](#), [Richard Beasley](#), [Paul J Young](#)

HIPOTERMİJA IN SEPSA

- Hipotermija (incidenca 10-30 %) pomeni slabo prognozo in večjo incidenco bolnišničnih okužb
- VZROKI? – zamuda pri diagnozi

CLINICAL INVESTIGATIONS

Impact of Body Temperature Abnormalities on the Implementation of Sepsis Bundles and Outcomes in Patients With Severe Sepsis: A Retrospective Sub-Analysis of the Focused Outcome Research on Emergency Care for Acute Respiratory Distress Syndrome, Sepsis and Trauma Study

Kushimoto, Shigeki MD, PhD¹; Abe, Toshikazu MD, PhD²⁻³; Ogura, Hiroshi MD, PhD⁴; Shiraishi, Atsushi MD,

Critical Care Medicine 47(5):p 691-699, May 2019. | DOI: 10.1097/CCM.0000000000003688

Conclusions:

Hypothermia was associated with a significantly higher disease severity, mortality risk, and lower implementation of sepsis bundles.

CLINICAL INVESTIGATIONS

Determinants of temperature abnormalities and influence on outcome of critical illness*

Laupland, Kevin B. MD; Zahar, Jean-Ralph MD; Adrie, Christophe MD, PhD; Schwebel, Carole MD, PhD; Goldgran-Toledano, Dany MD; Azoulay, Elie MD, PhD; Garrouste-Orgeas, Maité MD; Cohen, Yves MD, PhD; Jamali, Samir MD; Souweine, Bertrand MD; Darmon, Michael MD, PhD; Timsit, Jean-François MD, PhD

Critical Care Medicine 40(1):p 145-151, January 2012. | DOI: 10.1097/CCM.0b013e31822f061d

Conclusions:

Temperature abnormalities are common among patients presenting to the intensive care unit. Hypothermia is a major, potentially modifiable factor associated with increased risk for death.

TERAPEVTSKA HIPOTERMİJA

- poškoda glave
- po primarnem srčnem zastoju
- možganski edem



Cochrane Database of Systematic Reviews

Hypothermia for neuroprotection in adults after cardiac arrest (Review)

Arrich J, Schütz N, Oppenauer J, Vendt J, Holzer M, Havel C, Herkner H

Andresen et al. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* (2015) 23:42
DOI 10.1186/s13049-015-0121-3



REVIEW

Open Access



Therapeutic hypothermia for acute brain injuries

Max Andresen¹, Jose Tomás Gazmuri², Arnaldo Marín¹, Tomas Regueira¹ and Maximiliano Rovegno^{1*}

Neurocrit Care (2020) 32:647–666
<https://doi.org/10.1007/s12028-020-00959-7>



NCS GUIDELINE



Guidelines for the Acute Treatment of Cerebral Edema in Neurocritical Care Patients

Aaron M. Cook^{1*}, G. Morgan Jones², Gregory W. J. Hawryluk³, Patrick Mailloux⁴, Diane McLaughlin⁵, Alexander Papangelou⁶, Sophie Samuel⁷, Sheri Tokumaru⁸, Chitra Venkatasubramanian⁹, Christopher Zacko¹⁰, Lara L. Zimmermann¹¹, Karen Hirsch⁹ and Lori Shutter¹²

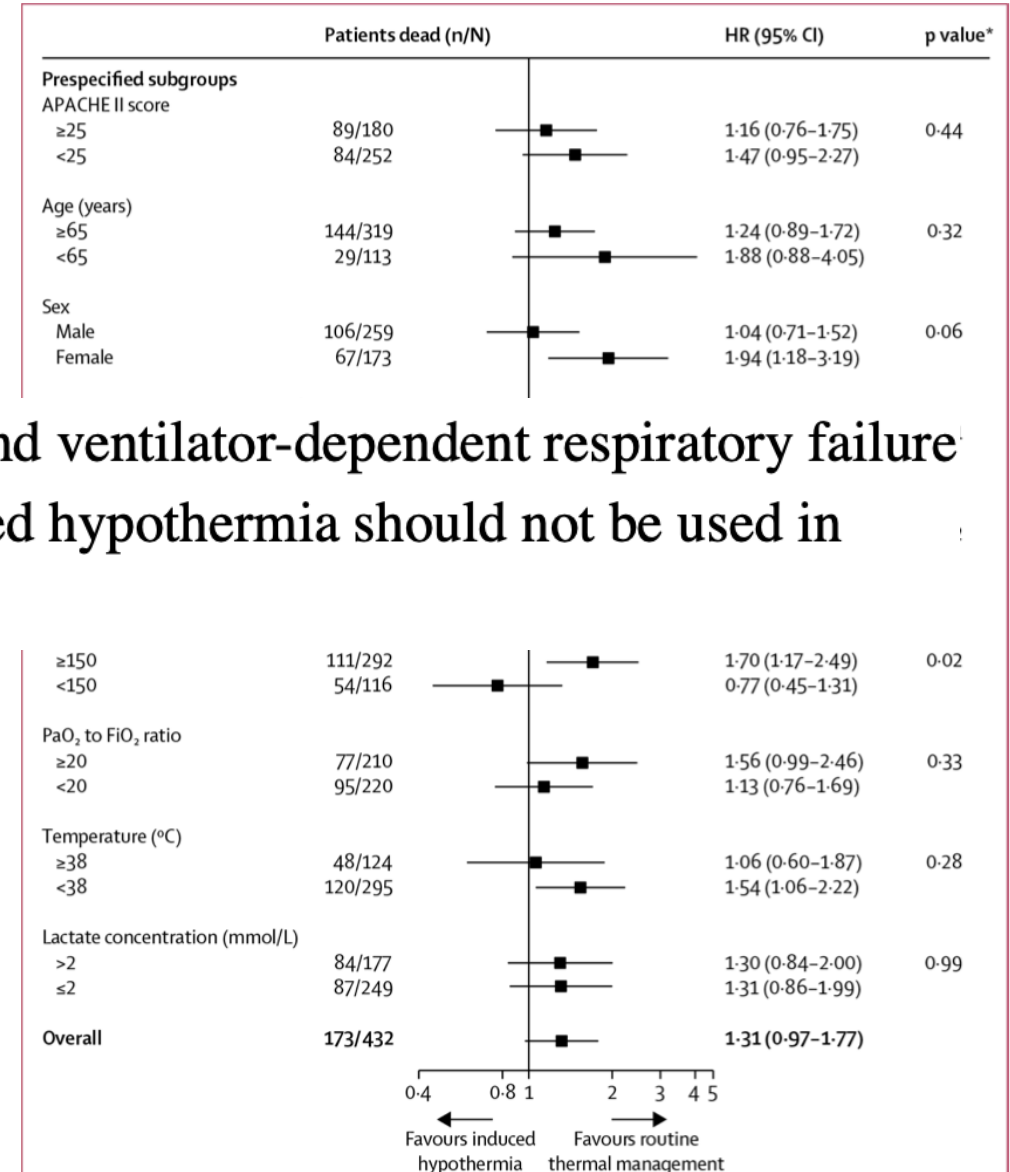
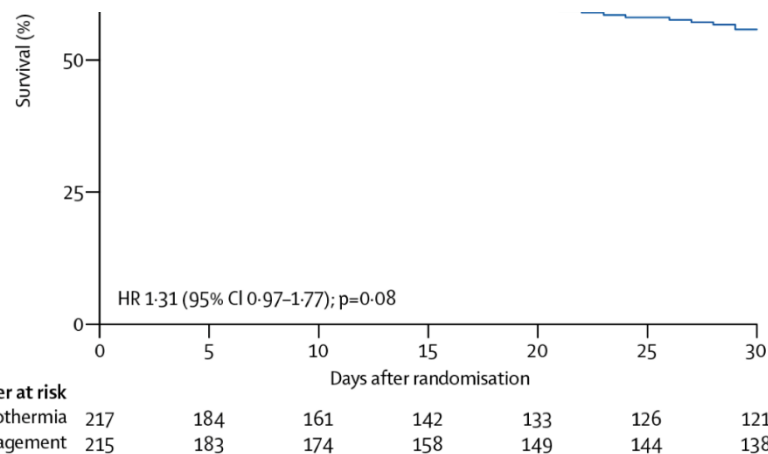
INDUCIRANA HIPOTERMİJA PRI SEPSI

Lancet Respir Med. 2018 March ; 6(3): 183–192. doi:10.1016/S2213-2600(18)30004-3.

Induced hypothermia in patients with septic shock and respiratory failure (CASS): a randomised, controlled, open-label trial

Theis Skovsgaard Itenov^{*},

Interpretation—Among patients with septic shock and ventilator-dependent respiratory failure induced hypothermia does not reduce mortality. Induced hypothermia should not be used in patients with septic shock.



TERAPEVTSKA HIPOTERMMIJA PRI OKUŽBAH OŽS

Original Investigation | Caring for the Critically Ill Patient

FREE

November 27, 2013

Induced Hypothermia in Severe Bacterial Meningitis

A Randomized Clinical Trial

Bruno Mourvillier, MD¹; Florence Tubach, MD, PhD²; Diederik van de Beek, MD, PhD³; [et al](#)

Table 1: Presumed causes of death

Presumed causes of death		Hypothermia group (n)	Control group (n)
Systemic cause	Septic shock	5	2
	Respiratory failure	0	3
	Multiorgan failure	7	3
	Others	2 ^a	3 ^b
Neurologic cause	Diffuse cerebral edema	6	5
	Cerebral infarction	1	1
	Life support withdraw because of poor neurologic outcome	6	3
	Brain death	4	0



Level I

Therapeutic hypothermia is associated with a higher mortality rate in bacterial meningitis patients.

TERAPEVTSKA HIPERtermIJA?

Therapeutic hyperthermia for the treatment of infection—a narrative review

Andrej Markota^{1,2*}, Žiga Kalamar¹, Jure Fluher^{1,2} and Sergej Pirkmajer³

¹Medical Intensive Care Unit, University Medical Centre Maribor, Maribor, Slovenia, ²Faculty of Medicine, University of Maribor, Maribor, Slovenia, ³Institute of Pathophysiology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

- Učinki aktivne hipertermije:
 - boljša perfuzija
 - višje koncentracije antibiotikov
 - aktivacija imunskega sistema
- normotermične bolnike s septičnim šokom so ogrevali za 1.5 C – boljše 28-dnevno preživetje
- Clinicaltrials.gov NCT04961151 – ogrevanje na 39C

Therapeutic Hyperthermia Is Associated With Improved Survival in Afebrile Critically Ill Patients With Sepsis: A Pilot Randomized Trial

Drewry, Anne M. MD, MSc¹; Mohr, Nicholas M. MD, MS²⁻⁴; Ablordeppey, Enyo A. MD, MPH^{1,5}; Dalton, Catherine M. BA¹; Doctor, Rebecca J. BA¹; Fuller, Brian M. MD, MSc¹; Kollef, Marin H. MD⁶; Hotchkiss, Richard S. MD¹

[Author Information](#) ☺

Critical Care Medicine 50(6):p 924-934, June 2022. | DOI: 10.1097/CCM.0000000000005470

WITHDRAWN ⓘ

Low enrollment

Working Toward the Advancement of Recovery Using Modulated Therapeutic Hyperthermia (WARMTH) in Sepsis - Pilot (WARMTH)

ALI NAJ NIŽAM VROČINO PRI SEPSI?

OPEN

Antipyretic Therapy in Critically Ill Septic Patients: A Systematic Review and Meta-Analysis

Anne M. Drewry, MD, MSCI¹; Enyo A. Ablordeppey, MD, MPH²; Ellen T. Murray, BA³;
Carolyn R. T. Stoll, MPH, MSW⁴; Sonya R. Izadi, BA⁴; Catherine M. Dalton, BA¹; Angela C. Hardi, MLS⁵;
Susan A. Fowler, MLIS⁵; Brian M. Fuller, MD, MSCI²; Graham A. Colditz, MD, DrPH⁴

Conclusions: Antipyretic treatment does not significantly improve 28-day/hospital mortality in adult patients with sepsis. (*Crit Care Med* 2017; 45:806–813)

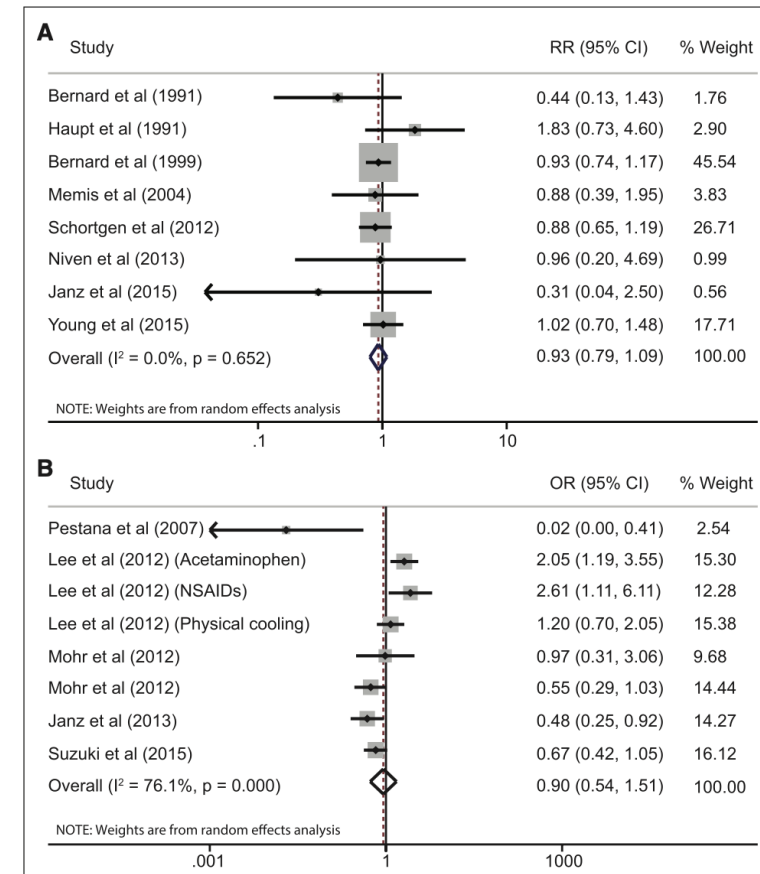


Figure 2. Results of meta-analysis for 28 days per hospital mortality in (A) randomized studies and (B) observational studies. A relative risk (RR) or odds ratio (OR) less than 1 favors antipyretic therapy. The size of the grey box corresponds to weight in the random effects analysis. NSAID = nonsteroidal anti-inflammatory drug.

ALI NAJ NIŽAM VROČINO PRI SEPSI?

Fever therapy in febrile adults: systematic review with meta-analyses and trial sequential analyses

Johan Holgersson,^{1,2} Ameldina Ceric,^{1,2} Naqash Sethi,³ Niklas Nielsen,^{1,2,*}
Janus Christian Jakobsen^{3,4,*}

thebmj | BMJ 2022;378:e069620 | doi: 10.1136/bmj-2021-069620

CONCLUSIONS

Fever therapy does not seem to affect the risk of death and serious adverse events.

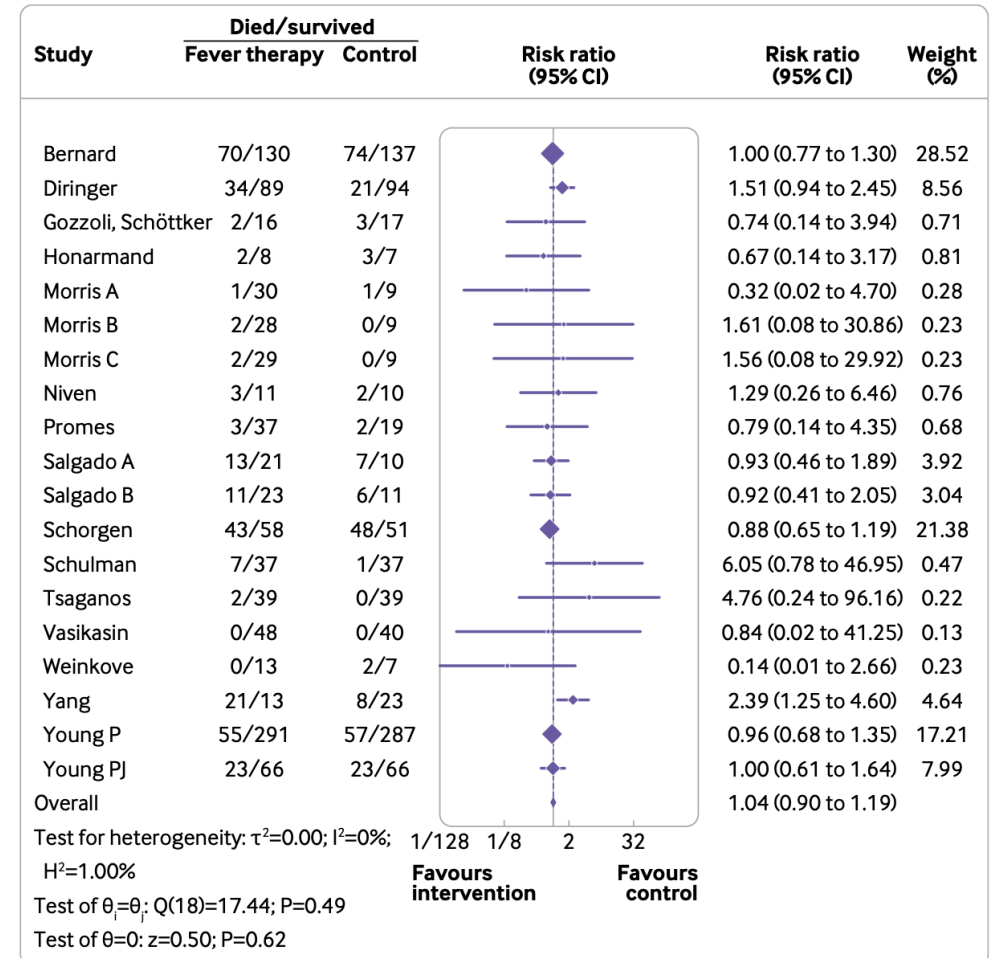
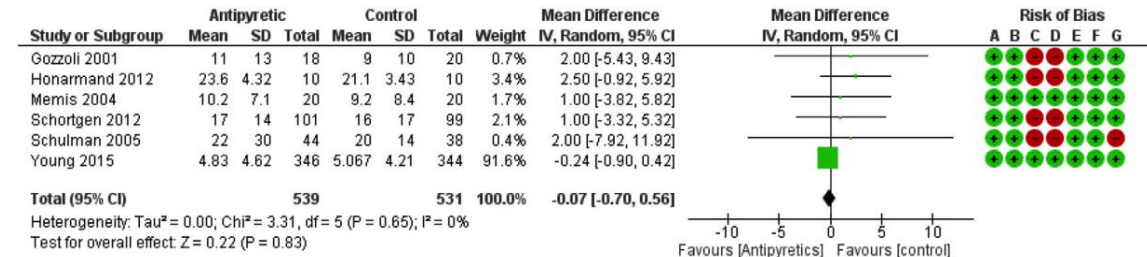


Fig 2 | Random effects meta-analysis comparing fever therapy versus control interventions for all cause mortality (risk ratio 1.04, 95% confidence interval 0.90 to 1.19; $P=0.62$; $I^2=0\%$; 16 trials)

ALI NAJ NIŽAM VROČINO AGRESIVNO ALI PERMISSIVNO?

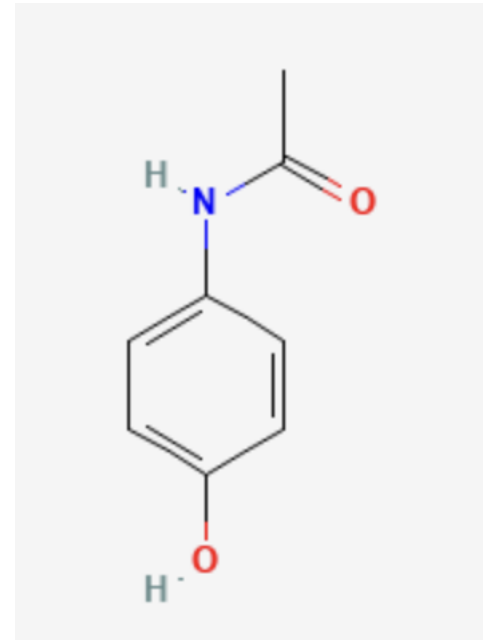
Temperature control in critically ill patients with fever: A meta-analysis of randomized controlled trials

Abdullah Sakkat ^{a,*,1}, Mustafa Alquraini ^{b,1}, Jafar Aljazeeri ^c, Mohammed A.M. Farooqi ^a,
Fayez Alshamsi ^d, Waleed Alhazzani ^{a,e}



PARACETAMOL

- Niža hipotalamični set-point
- Neželeni učinki: hepatopatija (hepatična citoliza)
- HEAT študija, NEJM 2017



THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Acetaminophen for Fever in Critically Ill Patients with Suspected Infection

Paul Young, M.D., Manoj Saxena, M.D., Rinaldo Bellomo, M.D., Ross Freebairn, M.D., Naomi Hammond, R.N., M.P.H., Frank van Haren, M.D., Ph.D., Mark Holliday, B.Sc., Seton Henderson, M.D., Diane Mackle, M.N., Colin McArthur, M.D., Shay McGuinness, M.D., John Myburgh, M.D., Ph.D., Mark Weatherall, M.D., Steve Webb, M.D., Ph.D., and Richard Beasley, M.D., D.Sc., for the HEAT Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group*

CONCLUSIONS

Early administration of acetaminophen to treat fever due to probable infection did not affect the number of ICU-free days. (Funded by the Health Research Council of New Zealand and others; HEAT Australian New Zealand Clinical Trials Registry number, ACTRN12612000513819.)

N Engl J Med 2015;373:2215-24.
DOI: 10.1056/NEJMoa1508375

Table 2. Study Outcomes.*

Outcome	Acetaminophen (N = 346)	Placebo (N = 344)	Absolute Difference† days (95% CI)		P Value	
Primary outcome: ICU-free days — median (IQR)	23 (13–25)	22 (12–25)	0 (0–1)‡		0.07	
Key secondary outcomes						
Hospital-free days — median (IQR)	12 (0–19)	10 (0–18)	0 (0–0)		0.27	
Days free from mechanical ventilation — median (IQR)	27 (19–28)	26 (17–28)	0 (0–0)		0.14	
Days free from inotropes or vaso-pressors — median (IQR)	27 (25–28)	27 (24–28)	0 (0–0)		0.36	
Days free from renal-replacement therapy — median (IQR)	28 (28–28)	28 (28–28)	0 (0–0)		0.53	
Days free from ICU support — median (IQR)	26 (16–27)	25 (15–27)	0 (0–1)		0.14	
			Relative Risk (95% CI)		P Value	
			Unadjusted	Adjusted§	Unadjusted	Adjusted§
Death by day 28 — no. (%)	48 (13.9)	47 (13.7)	1.02 (0.68–1.52)	1.00 (0.67–1.50)	0.94	0.99
Death by day 90 — no. (%)¶	55 (15.9)	57 (16.6)	0.96 (0.66–1.39)	0.94 (0.65–1.35)	0.84	0.73

NESTEROIDNI ANTIREVMATIKI

- Znižajo tvorbo PEG 2 preko inhibicije ciklookigenaze
- Neželeni učinki: GIT krvavitev, KI ALO
- Več RTC o vplivu uporabe na smrtnost – nobena ni dokazala učinka.

Morris et al. *Critical Care* 2010, **14**:R125
<http://ccforum.com/content/14/3/R125>



RESEARCH

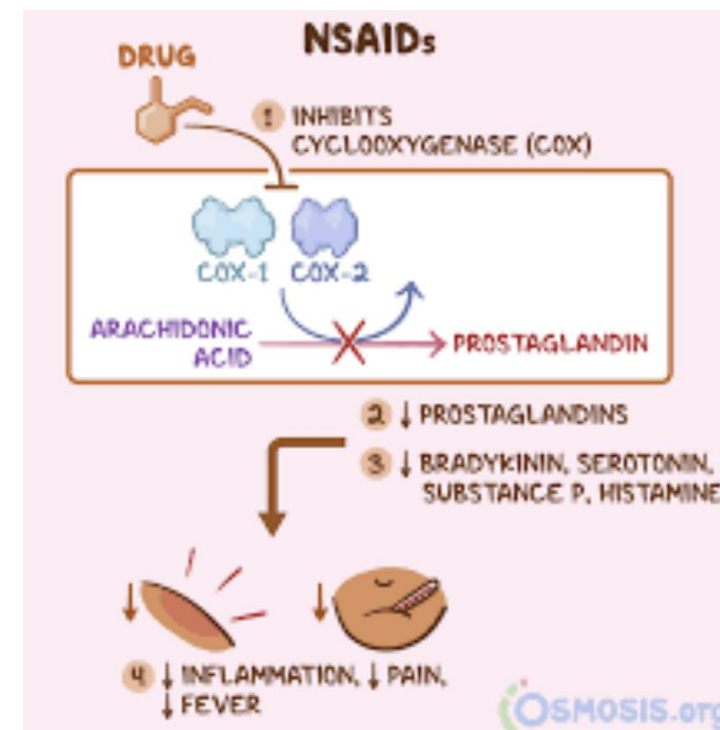
Open Access

A multi-center, randomized, double-blind, parallel, placebo-controlled trial to evaluate the efficacy, safety, and pharmacokinetics of intravenous ibuprofen for the treatment of fever in critically ill and non-critically ill adults

Peter E Morris^{*1}, John T Promes², Kalpalatha K Guntupalli³, Patrick E Wright⁴ and Murray M Arons⁵

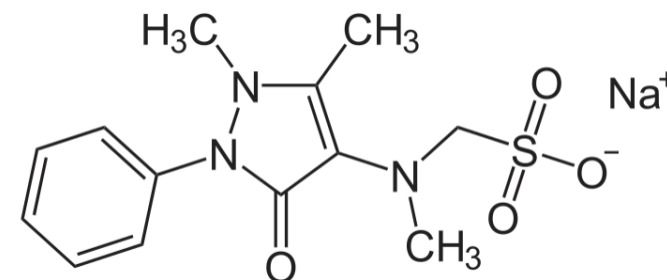
Conclusions

All doses of IV ibuprofen tested reduced fever at four hours and throughout a 24-hour dosing period. Only the 400 mg dose was effective in lowering and maintaining temperature to the normothermic range over the 24-hour period of observation. IV ibuprofen was effective in reducing fevers both in critically ill and non-critically ill groups but was slightly more effective in the latter. We found no clinically significant differences in renal function, bleeding or need for renal replacement therapy or transfusions through study Day 28 in those receiving IV ibuprofen vs. those receiving the placebo. Thus, IV ibuprofen appears to be safe and effective for the short term treatment of fever in hospitalized patients unable to tolerate oral medications.



METAMIZOL

- Inhibira COX-3 v OŽS, kar ima za posledico nižjo tvorbo PG
- Neželeni učinki: agranulocitoza, nevtropenija – ni raziskav zaradi prepovedi prometa v nekaterih državah (ZDA, UK, Francija, Švedska, Norveška, Avstralija)
- 20.9.2019: EMA (max i.v. odmerek 5g/dan)
 - EMA has completed a review of the painkiller metamizole, used in many EU countries to treat severe pain and fever that cannot be controlled with other treatments.
 - EMA has recommended changes to the product information of metamizole, to ensure that advice on the maximum daily doses and warnings not to use the medicine during the last 3 months of pregnancy or during breastfeeding are consistent across the EU. A summary of the recommended changes will be published on the EMA website.



ZUNANJE HLAJENJE

- Površinsko hlajenje: hladilne blazine, ogs
- Endovaskularno hlajenje – nevarno zaradi enodvaskularnega pristopa
- Ne deluje na hipotalamus – hipotalamus zato odreagira – tresenje, tahikardija, periferna vazokinstrikcija (diskomfort, povečana poraba kisika) – sedacija, relaksacija





Fever Control Using External Cooling in Septic Shock A Randomized Controlled Trial

Frédérique Schortgen^{1,2}, Karine Clabault³, Sandrine Katsahian⁴, Jerome Devaquet⁵, Alain Mercat⁶, Nicolas Deye⁷, Jean Dellamonica⁸, Lila Bouadma⁹, Fabrice Cook¹⁰, Olfa Beji¹, Christian Brun-Buisson¹, François Lemaire¹, and Laurent Brochard^{1,2,11}

- RCT; 200 bolnikov s septičnim šokom – zunanje hlajenje vs. placebo
- Smrtnost 14-d statistično nižja, nižja potreba po vazopr.

TABLE 3. OTHER TREATMENTS GIVEN AFTER INCLUSION AND DURING THE 48-HOUR STUDY-TREATMENT PERIOD

	Cooling (n = 101)	No Cooling (n = 99)	P Value
Treatments for hemodynamic stabilization			
Volume of fluids,* L	1.5 (0.5–2.0)	1.0 (0–2.5)	0.95
New treatment for shock			
Corticosteroids	17	21	0.69
Activated protein C	2	3	0.68
Vasopressin	1	1	>0.99
Dobutamine	6	7	>0.99
Other treatments			
Sedation, n	98	96	>0.99
Neuromuscular blockers, n	16	16	>0.99
Initiation of renal replacement therapy	10	21	0.030

TABLE 4. SECONDARY OUTCOMES

	Cooling (n = 101)	No Cooling (n = 99)	Between-Group Absolute Difference (95% CI)	P Value
Vasopressor requirement				
Patients requiring a vasopressor dose increase during the study-treatment period, n	35	52	–18 (–31 to –4)	0.011
Shock reversal in the ICU, n	87	72	13 (2 to 25)	0.021
Time course of organ failures on Day 14				
SOFA _{max} score, mean (SD)	11.4 (3.7)	12.3 (3.6)	–0.9 (–1.9 to 0.2)	0.10
ΔSOFA score, mean (SD)	0.2 (2.1)	1.1 (2.7)	–0.9 (–1.6 to –0.2)	0.010
Mortality rates				
Day 14, n	19	34	–16 (–28 to –4)	0.013
ICU discharge, n	35	43	–9 (–22 to 5)	0.20
Hospital discharge, n	43	48	–6 (–19 to 8)	0.40
Length of stay				
In the ICU (d), mean (SD)	17 (14)	16 (17)	1 (–3 to 5)	0.67
Among ICU survivors	17 (14)	19 (16)	–2 (–6 to 2)	0.38
In the hospital (d), mean (SD)	36 (40)	28 (31)	9 (–1 to 19)	0.09
Among hospital survivors	43 (39)	35 (26)	8 (–2 to 17)	0.56

Definition of abbreviation: ICU = intensive care unit.

Conclusions: In this study, fever control using external cooling was safe and decreased vasopressor requirements and early mortality in septic shock.

SKLEPI

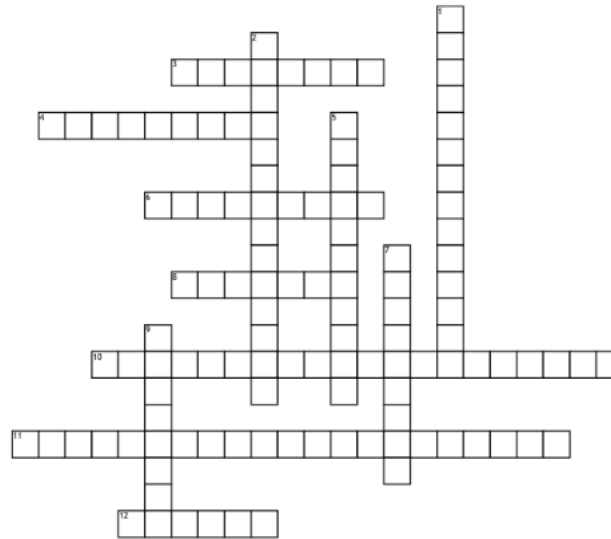
- SSC se ni opredelil glede tega vprašanja
- vročina se pri bolnikih v EIT pojavlja pogosto (cca. 50 %)
- “le” polovica epizod vročine v EIT vezanih na okužbo/sepso
- pomembno je zgodnje prepoznavanje sepse in zgodnja uvedba antibiotika
- neustrezno/nepotrebno predpisan antibiotik nosi tveganja –
STRANSKI UČINKI, PROTIMIKROBNA ODPORNOST

SKLEPI

- vročina nad 39.5 C je povezana z povišano smrtnostjo ne glede na vzrok
- Hipotermija (terapevtska in spontana) je povezana s slabšim izidom pri sepsi
- metaanalize kažejo, da antipiretiki NE vplivajo na boljše preživetje ali dolžino bolnišničnega zdravljenja
- Pri sepsi nižati do 38.2 C
- Izogniti se tresenju
- Razmislek o ogrevanju?

HVALA ZA POZORNOST

Thermoregulation



Across

3. Area of hypothalamus that controls heat loss
4. Area of hypothalamus that controls heat production
6. counterintuitive complication of cooling patients too quickly
8. Antipyretic that shouldn't be given to children
10. Intervention for rewarming frostbitten skin (3 words)

11. a rare hereditary disorder causing a deficit in calcium transport. Occurs with inhaled anesthetics (two words)

12. Occurs after prolonged exposure to elevated temperature overwhelms heat loss mechanism- heat

Down

1. Occurs when profuse diaphoresis results in excess water and electrolyte loss (two words)

2. commonly occurs in children with high fever ages 6 months to 3 years old (two words)

5. Two groups of people who are most at risk for alterations in thermoregulation (3 words)

7. Occurs when ice crystals form inside the cells and damage tissue

9. Type of adipose found in newborns