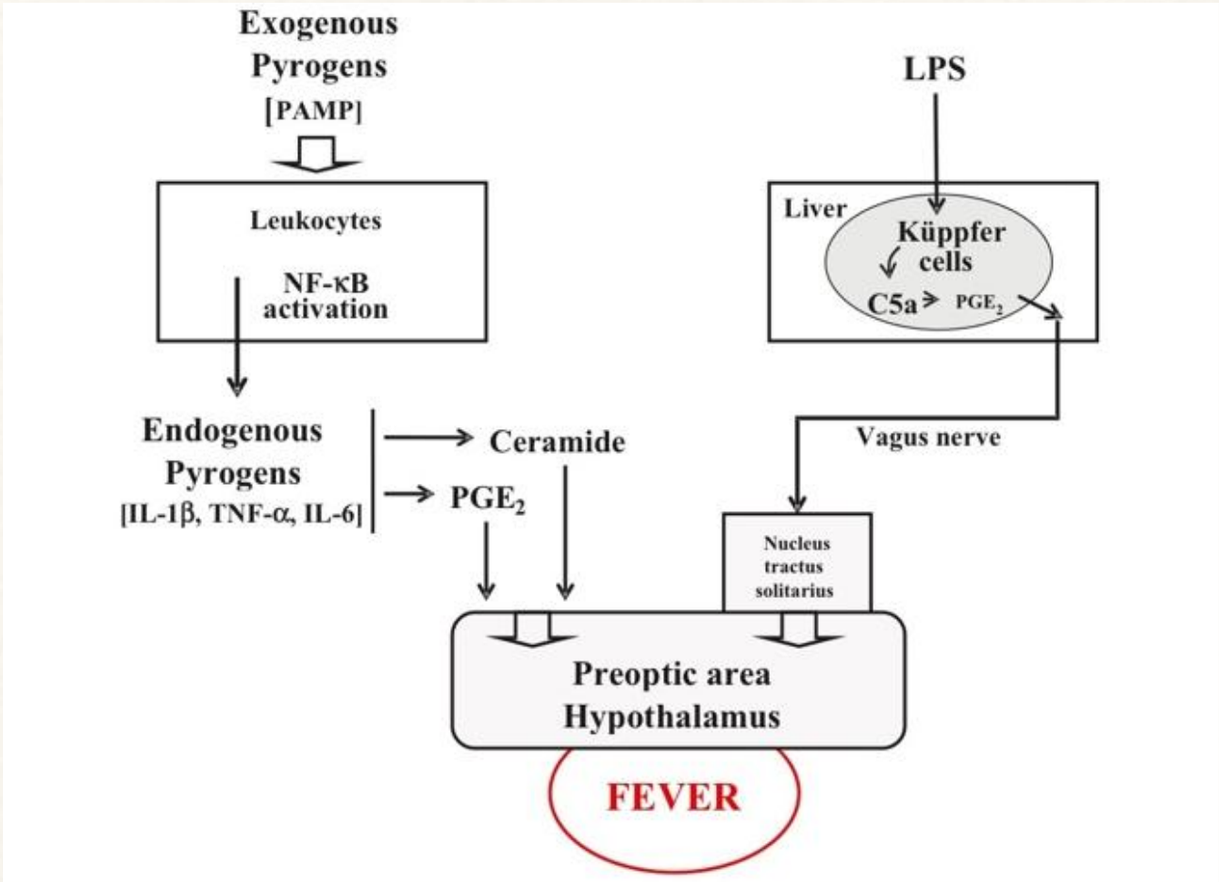
Come inquadrare clinicamente il problema della febbre in Terapia Intensiva

Magda D’Astuto - A.O. Provincia di Lecco

ECOCARDIOCHIRURGIA - Milano, 20-21 maggio 2013

Fisiologia della Febbre



Attivazione dell'ipotalamo da parte di pirogeni esogeni

Launey et al. Crit Care 2011, 15:222

Il Paziente Febbrile

- Nelle linee guida del 2008 dell'American College of Critical Care Medicine e Infectious Diseases Society of America viene definito febbrile un paziente con due consecutive misurazioni superiori a 38.3 °C

- Si considerano piu' accurate le temperature ricavate da:
  - PAC
  - Thermistor su catetere vescicale
  - Sonda esofagea
  - Sonda rettale (con riserve nei pazienti neutropenici)

Febbre Sempre Deleteria?

Egi et al. Critical Care 2012, 16:R33
http://ccforum.com/content/16/1/R33

CRITICAL CARE

RESEARCH Open Access

Association of body temperature and antipyretic treatments with mortality of critically ill patients with and without sepsis: multi-centered prospective observational study

for Fever and Antipyretic in Critically ill patients Evaluation (FACE) Study Group, Byung Ho Lee[1], Daisuke Inui[2], Gee Young Suh[3], Jae Yeol Kim[4], Jae Young Kwon[5], Jisook Park[6], Keiichi Tada[7], Keiji Tanaka[8], Kenichi Ietsugu[9], Kenji Uehara[7], Kentaro Dote[10], Kimitaka Tajimi[11], Kiyoshi Morita[12], Koichi Matsuo[13], Koji Hoshino[14], Koji Hosokawa[15], Kook Hyun Lee[16], Kyoung Min Lee[17], Makoto Takatori[7], Masaji Nishimura[2], Masamitsu Sanui[18], Masanori Ito[9], Moritoki Egi[12*], Naofumi Honda[14], Naoko Okayama[19], Nobuaki Shime[15], Ryosuke Tsuruta[20], Satoshi Nogami[7], Seok-Hwa Yoon[21], Shigeki Fujitani[22], Shin Ok Koh[23], Shinhiro Takeda[8], Shinsuke Saito[9], Sung Jin Hong[24], Takeshi Yamamoto[8], Takeshi Yokoyama[14], Takuhiro Yamaguchi[25], Tomoki Nishiyama[26], Toshiko Igarashi[11], Yasuyuki Kakihana[19] and Younsuck Koh[27]

- Association of body temperature and antypiretic treatments with mortality of critically ill patients with and without sepsis: multi-centered prospective observational study; Lee BH et al; Crit Care 2012;38:437-44
- The effect of antypiretic therapy upon outcomes in critically ill patients: a randomized, prospective study; Schulman CI, Namias N, Doherty J, et al; Surg Infect 2006;6:369-75

Lo Studio Face

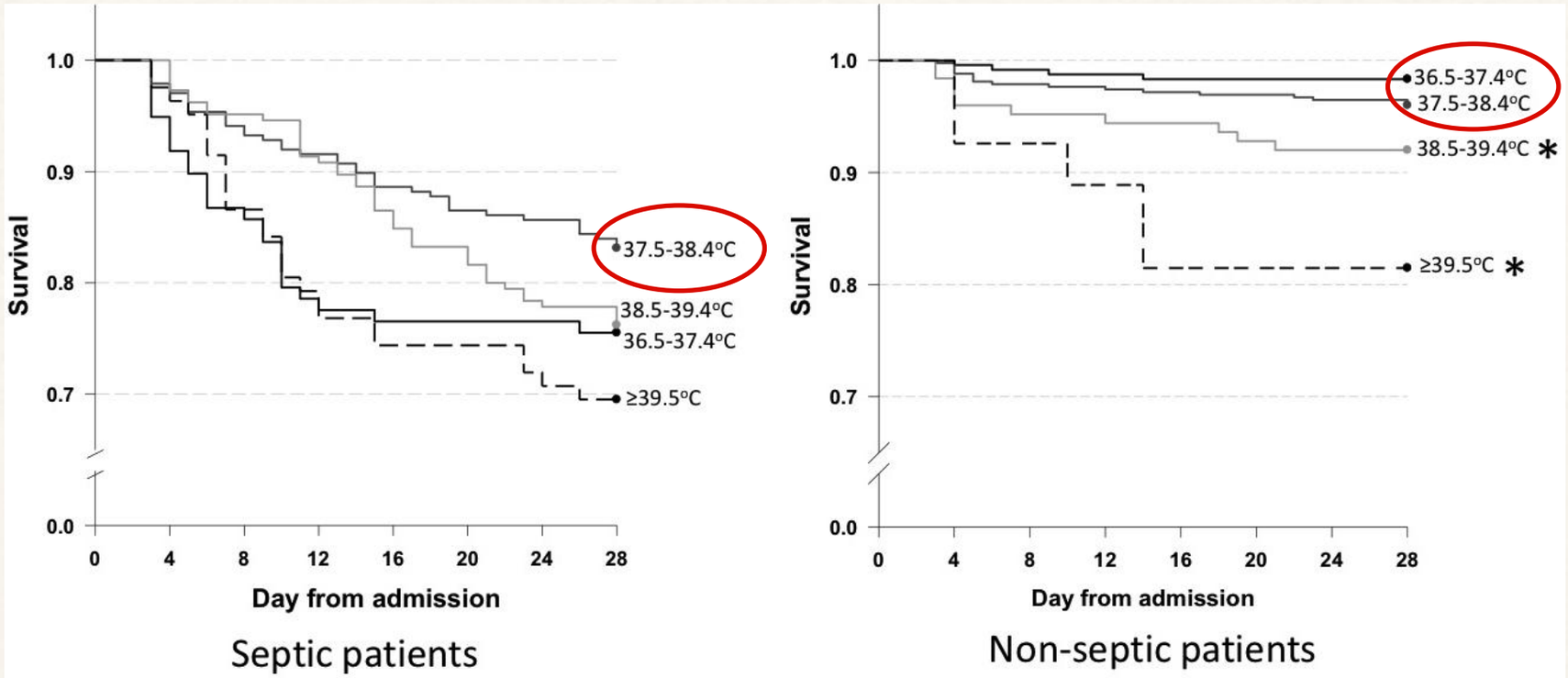


Figure 3 Maximum body temperature during ICU stay and survival of patients with and without sepsis. This figure shows Kaplan-Meier estimates for the probability of survival, which at 28 days was greater in non-septic patients with MAX_{ICU} 38.5°C to 39.4°C and ≥ 39.5°C than those with 36.5°C to 37.4°C. In septic patients, there were no significant differences of provability of survival in each category compared with patients of MAX_{ICU} with 36.5°C to 37.4°C. *, significantly different probability of survival at 28 days after ICU admission than patients with 36.5°C to 37.4°C.

Association of body temperature and antypiretic treatments with mortality of critically ill patients with and without sepsis: multi-centered prospective observational study; Lee BH et al; Crit Care 2012;38:437-44

Meglio Raffreddare?

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

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

[1]Assistance Publique-Hôpitaux de Paris (AP-HP), Groupe Hospitalier Henri Mondor, Réanimation Médicale, Créteil, France; [2]Institut National de la Santé et de la Recherche Médicale, U955, Faculté de Médecine, Créteil, France; [3]Réanimation Médicale, Centre Hospitalier Universitaire de Rouen, Rouen, France; [4]AP-HP, Groupe Hospitalier Henri Mondor, Unité de Recherche Clinique, Créteil, France; [5]Réanimation Polyvalente, Hôpital Foch, Suresnes, France; [6]Réanimation Médicale, Centre Hospitalier Universitaire de Angers, Angers, France; [7]AP-HP, Hôpital Lariboisière, Réanimation Médicale et Toxicologique, Paris, France; [8]Réanimation Médicale, Centre Hospitalier Universitaire de Nice, Nice, France; [9]AP-HP, Hôpital Bichat-Claude Bernard, Réanimation Médicale et Infectieuse, Paris, France; [10]AP-HP, Groupe Hospitalier Henri Mondor, Réanimation Chirurgicale, Créteil, France; and [11]Soins Intensifs, Hôpitaux Universitaires de Genève, University of Geneva, Geneva, Switzerland

Rationale: Fever control may improve vascular tone and decrease oxygen consumption, but fever may contribute to combat infection.
Objectives: To determine whether fever control by external cooling diminishes vasopressor requirements in septic shock.
Methods: In a multicenter randomized controlled trial, febrile patients with septic shock requiring vasopressors, mechanical ventilation, and sedation were allocated to external cooling ($n = 101$) to achieve normothermia (36.5–37°C) for 48 hours or no external cooling ($n = 99$). Vasopressors were tapered to maintain the same blood pressure target in the two groups. The primary endpoint was the number of patients with a 50% decrease in baseline vasopressor dose after 48 hours.
Measurements and Main Results: Body temperature was significantly lower in the cooling group after 2 hours of treatment (36.8 ± 0.7 vs. 38.4 ± 1.1°C; $P < 0.01$). A 50% vasopressor dose decrease was significantly more common with external cooling from 12 hours of treat-

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The benefits and risks of fever control in severe sepsis remain debated. Although fever is common in sepsis, few comparative studies on fever management are available.

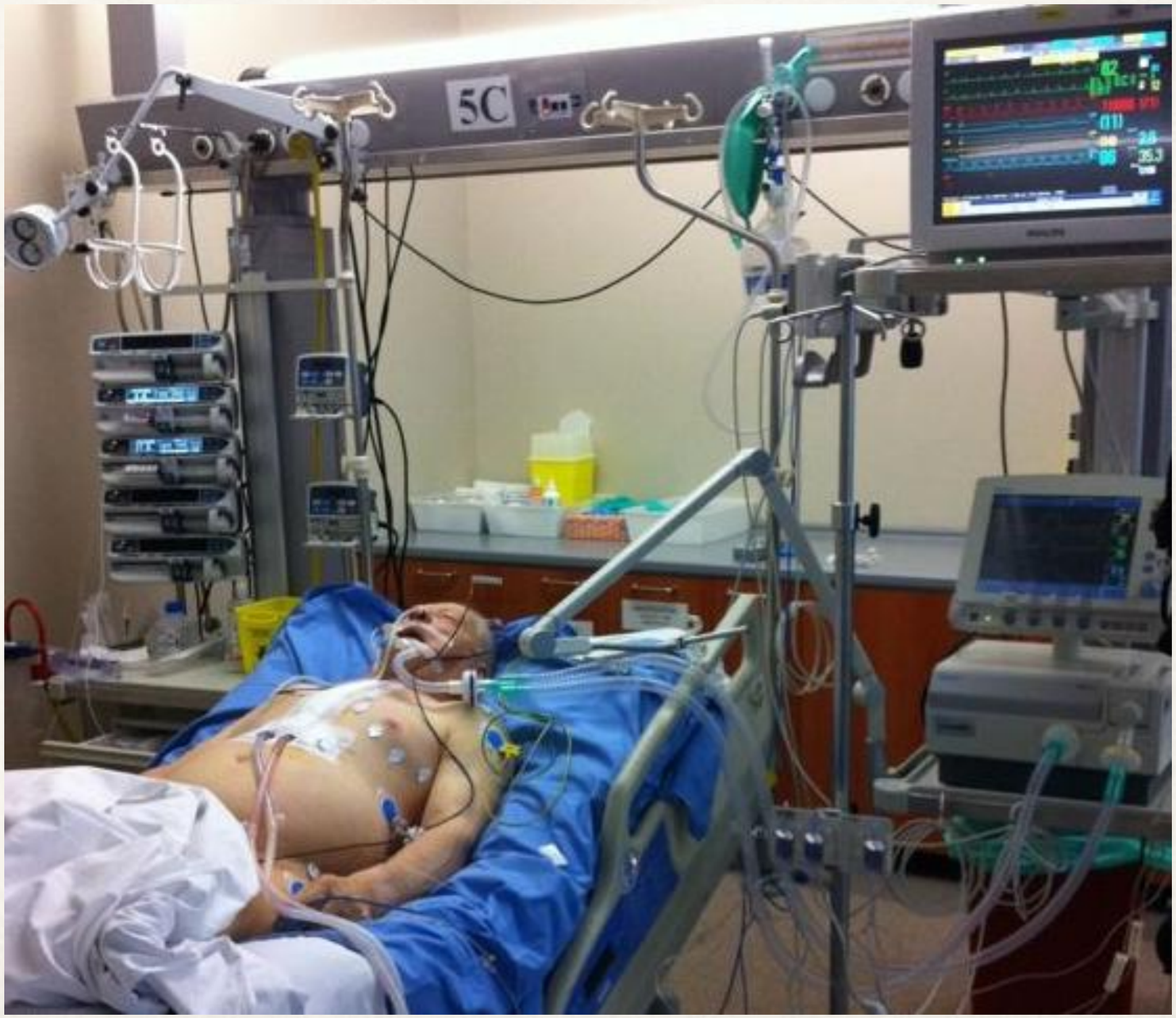
What This Study Adds to the Field

Fever control using external cooling in sedated patients with septic shock is safe and decreases vasopressor requirement and early mortality.

Fever control using external cooling in septic shock: a randomized clinical trial; Schortgen F, et al; Am J Respir Crit Care Med, 185:1088-1095

To Treat Or Not To Treat?

- ↑ HR
- ↑ RR
- ↑ metabolismo
- ↑ consumo O_2



Sepsi: Linee Guida 2012 (1)

Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)
Sepsis-induced hypotension
Lactate above upper limits laboratory normal
Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation
Acute lung injury with Pao_2/Fio_2 < 250 in the absence of pneumonia as infection source
Acute lung injury with Pao_2/Fio_2 < 200 in the presence of pneumonia as infection source
Creatinine > 2.0 mg/dL (176.8 µmol/L)
Bilirubin > 2 mg/dL (34.2 µmol/L)
Platelet count < 100,000 µL
Coagulopathy (international normalized ratio > 1.5)

Adapted from Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31: 1250–1256.

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012; Crit Care Med 2013; 41(2):580-637

Sepsi: Linee Guida 2012 (2)

SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:
1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4mmol/L

TO BE COMPLETED WITHIN 6 HOURS:
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation ($Scvo_2$)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $Scvo_2$ of ≥70%, and normalization of lactate.

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012; Crit Care Med 2013; 41(2):580-637

Incidenza di Shock Settico

- Lo studio EPISS (Epidemiology of Septic Shock in French Intensive care units): incidenza in 14 terapia intensive francesi dal novembre 2009 al marzo 2011.

- L’incidenza di shock settico su 10.000 inclusi nello studio era del 13.7%, mortalita’ a 28 giorni 42%

The epidemiology of septic shock in French intensive care units: the prospective multicenter cohort EPISS study; Quenot JP, Binquet C, Kara F, Martinet O, Ganster F, Navellou JC, Castelain V, Barraud D, Cousson J, Louis G, Perez P, Kuteifan K, Noirot A, Badie J, Mezher C, Lessire H, Pavon A, Study Group E; Crit Care. 2013 Apr 5;17(2):R65

Cause Non Infettive Di Febbre

- IMA
- Sindrome di Dressler
- Tromboembolia
- TVP
- Ipertermia Maligna (anestetici)
- Malignant Neuroleptic Syndrome (farmaci antipsicotici come le fenotiazine)
- Serotonin Syndrome

Cause Infettive Di Febbre

- Polmoniti 46.9%
- Infezioni delle basse vie respiratorie 17.8%
- Infezioni urinarie 17.6%
- Setticemie 12%

The prevalence of nosocomial infection in ICU in Europe. Results of the European Prevalence of Infection in ICU. EPIC international Advisory Committee. JAMA 1995;274(8);639-44

Le Endocarditi Infettive (1)

- Incidenza di 3/10 episodi nella popolazione generale su 100.000
- Incidenza di 14.5 episodi su 100.000, fra 70 e 80 anni
- IE con emocoltura positiva (nell'85% dei casi da Stafilocco, streptococco, enterococco)
- IE con emocoltura negativa (HACEK group, Coxiella burneti, Bartonella, Chlamydia)

Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009) ; The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC); European Heart Journal (2009) 30, 2369–2413

Le Endocarditi Infettive (2)

IE must be suspected in the following situations

1. New regurgitant heart murmur
2. Embolic events of unknown origin
3. Sepsis of unknown origin (especially if associated with IE causative organism)
4. Fever: the most frequent sign of IE.*

   IE should be suspected if fever is associated with:

   a. Intracardiac prosthetic material (e.g. prosthetic valve, pacemaker, implantable defibrillator, surgical baffle/conduit)
   b. Previous history of IE
   c. Previous valvular or congenital heart disease
   d. Other predisposition for IE (e.g. immunocompromised state, IVDA)
   e. Predisposition and recent intervention with associated bacteraemia
   f. Evidence of congestive heart failure
   g. New conduction disturbance
   h. Positive blood cultures with typical IE causative organism or positive serology for chronic Q fever (microbiological findings may precede cardiac manifestations)
   i. Vascular or immunologic phenomena: embolic event, Roth spots, splinter haemorrhages, Janeway lesions, Osler's nodes
   j. Focal or non-specific neurological symptoms and signs
   k. Evidence of pulmonary embolism/infiltration (right-sided IE)
   l. Peripheral abscesses (renal, splenic, cerebral, vertebral) of unknown cause

Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009) ; The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC); European Heart Journal (2009) 30, 2369–2413

Esami Diagnostici (1)

Nel sospetto di SETTICEMIA:

- Tre/quattro emocolture per aerobi/anaerobi nelle prime 24 ore dalla comparsa della febbre.

- Ripetere successivamente solo nel sospetto di infezione non controllata e del persistere della febbre.

- Ripetere emocolture a 48/96 ore dall'inizio della terapia.

- I cateteri vascolari centrali rimossi vanno inviati per coltura SOLO nel sospetto clinico di infezione, il 20% dei cateteri centrali infatti risultano colonizzati e questo potrebbe portare ad un aumento di terapie inappropriate.

Esami Diagnostici (2)

Nel sospetto di VAP o POLMONITE:

- Esami radiologici (TC/RX)
- Esame microbiologico dell'escreato (a seconda delle condizioni del paziente e dei presidi piu' o meno invasivi, escreato/broncoaspirato/BAL)
- Antigeni urinari (Legionella, S. Pneumoniae, M. Tubercolosis)
- Esami ematici (Ag CMV, beta-D-glucan, galattomannano, Ac anti-mannano per la diagnosi di candidosi sistemiche, utile per l'alto valore predittivo nel caso di diagnosi differenziale in pazienti a rischio)

Esami Diagnostici (3)

FEBBRE POSTOPERATORIA:

- Controllare quotidianamente la ferita ed eseguire tamponi SOLO nel caso di sospetto di infezione.
- La febbre puo' essere anche segnale di TVP o di tromboembolia.
- Il drenaggio di una infezione superficiale della ferita puo' essere sufficiente se non vi sono segni di infezione sistemica, senza che venga iniziata una terapia antibiotica di copertura.

Esami Diagnostici (4)

- Nel paziente con diarrea in ICU e che ha avuto terapia antibiotica nei due mesi precedenti, il Clostridium difficile rappresenta dal 10% al 25% delle cause di diarrea. Gli esami che si possono eseguire oltre alla coltura delle feci, che puo' richiedere alcuni giorni per la risposta, e' la ricerca dell'Antigene del C. diff., o l'EIA per la tossina A e B

- Ricordarsi della possibilita' di sinusiti, quindi valutare una TC del massiccio facciale oppure eseguire colture delle secrezioni (soprattuto per pazienti intubati per via NT).

Terapia della sepsi severa (1)

TABLE 5. Recommendations: Initial Resuscitation and Infection Issues

A. Initial Resuscitation

1. Protocolized, quantitative resuscitation of patients with sepsis- induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/L). Goals during the first 6 hrs of resuscitation:
   a) Central venous pressure 8–12 mm Hg
   b) Mean arterial pressure (MAP) ≥ 65 mm Hg
   c) Urine output ≥ 0.5 mL/kg/hr
   d) Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively (grade 1C).
2. In patients with elevated lactate levels targeting resuscitation to normalize lactate (grade 2C).

B. Screening for Sepsis and Performance Improvement

1. Routine screening of potentially infected seriously ill patients for severe sepsis to allow earlier implementation of therapy (grade 1C).
2. Hospital–based performance improvement efforts in severe sepsis (UG).

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012; Crit Care Med 2013; 41(2):580-637

Terapia della sepsi severa (2)

C. Diagnosis

1. Cultures as clinically appropriate before antimicrobial therapy if no significant delay (> 45 mins) in the start of antimicrobial(s) (grade 1C). At least 2 sets of blood cultures (both aerobic and anaerobic bottles) be obtained before antimicrobial therapy with at least 1 drawn percutaneously and 1 drawn through each vascular access device, unless the device was recently (<48 hrs) inserted (grade 1C).
2. Use of the 1,3 beta-D-glucan assay (grade 2B), mannan and anti-mannan antibody assays (2C), if available and invasive candidiasis is in differential diagnosis of cause of infection.
3. Imaging studies performed promptly to confirm a potential source of infection (UG).

D. Antimicrobial Therapy

1. Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) as the goal of therapy.

2a. Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (grade 1B).

2b. Antimicrobial regimen should be reassessed daily for potential deescalation (grade 1B).

3. Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection (grade 2C).

4a. Combination empirical therapy for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp. (grade 2B). For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is for *P. aeruginosa* bacteremia (grade 2B). A combination of beta-lactam and macrolide for patients with septic shock from bacteremic *Streptococcus pneumoniae* infections (grade 2B).

Terapia della sepsi severa (3)

TABLE 5. (*Continued*) Recommendations: Initial Resuscitation and Infection Issues

4b. Empiric combination therapy should not be administered for more than 3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (grade 2B).

5. Duration of therapy typically 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *S. aureus;* some fungal and viral infections or immunologic deficiencies, including neutropenia (grade 2C).

6. Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin (grade 2C).

7. Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause (UG).

E. Source Control

1. A specific anatomical diagnosis of infection requiring consideration for emergent source control be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the first 12 hr after the diagnosis is made, if feasible (grade 1C).

2. When infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred (grade 2B).

3. When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (eg, percutaneous rather than surgical drainage of an abscess) (UG).

4. If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established (UG).

F. Infection Prevention

1a. Selective oral decontamination and selective digestive decontamination should be introduced and investigated as a method to reduce the incidence of ventilator-associated pneumonia; This infection control measure can then be instituted in health care settings and regions where this methodology is found to be effective (grade 2B).

1b. Oral chlorhexidine gluconate be used as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia in ICU patients with severe sepsis (grade 2B).

Monitoraggio Della Terapia (1)

Si consiglia la rivalutazione GIORNALIERA della terapia antibiotica.

“We conclude that for patients with VAP not due to NF-GNB, a short fixed-course (seven or eight days) antibiotic therapy may be more appropriate than a prolonged course (10 to 15 days). Use of an individualised strategy (incorporating clinical features or serum procalcitonin) appears to safely reduce duration of antibiotic therapy for VAP.”

Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults; Pugh R, Grant C, Cooke RP, Dempsey G Cochrane Library 2012 issue 2

Monitoraggio Della Terapia (2)

Validato l'uso della PCT come guida alla prosecuzione/interruzione della terapia antibiotica.

"Use of procalcitonin to guide initiation and duration of antibiotic treatment in patients with ARI was not associated with higher mortality rates or treatment failure. Antibiotic consumption was significantly reduced across different clinical settings and ARI diagnoses."

Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections; Schuetz P, Müller B, Christ-Crain M, Stolz D, Tamm M, Bouadma L, Luyt CE, Wolff M, Chastre J, Tubach F, Kristoffersen KB, Burkhardt O, Welte T, Schroeder S, Nobre V, Wei L, Bhatnagar N, Bucher HC, Briel M; Cochrane Database Syst Rev. 2012 Sep 12;9

Monitoraggio Della Terapia (3)

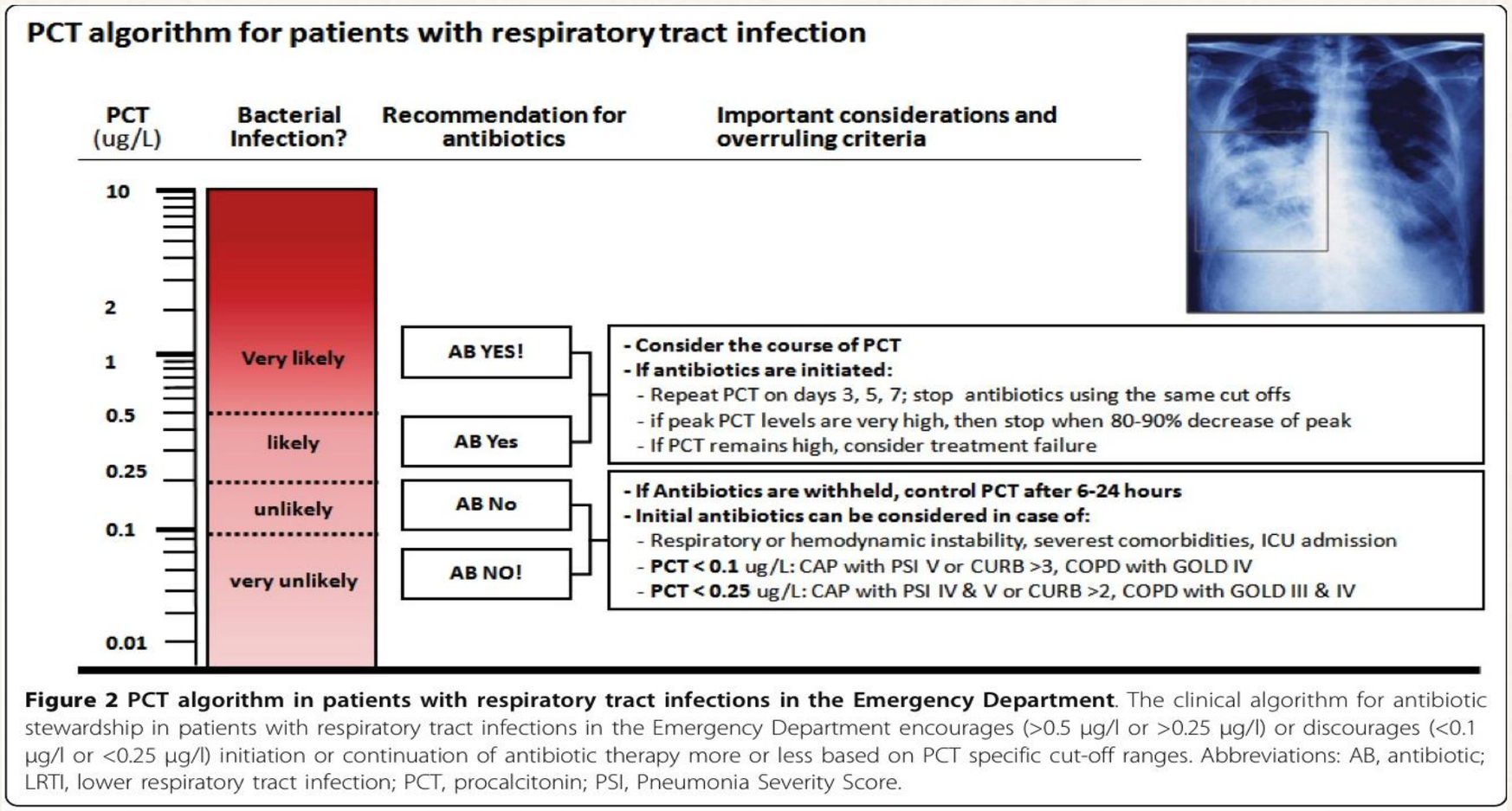


Figure 2 PCT algorithm in patients with respiratory tract infections in the Emergency Department. The clinical algorithm for antibiotic stewardship in patients with respiratory tract infections in the Emergency Department encourages (>0.5 μg/l or >0.25 μg/l) or discourages (<0.1 μg/l or <0.25 μg/l) initiation or continuation of antibiotic therapy more or less based on PCT specific cut-off ranges. Abbreviations: AB, antibiotic; LRTI, lower respiratory tract infection; PCT, procalcitonin; PSI, Pneumonia Severity Score.

Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future; Schuetz P, Albrich W, Mueller B; BMC Med. 2011 Sep 22;9:107

Monitoraggio Della Terapia (4)

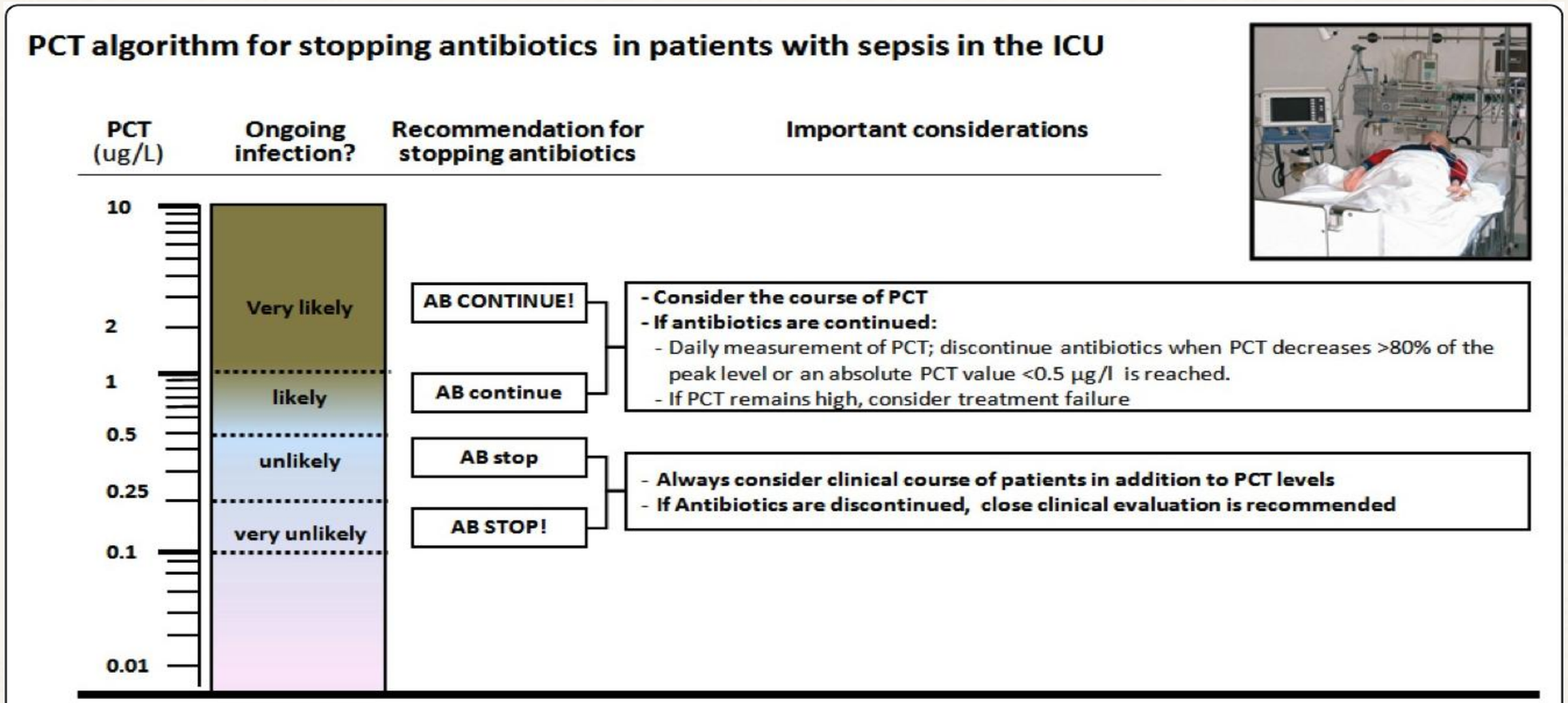


Figure 3 PCT algorithm in patients with sepsis in the ICU. In critically ill patients in the ICU, cut-offs are higher and initial empiric antibiotic therapy should be encouraged in all patients with suspicion of sepsis. PCT cut-offs are helpful in the subsequent days after admission to shorten the courses of antibiotic therapy in patients with clinical improvement. Abbreviations: AB, antibiotic; PCT, procalcitonin.

Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future; Schuetz P, Albrich W, Mueller B; BMC Med. 2011 Sep 22;9:107

Grazie Per L’Attenzione

Dott.ssa Magda D’Astuto
Terapia Intensiva Cardiochirurgica
A.O. Provincia di Lecco

magdadas@gmail.com