SOCIETÀ MEDICA
DI SANTA MARIA NUOVA

IX EDIZIONE

Giornate Mediche di
Santa Maria Nuova 2017

LA DIMISSIONE
OSPEDALIERA "RITARDATA":
Complicanze intraospedaliere
e criticità gestionali

5-6 Ottobre 2017

Quando lo stato settico "sfugge di mano": il ruolo del rianimatore

V. Pavoni

Anestesia e Rianimazione

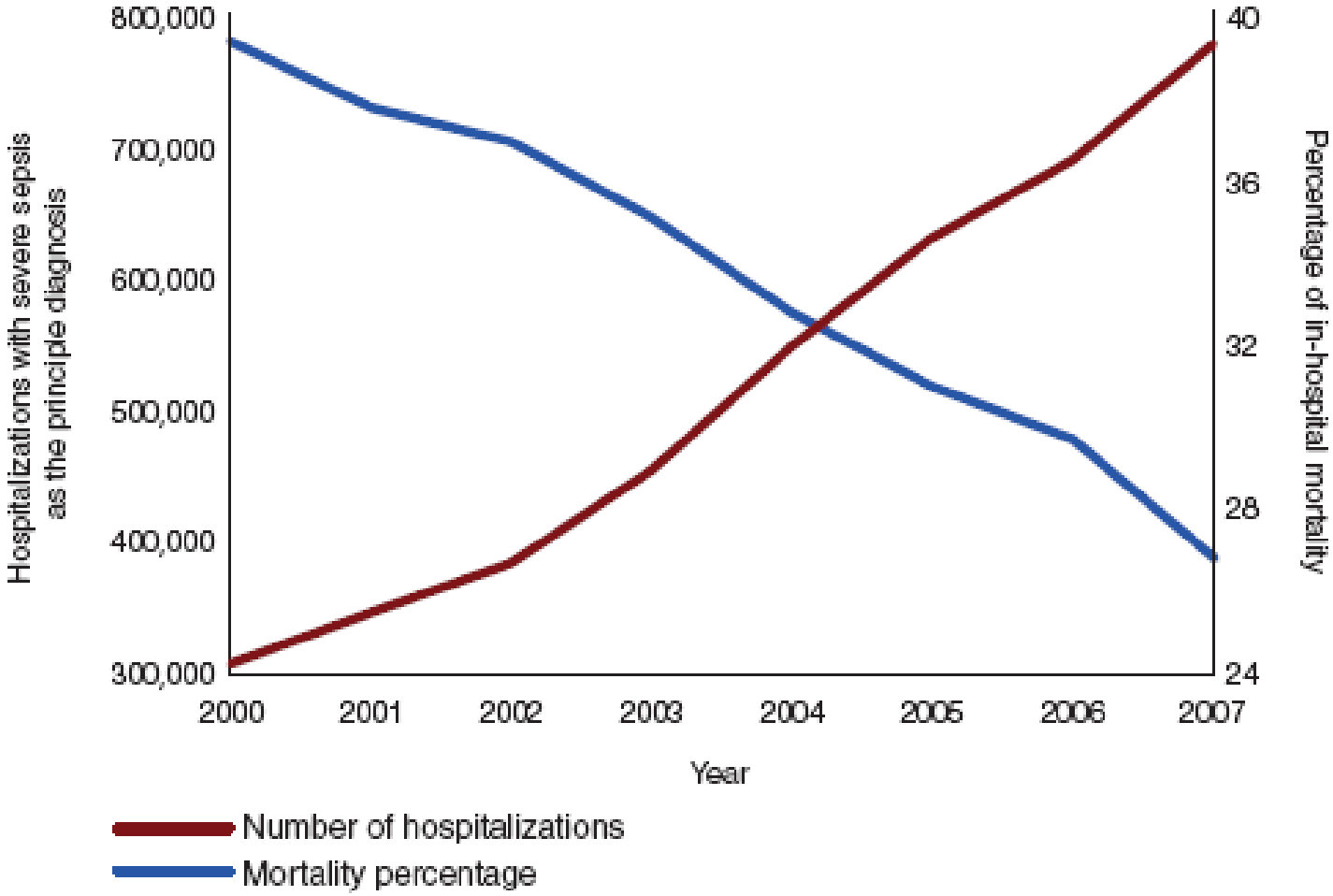
PO di Santa Maria Nuova

Knowledges flows continuously…

- Infection + inflammation ➔ SEPSIS
  - Def moved to Sepsis 3
  - Inflammation kills, not infection itself
- Sepsis Incidence ↗
- Co-morbidity ↗
- Mortality ↘
- Severity better scored
  - SAPS2, APACHE2, SOFA (OF Score)
- Defining OF not easy

- Supportive therapy is rationalized
  - The faster the better…
  - AB, Fluid, Vpressors…
  - MV, RRT, Early mobilisation
  - Stop Dopa, introduce VP
  - Discuss PDI drugs…
- Adjuvent therapies failed…
  - 40 RCTs ➔ failure
  - Basic research helped a lot…

Despite improving hospital care, **one in 1,200 Americans will die** of severe sepsis this year.



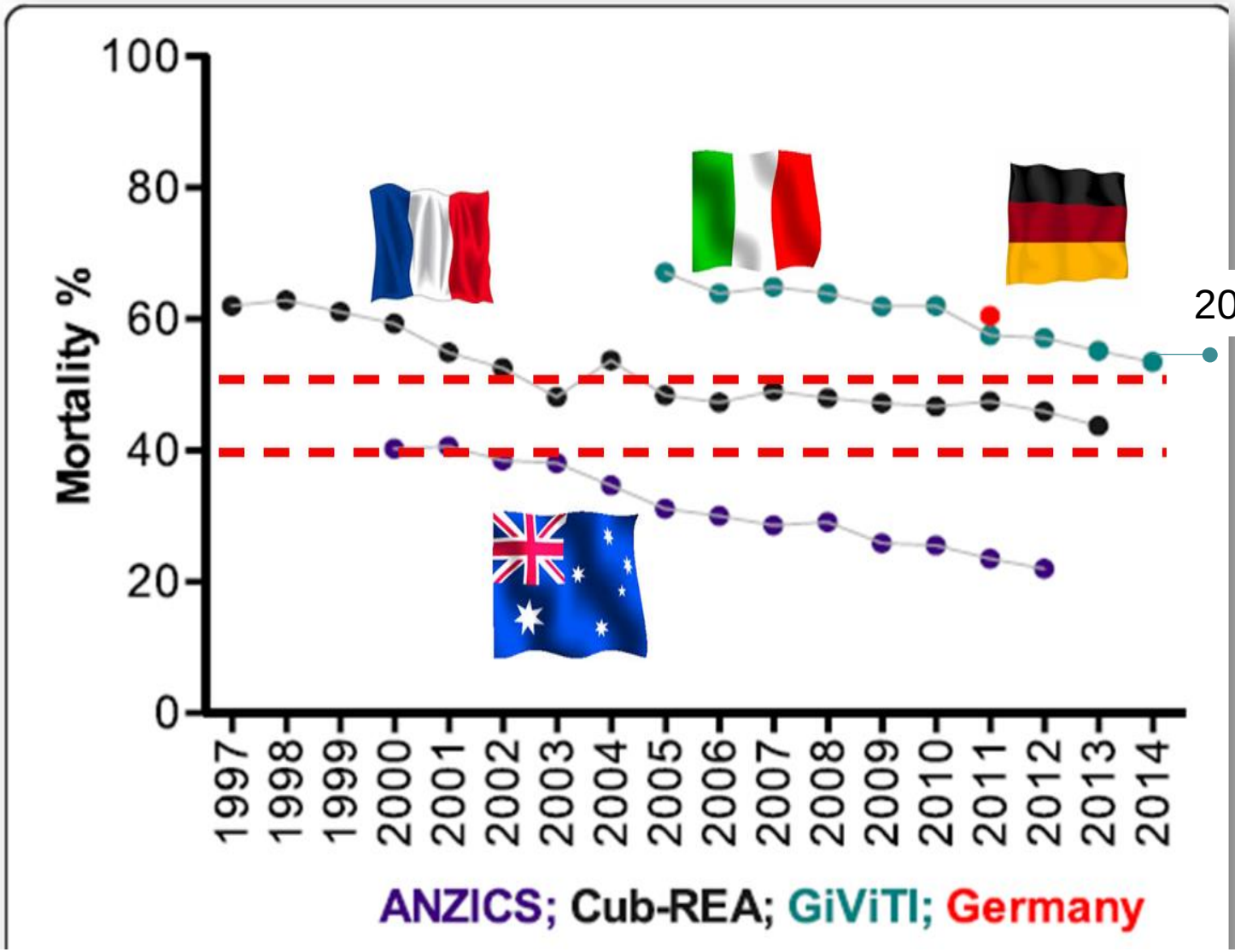
Chest **140**, 1223–1231 (2011).

Budget 1% of US IGrowth

SEPTIC SHOCK: MORTALITY IS STILL HIGH
(at least in Europe and in real life)

PROBLEM EXTENT

Shankar-Hari *et al. Critical Care* (2015) 19:445
DOI 10.1186/s13054-015-1164-6



The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

JAMA. 2016;315(8):801-810.

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

NEW DEFINITIONS

@Sepsis is defined as life-threatening **organ dysfunction** caused by a dysregulated host response to infection

@Organ dysfunction can be identified as an acute change in total SOFA score ≥ 2 points consequent to the infection

@Septic shock clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥ 65mmHg and having a serum lactate level >2 mmol/L (18mg/dL) despite adequate volume resuscitation.

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

‘ HYSTORICAL’ SEPSIS BUNDLES

Sepsis Six

- Oxygen
- Blood Cultures
- Antibiotics
- Fluids
- Lactate & Hb
- Insert Catheter & monitor urine output

- within 1 hour
- Then ensure Critical Care assistance if shocked to complete EGDT

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

PROBLEM EXTENT

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.

EBM and SEPSIS

GUIDELINES

Intensive Care Med (2008) 34:17–60
DOI 10.1007/s00134-007-0934-2

SPECIAL ARTICLE

R. Phillip Dellinger
Mitchell M. Levy
Jean M. Carlet
Julian Bion
Margaret M. Parker
Roman Jaeschke

Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008

50 Strong Recommendations (1 A-C)

19 Weak Recommendations (2 B-D)

Special Articles

February 2013

(*Crit Care Med* 2013; 41:580–637)

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

34 Strong Recommendations (1 A-C),

35 Weak Recommendations (2 B-D),

7 Ungraded Recommendations

CONFERENCE REPORTS AND EXPERT PANEL

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

31 Strong Recommendations (1 A-C)

42 Weak Recommendations (2 A-D)

18 Best Practice Statement (ungraded)

SEPSIS-SEPTIC SHOCK THERAPIES

NEGATIVE TRIALS SINCE…

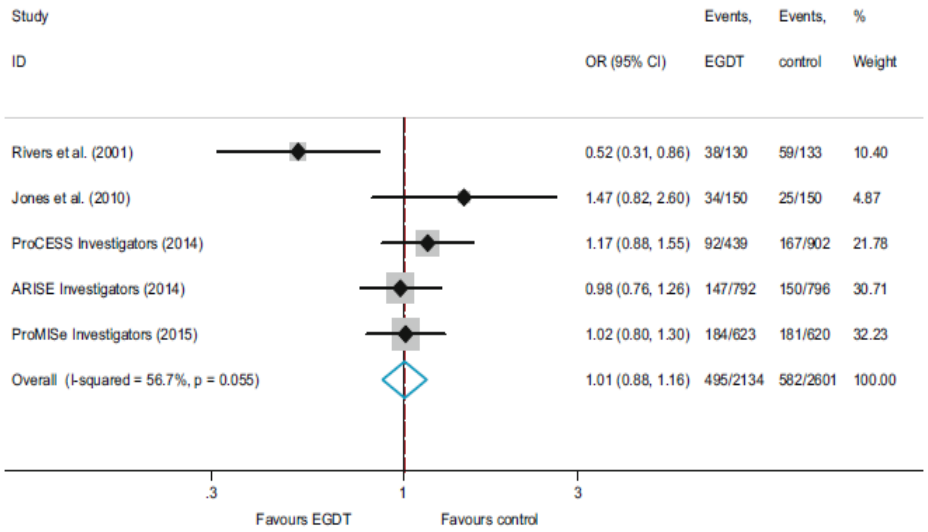
CEMETERY SECTION 2010-2015

EARLY GOAL DIRECTED THERAPY

A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators

Intensive Care Med (2015) 41:1549–1560
DOI 10.1007/s00134-015-3822-1

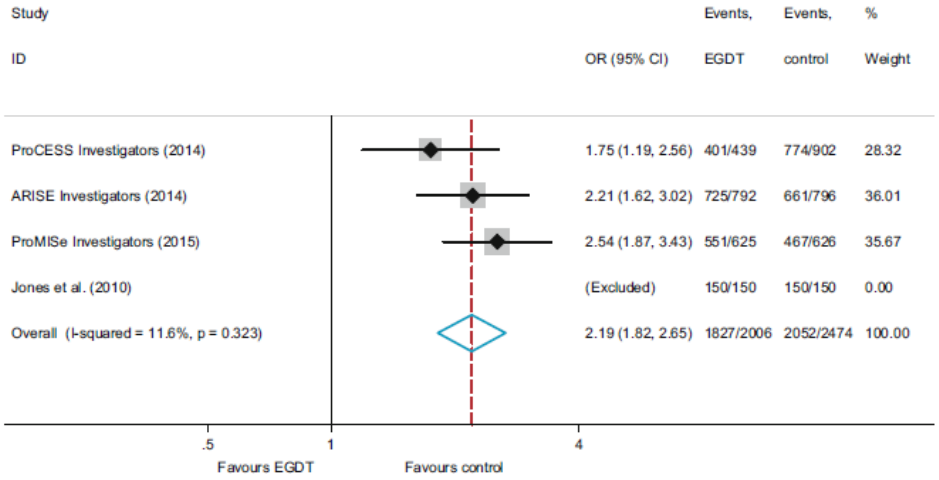
A Primary mortality outcome of each study



Primary objective

Rivers et al. [1]	USA	1	Adult	ED	Usual care	263	In-hospital
Jones et al. [19]	USA	3	Adult	ED	Lactate clearance[c]	300	In-hospital
ProCESS Investigators [8]	USA	31	Adult	ED	Usual care or protocol-based standard therapy[d]	1341	In-hospital[h]
ARISE Investigators [10]	Australasia[a]	51	Adult	ED	Usual care	1600	90-day
ProMISe Investigators [12]	England	56	Adult	ED	Usual care	1260	90-day

A ICU admission[a]



Our meta-analysis of all published randomised clinical trials of EGDT does not show improved survival for patients randomised to receive EGDT compared to usual care or to less invasive alternative haemodynamic resuscitation protocols. EGDT is, however, associated with increased admission to ICU. Our findings do not support the systematic use of EGDT in the management of all patients with septic shock or its inclusion in the Surviving Sepsis Campaign guidelines.

Stratificazione del rischio

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

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Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

qSOFA

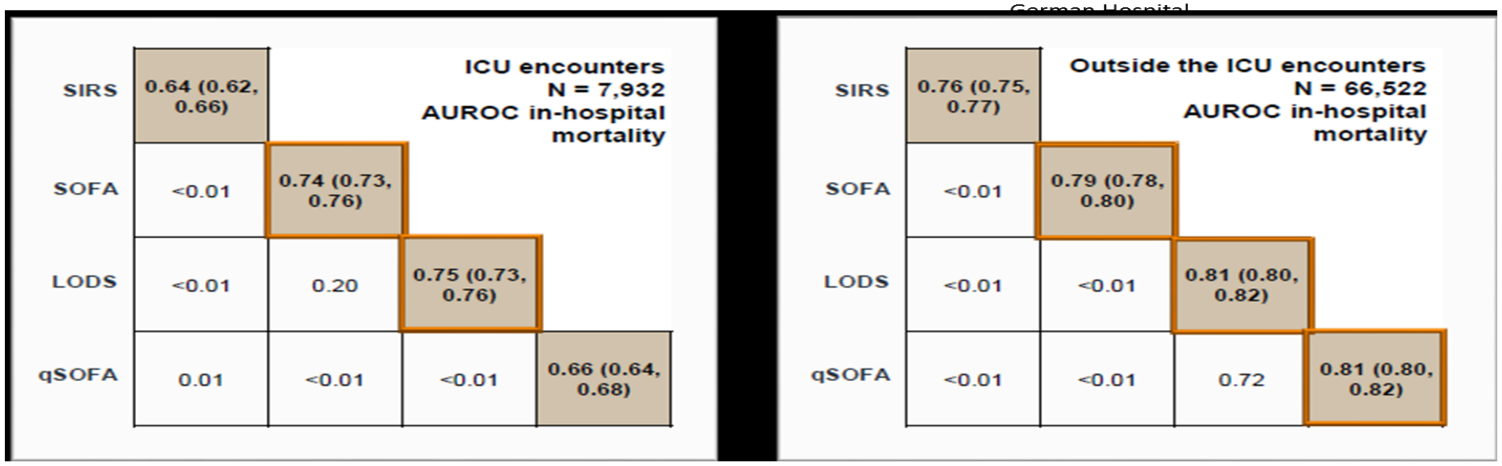
Patients with suspected infection **who are likely to have a prolonged ICU stay or to die** in the hospital can be promptly identified at the bedside with qSOFA (≥2)

1.alteration in mental status,

2.systolic blood pressure ≤100mmHg,

3.respiratory rate ≥ 22/min.

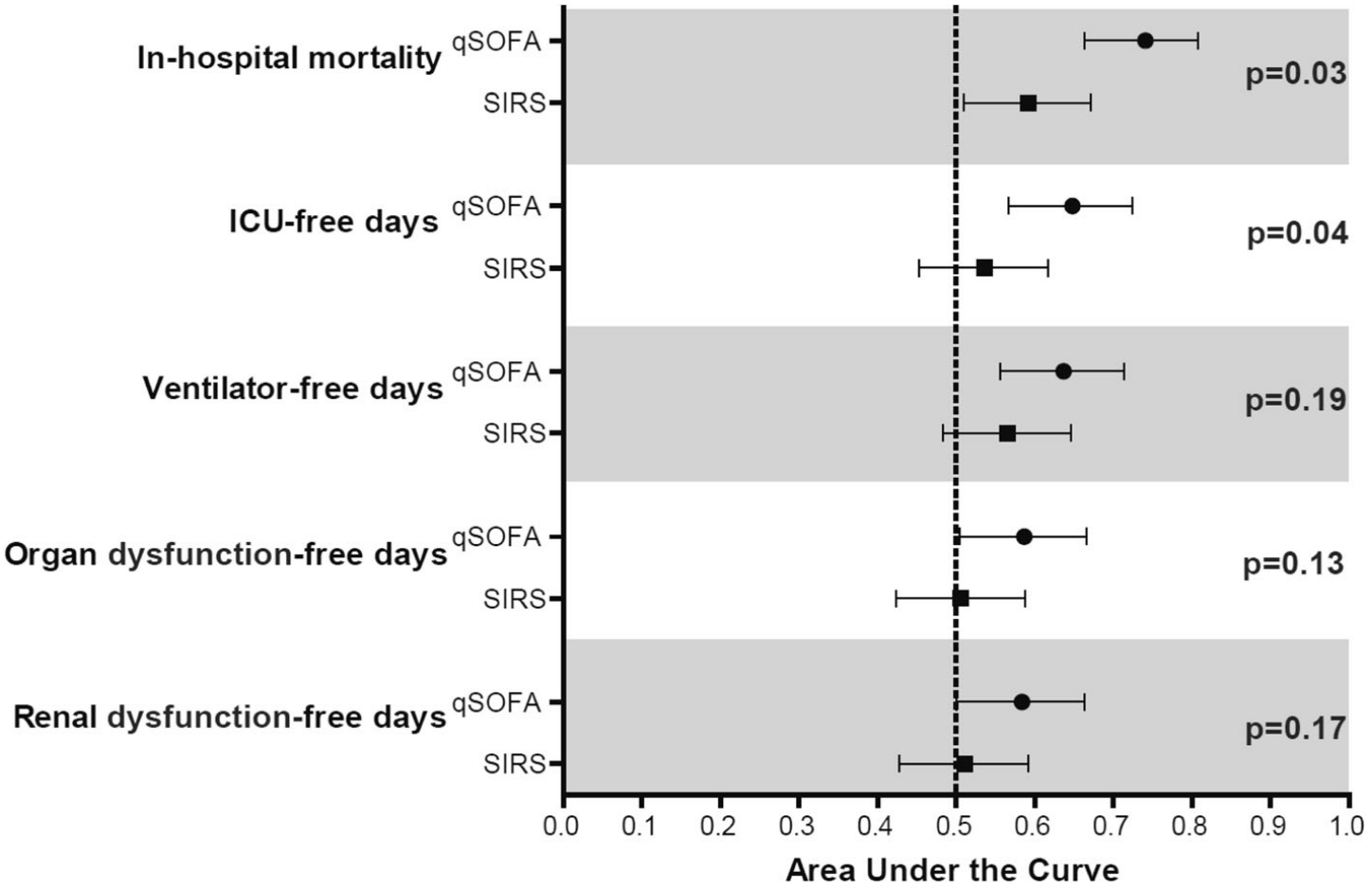
Figure 3. Area Under the Receiver Operating Characteristic Curve and 95% Confidence Intervals for In-Hospital Mortality of Candidate Criteria (SIRS, SOFA, LODS, and qSOFA) Among Suspected Infection Encounters in the UPMC Validation Cohort (N = 74 454)



SOFA and LODS are better in ICU

qSOFA is similar to more complex scores outside ICU

Comparison of qSOFA and SIRS with sospicion of sepsis outside ICU



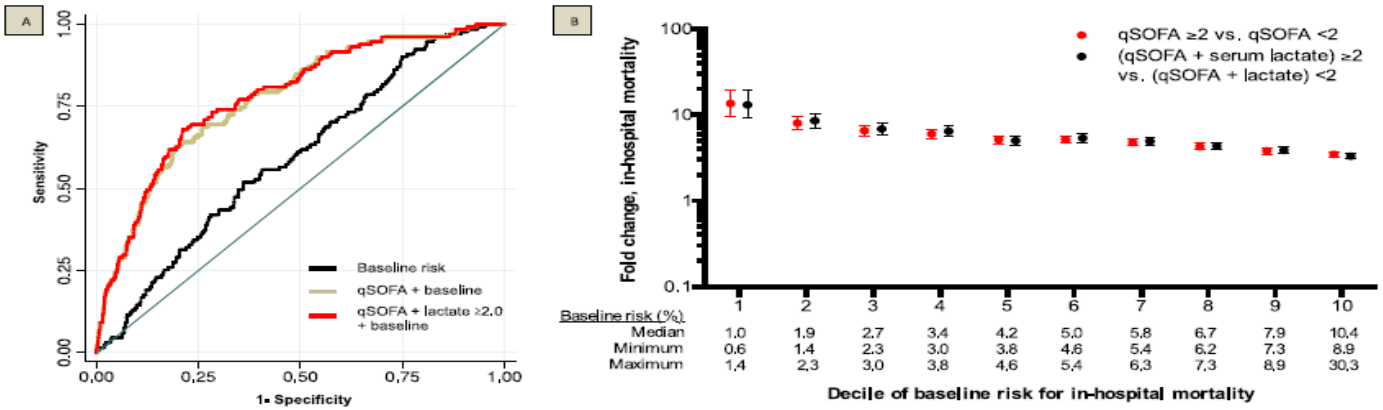
Cririca l care 2017

Lactate

@ During model building in UPMC data, serum lactate did not meet prespecified statistical thresholds for inclusion in qSOFA. But, lactate levels were not measured commonly in the UPMC data set

@ When serum lactate levels were added to qSOFA post hoc in the KPNC health system data set, in which measurement of lactate levels was common, the predictive validity was statistically increased but with little difference

eFigure 10. (A) Receiver operating characteristic curve for qSOFA with and without serum lactate ≥ 2.0 mmol/L compared to baseline risk of in-hospital mortality. (B) Fold change in rate of in-hospital mortality within decile of baseline risk comparing qSOFA with and without serum lactate. All data from KPNC (N=321,380).



The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

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Box 4. qSOFA (Quick SOFA) Criteria

Respiratory rate ≥22/min

Altered mentation

Systolic blood pressure ≤100 mm Hg

Chart 1: National Early Warning Score (NEWS)*

PHYSIOLOGICAL PARAMETERS	3	2	1	0	1	2	3
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations	≤91	92 - 93	94 - 95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart Rate	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Level of Consciousness				A			V, P, or U

MEWS (Modified Early Warning System)

	3	2	1	0	1	2	3
Respiratory Rate per minute		Less than 8		9-14	15-20	21-29	More than 30
Heart Rate per minute		Less than 40	40-50	51-100	101-110	111-129	More than 129
Systolic Blood Pressure	Less than 70	71-80	81-100	101-199		More than 200	
Conscious level (AVPU)	**U**nresponsive	Responds to **P**ain	Responds to **V**oice	**A**lert	New agitation Confusion		
Temperature (°c)		Less than 35.0	35.1-36	36.1-38	38.1-38.5	More than 38.6	
Hourly Urine	Less than	Less than	Less than				

Chart 2: NEWS thresholds and triggers

NEW scores	Clinical risk
0	Low
Aggregate 1–4	
RED score* (Individual parameter scoring 3)	Medium
Aggregate 5–6	
Aggregate 7 or more	High

EARLY WARNING SCORING SYSTEM FOR DETECTING ADULT PATIENTS WHO HAVE OR ARE DEVELOPING CRITICAL ILLNESS

IS THE SCORE FOR YOUR PATIENT 1-2? PERFORM 2 HOURLY OBSERVATIONS AND INFORM NURSE IN CHARGE

IS THE SCORE FOR YOUR PATIENT 3? PERFORM 1-2 HOURLY OBSERVATIONS AND INFORM NURSE IN CHARGE

*IF THE MEWS SCORE IS DETERIORATING : THE WARD S.H.O. OR DUTY DOCTOR **MUST** ATTEND*

IS THE SCORE FOR YOUR PATIENT 4 OR MORE? PERFORM OBSERVATIONS AT LEAST 1/2 HOURLY. ENSURE MEDICAL ADVICE IS SOUGHT AND CONTACT OUTREACH TEAM (see below)

Adjunctive Therapies

Surviving Sepsis Campaign

SPECIFIC ADJUNCTIVE THERAPIES & SSC GUIDELINES

	2004	2008	2012	2016
STEROIDS	shocked	refractory shock	refractory shock	refractory shock
TIGHT GLYCEMIC CONTROL (<150 mg/dl)				
rhAPC				
ANTITHROMBIN				
IMMUNOGLOBULINS	pediatric	pediatric		
BLOOD PURIFICATION	Not mentioned	Not mentioned	Not mentioned	
SELENIUM	Not mentioned	Not mentioned		

STEROIDS

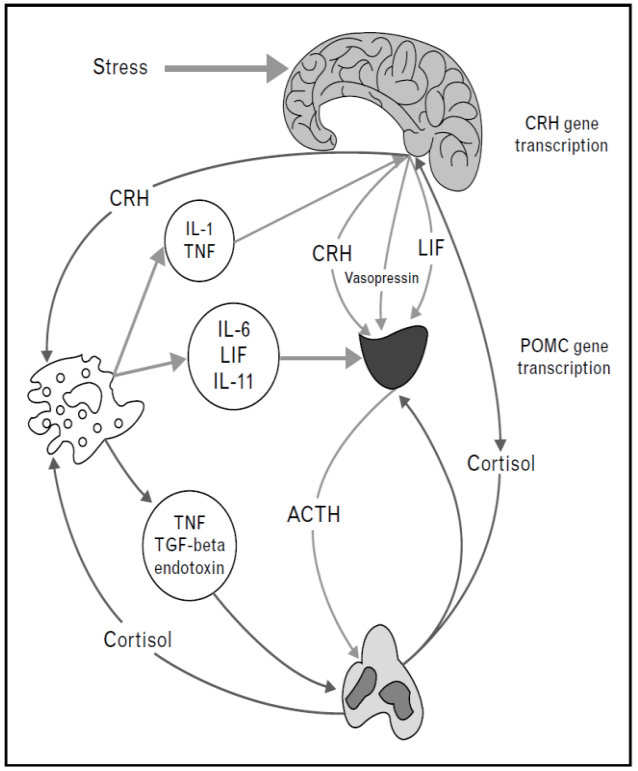
RATIONALE FOR USE IN SEPSIS

@ VASOACTIVE PROPRIETIES
- Maintain vascular tone
- Reactivity to angiotensin II and catecholamines
- Decrease NO production

@ ANTI-INFLAMMATORY PROPRIETIES
- Inhibit the extravasation of leucocytes
- Increase the migration of lymphocytes to the lymphoid tissues
- Inhibit the function of macrophages and antigen-presenting cells
- Inhibit phagocytosis by macrophages
- Inhibit production of TNF-alpha and interleukin-1

@ RELATIVE ADRENAL INSUFFICENCY
- Adrenal glands respond to stress by producing corticosteroids
- "relative insufficiency" means response not appropriate to the degree of stress
- Up to 50% with septic shock
- Lab or clinical diagnosis: uncertain

Figure 1 Activation of the hypothalamic–pituitary–adrenal axis (HPA) by a stressor and the interaction with the inflammatory response



ACTH, adrenocorticotrophic hormone; CRH, corticotrophin-releasing hormone; IL-6, interleukin-6; IL-11, interleukin-11; LIF, leukemia-inhibitory factor; POMC, pro-opiomelanocortin; TGF-beta, transforming growth factor-β; TNF, tumor necrosis factor.

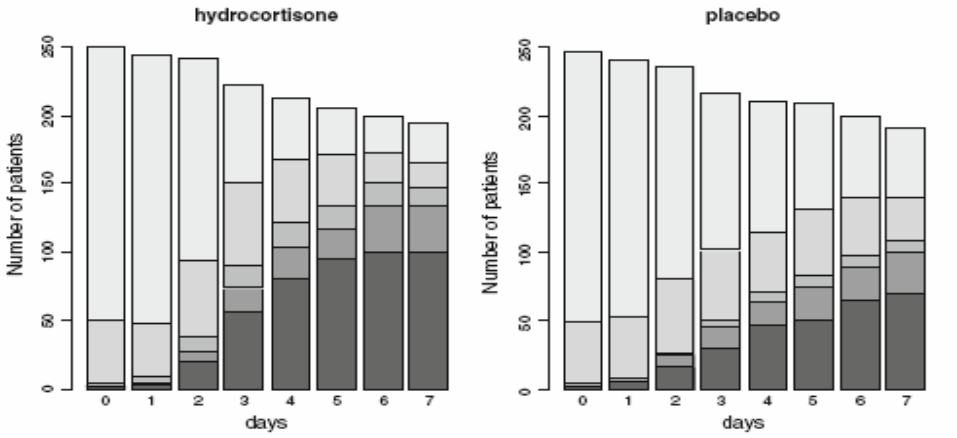
Annetta MG et al, ***Current Drug Targets*, 2009**
Marik P et al, **Cur Opin Cri Care, 2007**
Cooper MS et al, **NEJM, 2003**

STEROIDS

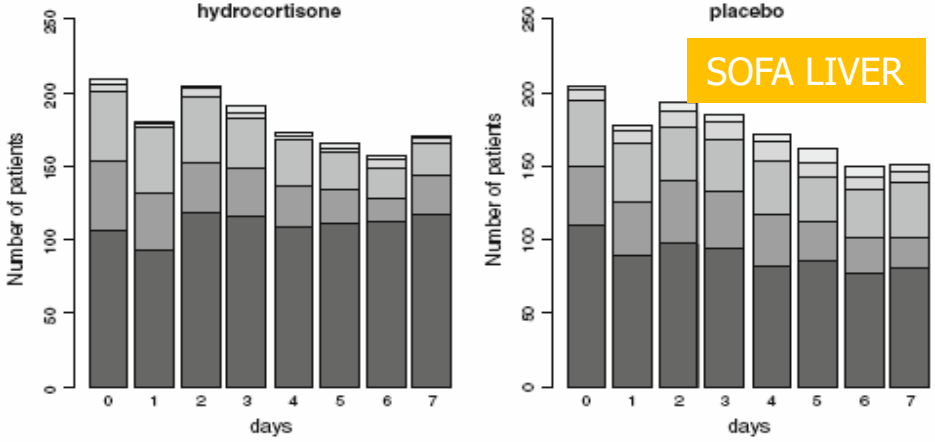
CLINICAL EVIDENCES

Fig. 2 Comparison of the SOFA sub-scores course in the two randomized groups, namely cardiovascular (*upper plots*) and liver (*lower plots*) components; the darker the *gray boxes*, the lower the SOFA sub-score values (ranging from 0 to 4)

SOFA CVS



SOFA LIVER



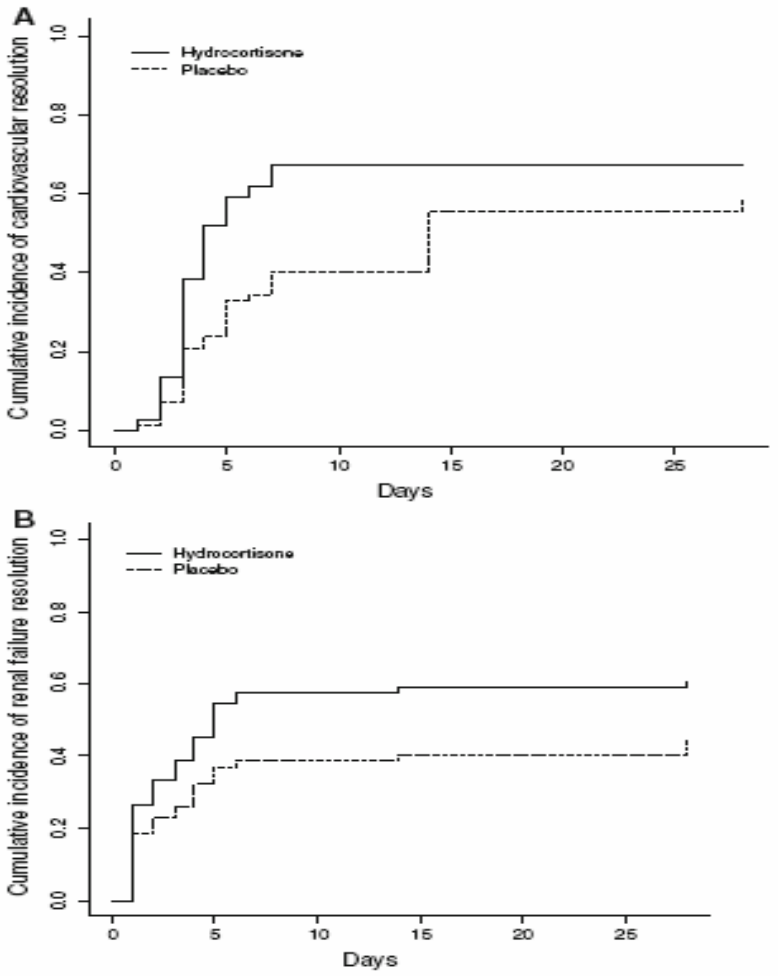


Fig. 3 Cumulative incidence of organ failure resolution (i.e., score value <3) according to treatment arm: cardiovascular failure (a), renal failure (b)

Intensive Care Med (2011) 37:1765–1772
DOI 10.1007/s00134-011-2334-x

ORIGINAL

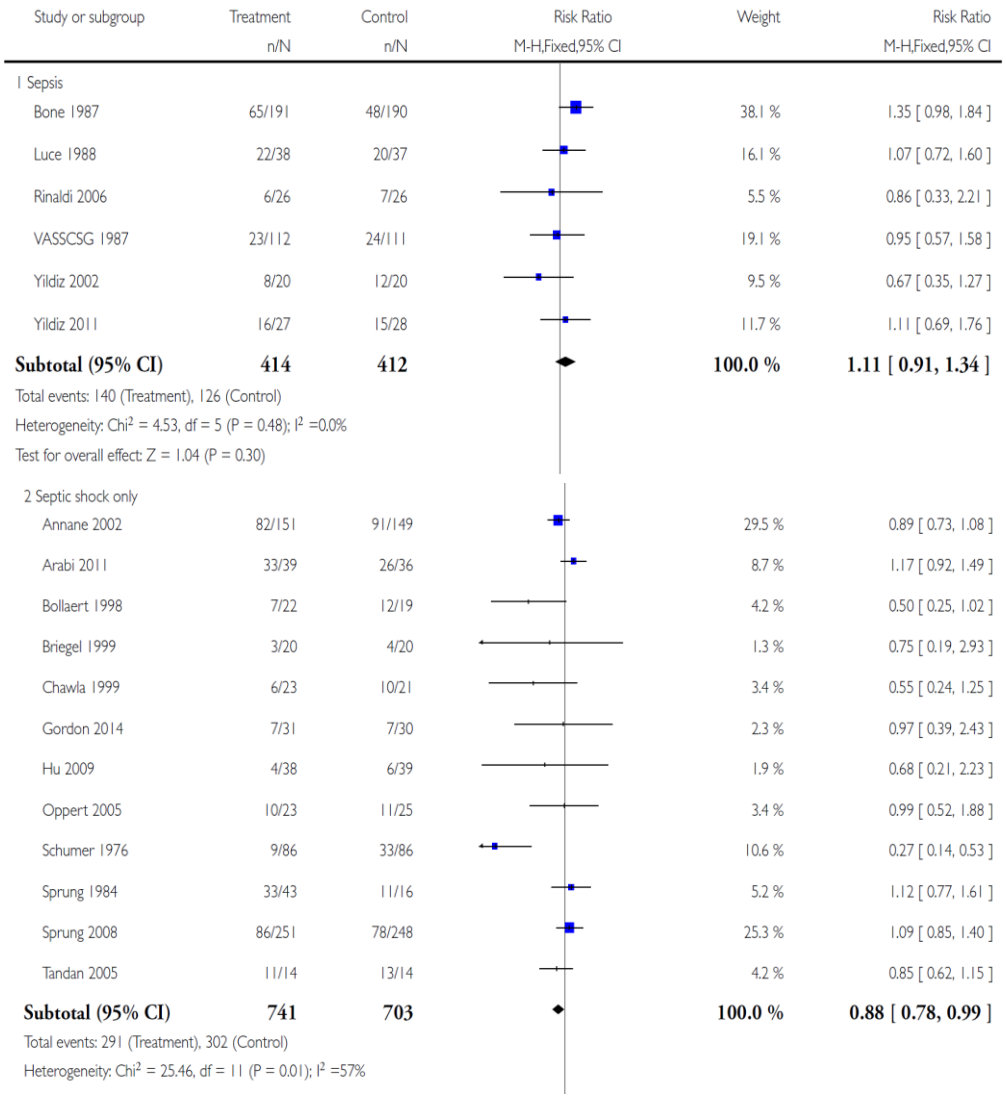
R. Moreno
C. L. Sprung
D. Annane
S. Chevret
J. Briegel

Time course of organ failure in patients with septic shock treated with hydrocortisone: results of the Corticus study

STEROIDS

THE COCHRANE COLLABORATION®

CLINICAL EVIDENCES



Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Sepsis					
Bone 1987	65/191	48/190		38.1 %	1.35 [0.98, 1.84]
Luce 1988	22/38	20/37		16.1 %	1.07 [0.72, 1.60]
Rinaldi 2006	6/26	7/26		5.5 %	0.86 [0.33, 2.21]
VASSCSG 1987	23/112	24/111		19.1 %	0.95 [0.57, 1.58]
Yildiz 2002	8/20	12/20		9.5 %	0.67 [0.35, 1.27]
Yildiz 2011	16/27	15/28		11.7 %	1.11 [0.69, 1.76]
Subtotal (95% CI)	**414**	**412**		**100.0 %**	**1.11 [0.91, 1.34]**
Total events: 140 (Treatment), 126 (Control)					
Heterogeneity: Chi² = 4.53, df = 5 (P = 0.48); I² =0.0%					
Test for overall effect: Z = 1.04 (P = 0.30)					
2 Septic shock only					
Annane 2002	82/151	91/149		29.5 %	0.89 [0.73, 1.08]
Arabi 2011	33/39	26/36		8.7 %	1.17 [0.92, 1.49]
Bollaert 1998	7/22	12/19		4.2 %	0.50 [0.25, 1.02]
Briegel 1999	3/20	4/20		1.3 %	0.75 [0.19, 2.93]
Chawla 1999	6/23	10/21		3.4 %	0.55 [0.24, 1.25]
Gordon 2014	7/31	7/30		2.3 %	0.97 [0.39, 2.43]
Hu 2009	4/38	6/39		1.9 %	0.68 [0.21, 2.23]
Oppert 2005	10/23	11/25		3.4 %	0.99 [0.52, 1.88]
Schumer 1976	9/86	33/86		10.6 %	0.27 [0.14, 0.53]
Sprung 1984	33/43	11/16		5.2 %	1.12 [0.77, 1.61]
Sprung 2008	86/251	78/248		25.3 %	1.09 [0.85, 1.40]
Tandan 2005	11/14	13/14		4.2 %	0.85 [0.62, 1.15]
Subtotal (95% CI)	**741**	**703**		**100.0 %**	**0.88 [0.78, 0.99]**
Total events: 291 (Treatment), 302 (Control)					
Heterogeneity: Chi² = 25.46, df = 11 (P = 0.01); I² =57%					

@ 33 eligible trials (n = 4268)

@ Low-quality evidence corticosteroids reduce mortality among patients with sepsis.

@ **Moderate-quality evidence** suggests that a long course of low-dose corticosteroids **reduced 28-day mortality** without inducing major complications (GI bleeding, superinfection and neuromuscular weakness)

Annane D, et al. Cochrane Database of Systematic Reviews 2015, Issue 12

STEROIDS

Oda et al. Journal of Intensive Care 2014, 2:55
http://www.jintensivecare.com/content/2/1/55

JOURNAL OF INTENSIVE CARE

GUIDELINE Open Access

The Japanese guidelines for the management of sepsis

Shigeto Oda[1*], Mayuki Aibiki[2], Toshiaki Ikeda[3], Hitoshi Imaizumi[4], Shigeatsu Endo[5], Ryoichi Ochiai[6], Joji Kotani[7],

Steroid

CQ1: What is the indication of steroid therapy in sepsis?

A1:

- The use of steroids is aimed at early recovery from shock in adult patients with septic shock who do not respond to initial fluid resuscitation and vasoactive drugs (2B).
- Adrenocorticotropic hormone (ACTH) testing is not required to determine the indication for steroid therapy (2B).
- Concerning the adverse effects of steroid therapy, it should be noted that the incidence of *de novo* sepsis and septic shock are significantly higher, other than hypernatremia and hyperglycemia (2B).

CQ2: When should steroid therapy be started?

A2: Steroids are administered at the early stage of shock onset (2C).

CQ3: How should steroids be administered and what should be the duration of treatment?

A3:

- Low-dose and long-term steroid therapy, such as ≤300 mg/day hydrocortisone for ≥5 days, is recommended (1A).
- For hydrocortisone, an equivalent dose of 200 mg/day is divided into four doses, or a continuous infusion of 10 mg/h (240 mg/day) is administered after a bolus dose of 100 mg (2B).

CQ4: What kind of steroid should be used?

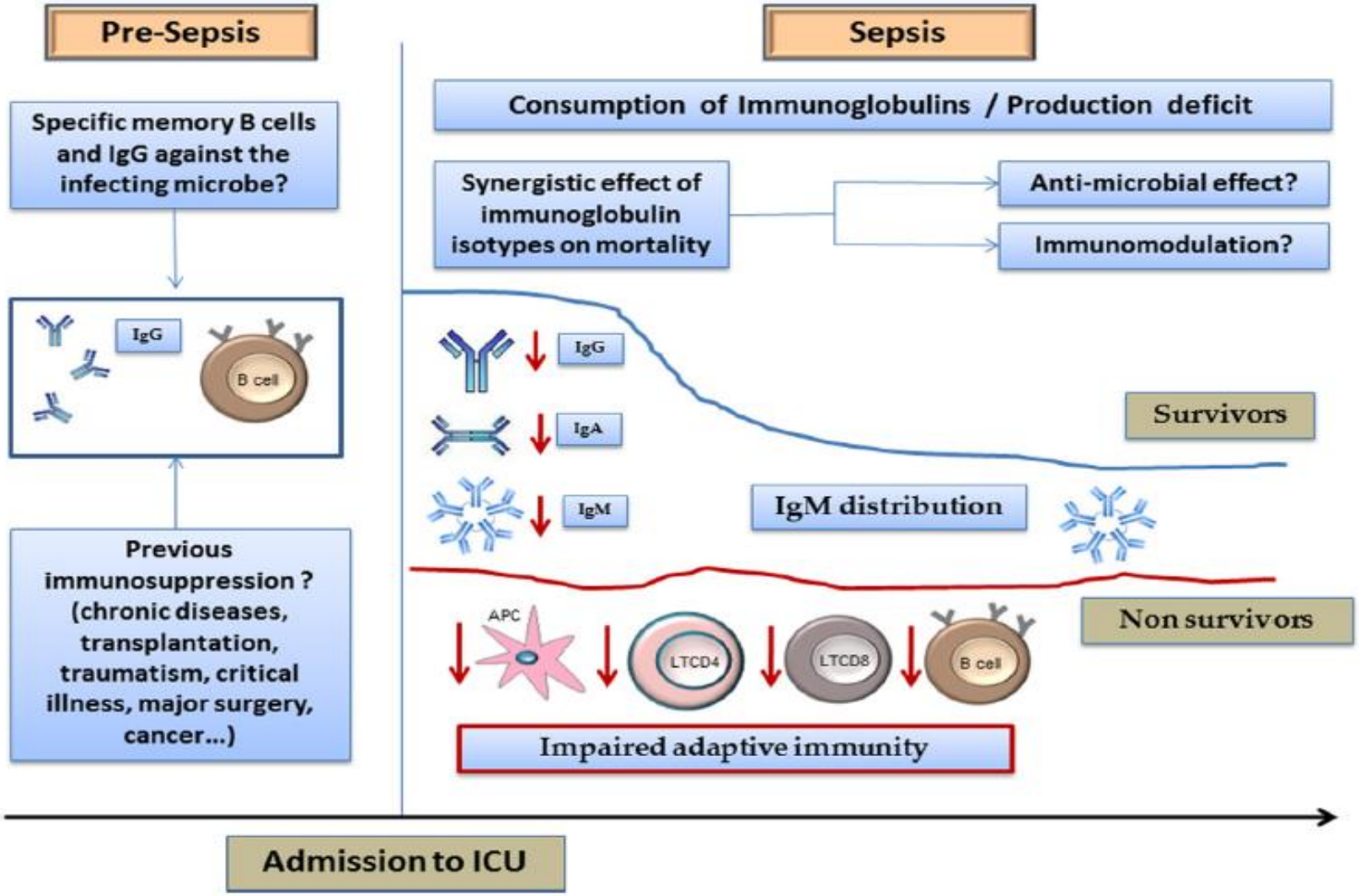
A4: Hydrocortisone should be used (1A). Methylprednisolone can be used as an alternative (2C); however, dexamethasone or fludrocortisone should not be administered (2B).

CQ5: How long should steroids be administered?

A5: Steroids should be gradually discontinued if administration of vasoactive drugs is no longer required (2D).

IMMUNOGLOBULINS

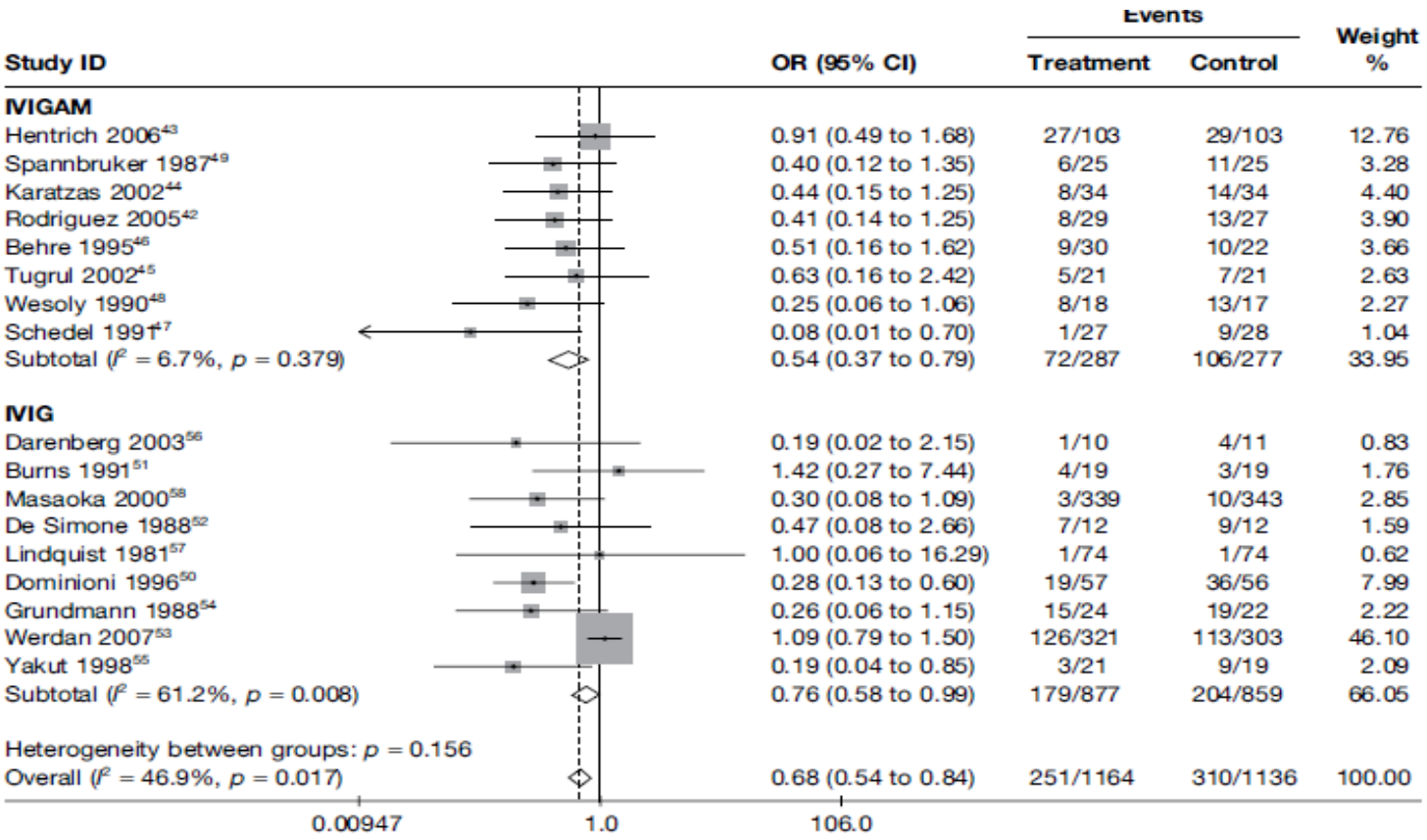
RATIONALE



Giamarellos-Bourboulis EJ et al. Int J Antimicrob Agents (2015) ;46; 1:S25-8.

IMMUNOGLOBULINS

CLINICAL EVIDENCES: IgG vs IgM



Studies using IgGAM showed a more consistent mortality reduction in the treatment arm as compared to those where standard polyclonal IgG were used.

Kreymann et al. Crit Care Med 2007
Soares et al. Health Technology Assessment 2010
Alejandra et al. Cochrane Database Syst Rev. 2013
Busani et al. Minerva Anestesiol 2016

IMMUNOGLOBULINS

Intensive Care Med
DOI 10.1007/s00134-017-4683-6

CONFERENCE REPORTS AND EXPERT PANEL

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Andrew Rhodes[1*], Laura E. Evans[2], Waleed Alhazzani[3], Mitchell M. Levy[4], Massimo Antonelli[5], Ricard Ferrer[6], Anand Kumar[7], Jonathan E. Sevransky[8], Charles L. Sprung[9], Mark E. Nunnally[2], Bram Rochwerg[3],

Surviving Sepsis Campaign

J. IMMUNOGLOBULINS

1. We suggest against the use of IV immunoglobulins in patients with sepsis or septic shock (weak recommendation, low quality of evidence).

IV immunoglobulin (IVIg). The most recent Cochrane meta-analysis [329] differentiates between standard polyclonal IV immunoglobulins (IVIgG) and immunoglobulin M-enriched polyclonal Ig (IVIgGM). In ten studies with IVIgG (1430 patients), mortality between 28 and 180 days was 29.6% in the IVIgG group and 36.5% in the placebo-group (RR 0.81; 95% CI 0.70–0.93), and for the seven studies with IVIgGM (528 patients), mortality between 28 and 60 days was 24.7% in the IVIgGM group and 37.5% in the placebo-group (RR 0.66; 95% CI 0.51–0.85). The certainty of the studies was rated as low for the IVIgG trials, based on risk of bias and heterogeneity, and as moderate for the IVIgGM trials, based on risk of bias. Comparable results were found in other meta-analyses [330]. However, after excluding low-quality trials, the recent Cochrane analysis [329] revealed no survival benefit.

Most IVIg studies are small, and some have a high risk of bias; the only large study (n = 624) showed no effect [328]. Subgroup effects between IgM-enriched and non-enriched formulations reveal significant heterogeneity. Indirectness and publication bias were considered, but not invoked in grading this recommendation. The low certainty of evidence led to the grading as a weak recommendation. The statistical information that comes from the high-quality trials does not support a beneficial effect of polyclonal IVIg. We encourage conduct of large multicenter studies to further evaluate the effectiveness of other IV polyclonal immunoglobulin preparations in patients with sepsis.

Intensive Care Med
DOI 10.1007/s00134-017-4683-6

CONFERENCE REPORTS AND EXPERT PANEL

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Andrew Rhodes[1*], Laura E. Evans[2], Waleed Alhazzani[3], Mitchell M. Levy[4], Massimo Antonelli[5], Ricard Ferrer[6], Anand Kumar[7], Jonathan E. Sevransky[8], Charles L. Sprung[9], Mark E. Nunnally[2], Bram Rochwerg[3],

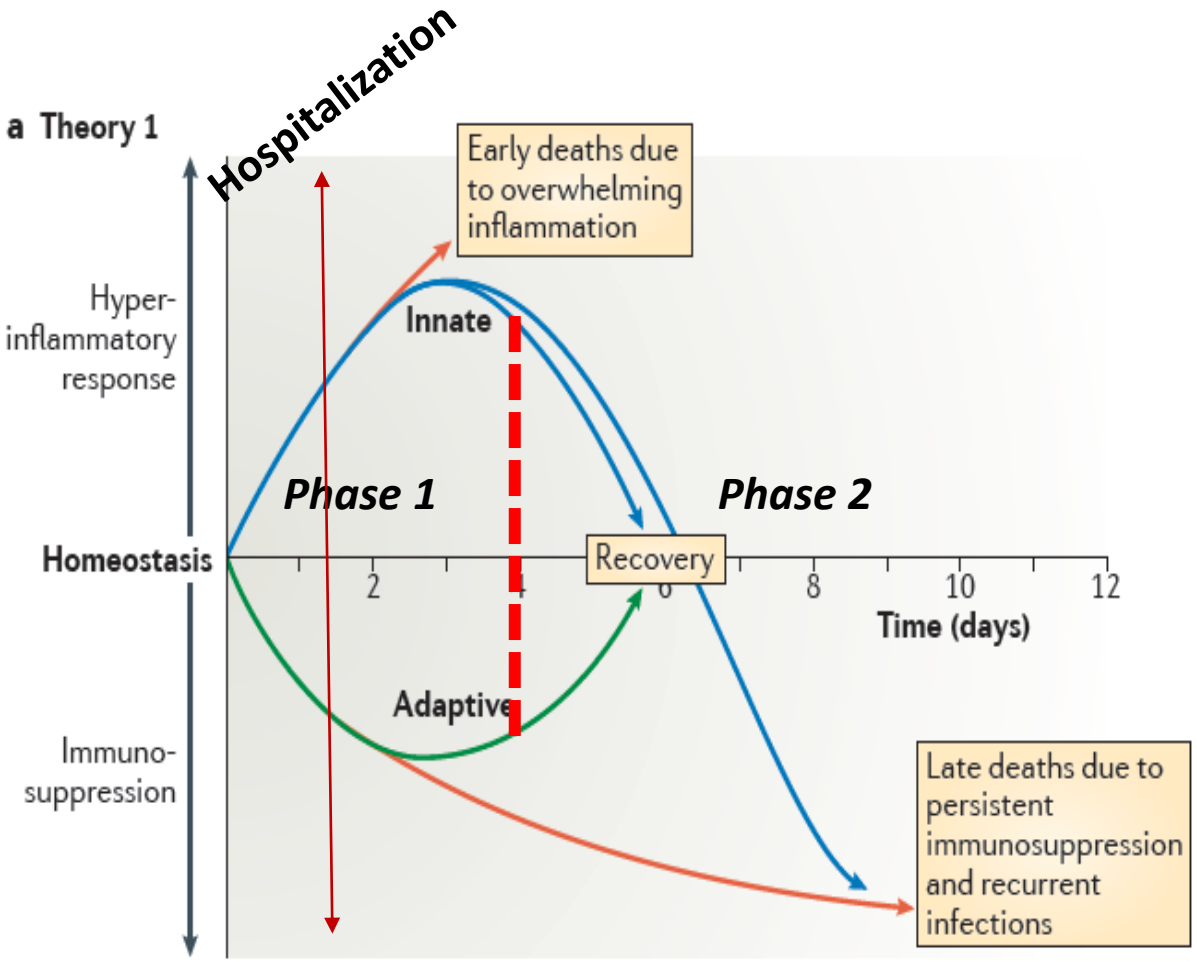
STEROIDS	We suggest **against** using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we **suggest IV hydrocortisone dose of 200 mg per day**	**weak recommendation low QoE**
IMMUNO GLOBULINS	We suggest **against** the use of IV immunoglobulins in patients with sepsis or septic shock	**weak recommendation low QoE**
BLOOD PURIFICATION	We make **no recommendation** regarding the use of blood purification techniques.	**No recommendation**
ANTI COAGULANTS	We recommend **against** the use of **antihrombin** for the treatment of sepsis and septic shock We make **no recommendation** regarding the use of **thrombomodulin** or **heparin** for the treatment of sepsis or septic shock.	**strong recommendation, moderate QoE** **weak recommendation low QoE**

Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

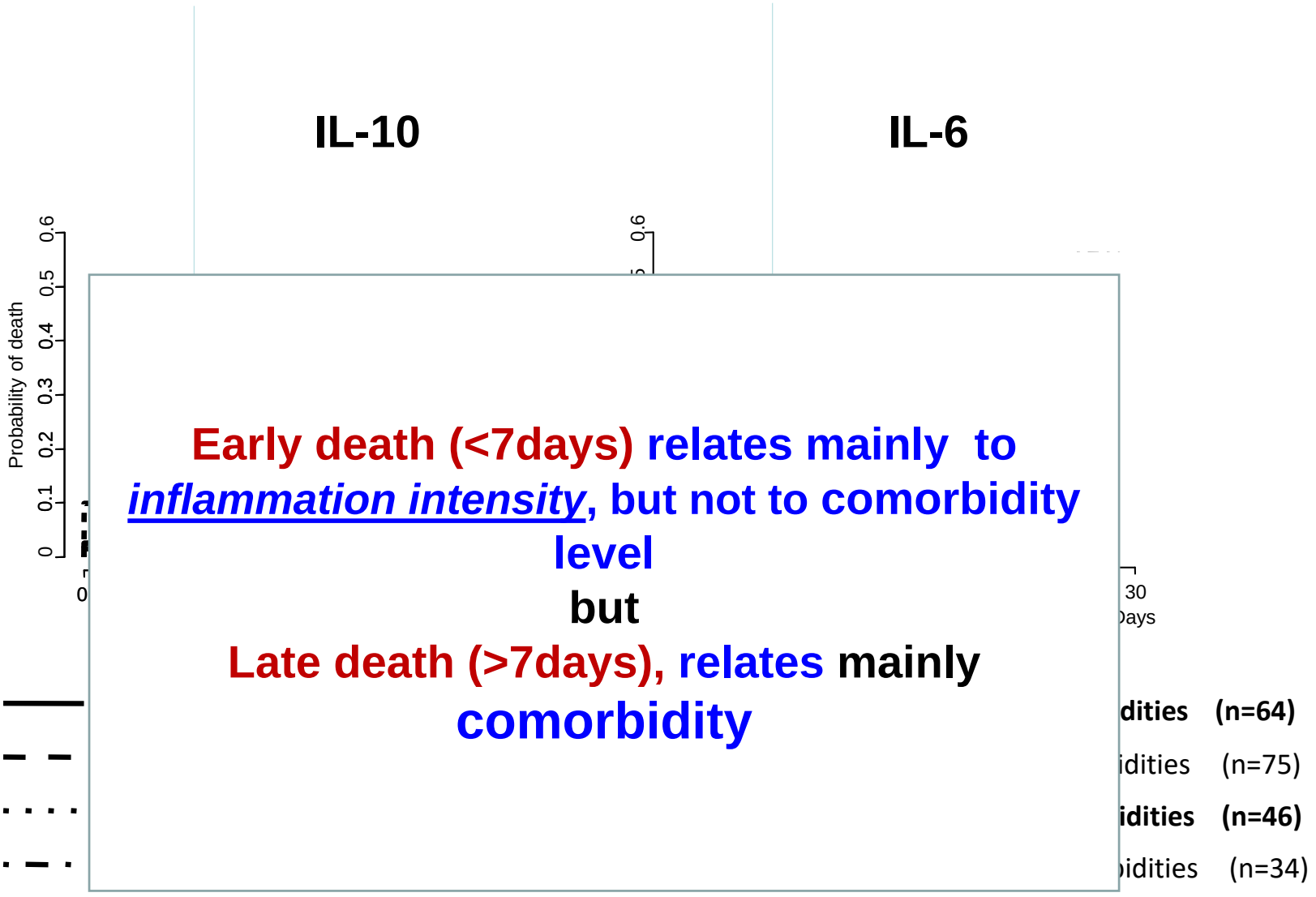
Nature Reviews Immunology | AOP, published online 15 November 2013; doi:10.1038/nri3552

Richard S. Hotchkiss[1], Guillaume Monneret[2] and Didier Payen[3]

Post-Agressive Immuno-Depression (PAID) Syndrome



202 SS Patients (multicentric)



Early death (<7days) relates mainly to *inflammation intensity*, but not to comorbidity level

but

Late death (>7days), relates mainly comorbidity

The Immunoscope…

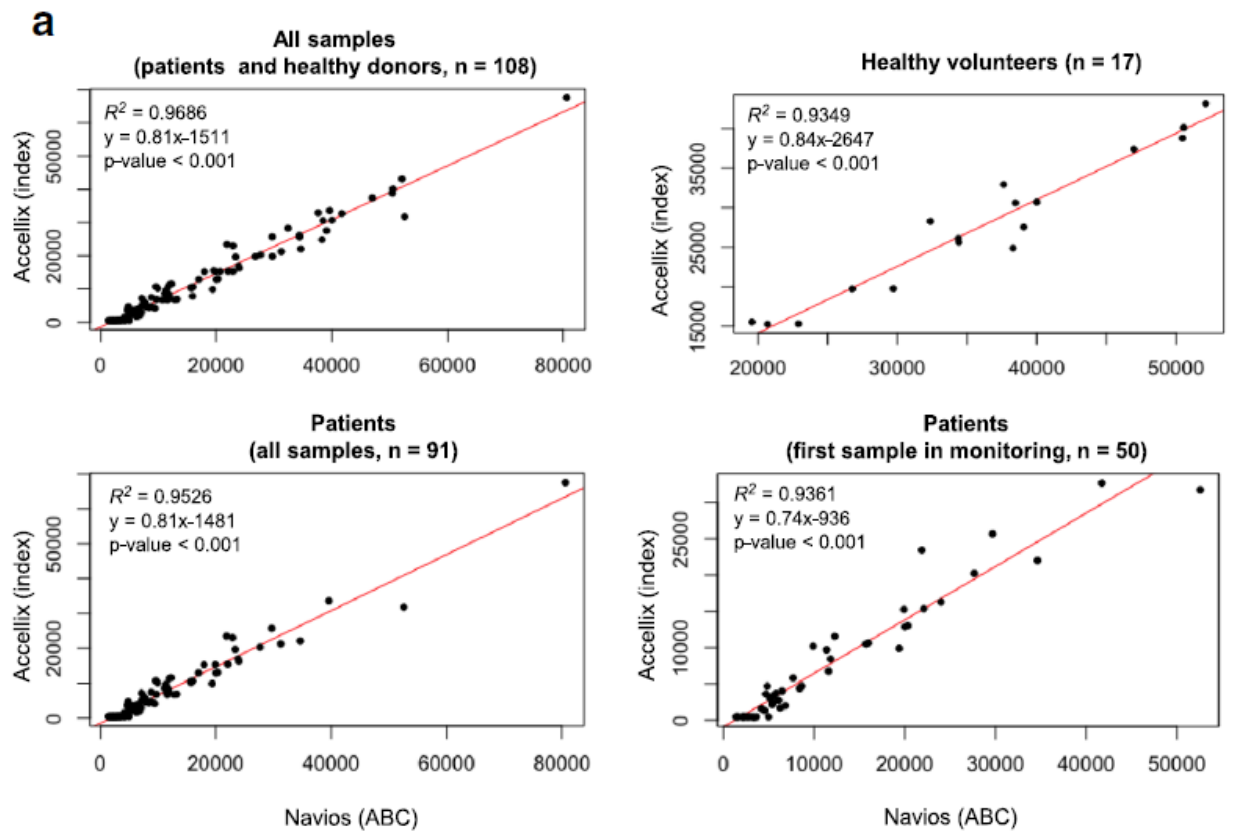
Inflammation monitoring is crucial

Automated bedside flow cytometer for mHLA-DR expression measurement: a comparison study with reference protocol

Zouiouich *et al. Intensive Care Medicine Experimental* (2017) 5:39
DOI 10.1186/s40635-017-0156-z

FL

Mehdi Zouiouich



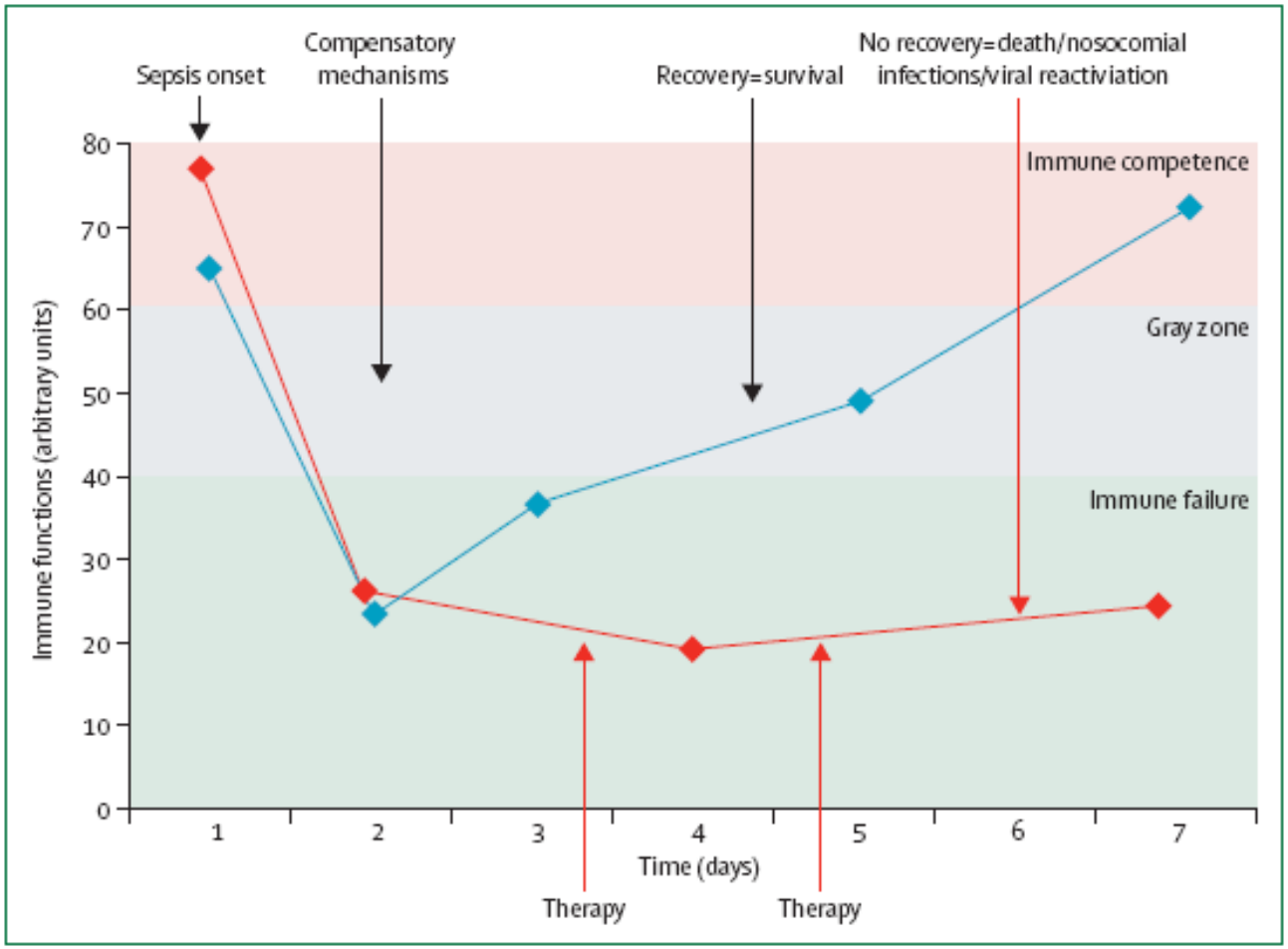
Conclusions: This fully automated table top cytometer appears to be a suitable tool for ICU patient monitoring and on-going clinical trials as there is no sample preparation and no need for specific skills in flow cytometry. Upon validation in

When PAID syndrome should be treated? For how long? By what type of drug?

Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach

Richard S Hotchkiss, Guillaume Monneret, Didier Payen

Immunostimulation therapy in sepsis: a new approach

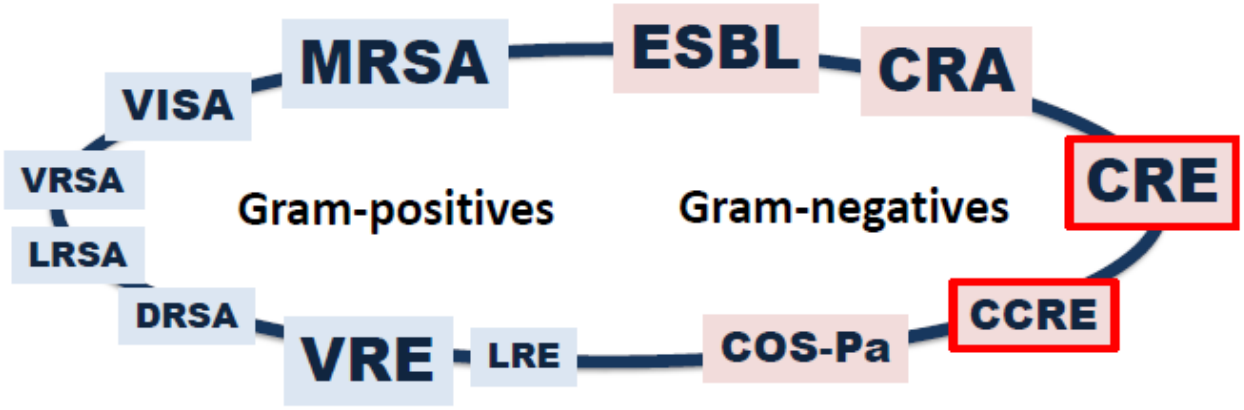


THELANCETID-D-12-00762R2 February 2013

Evoluzione della complessità nella diagnostica microbiologica

- Pazienti sempre più complessi (prematuri, grandi anziani, co-morbosità multiple, trattamenti immunosoppressivi)
- Malattie da microrganismi prima sconosciuti legate a cambiamenti climatici o ambientali che ne hanno permesso la sopravvivenza e la diffusione di nuovi vettori, l'adattamento di specie (SARS, H1N1,Chikungunia, WNV…)
- Turismo e migrazioni
- Incremento delle multiresistenze (panresistenze)

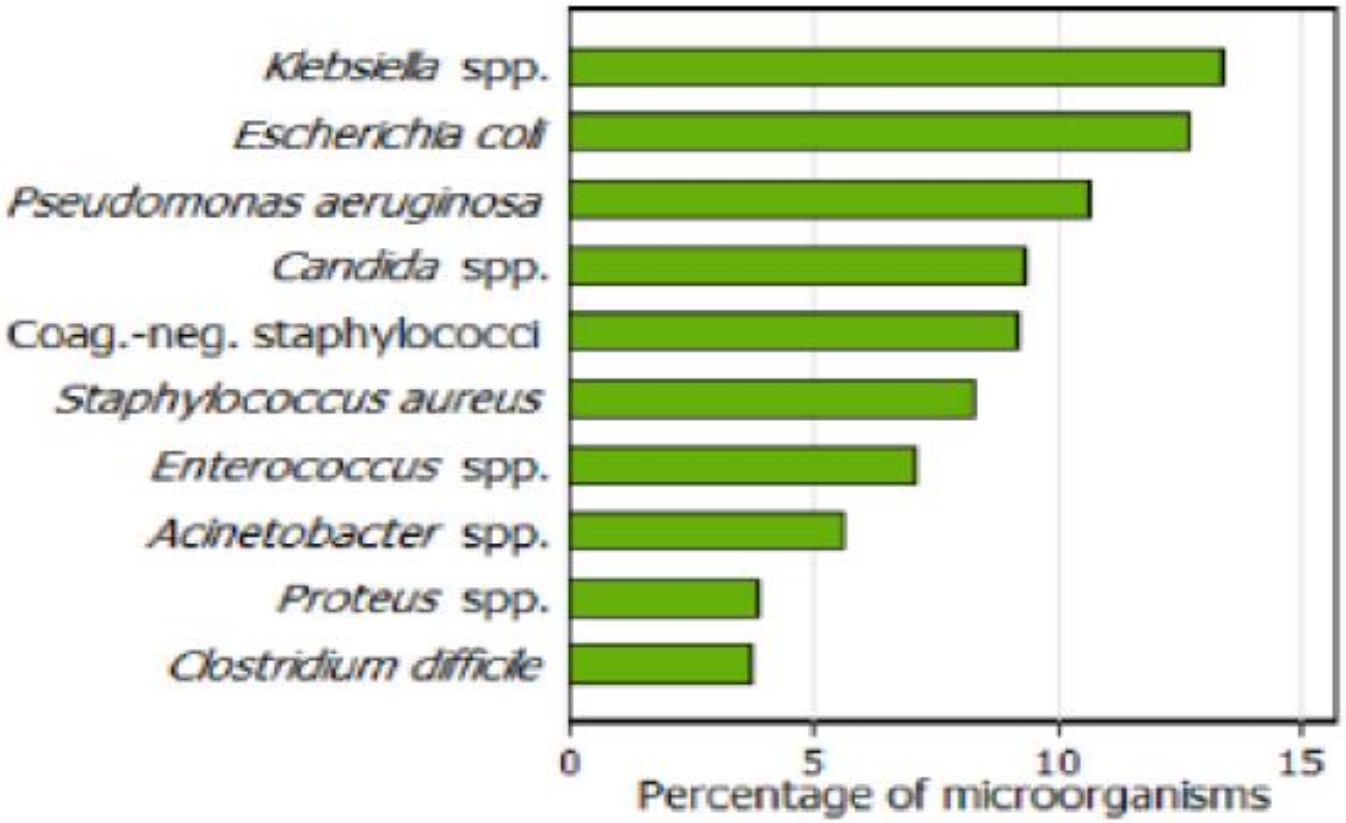
Vecchi e nuovi acronimi



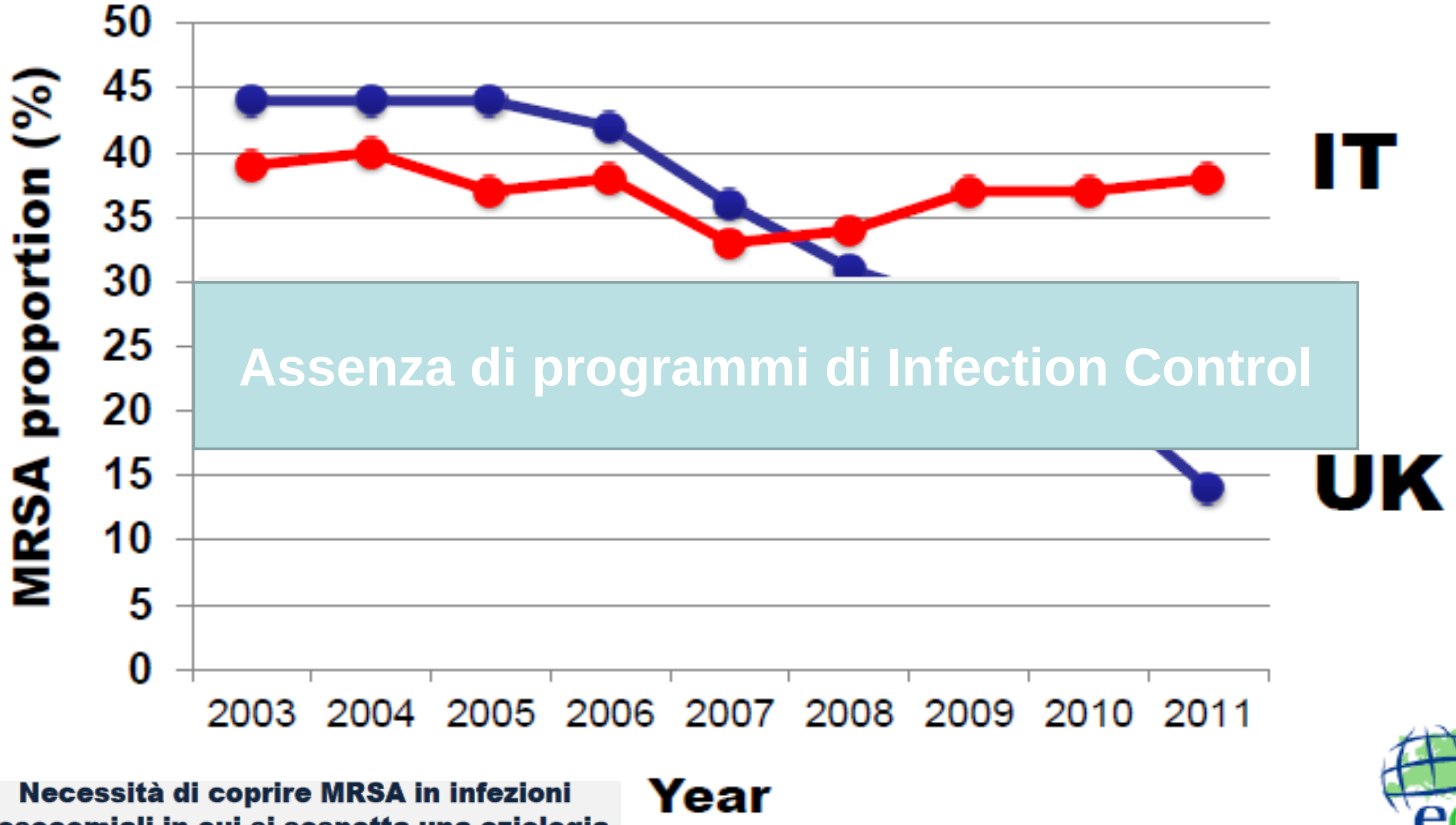
MRSA =S.aureus meticillina R
VISA = S.aureus vancomicina I
VRSA = S.aureus vancomicina R
LRSA = S.aureus linezolid R
DRSA = S.aureus daptomicina R
VRE = Enterococchi vancomicina R
LRE = Enterococchi linezolid resistenti

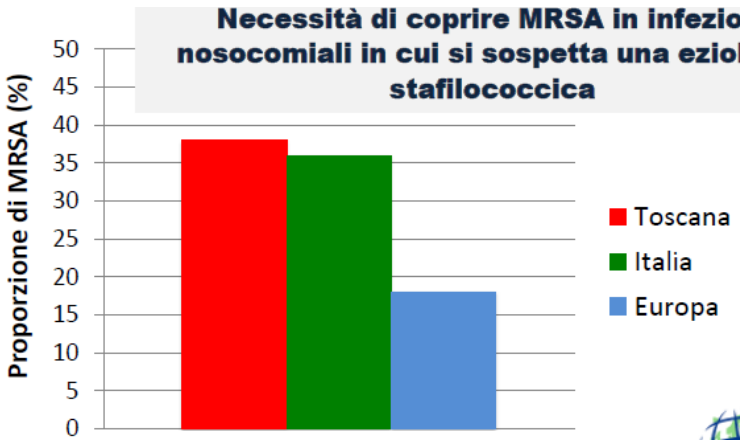
ESBL =betalattamasi a spettro esteso
CRA = Acinetobacter carbapenemi R
CRE = Enterobatteri carbapenemi R
CCRE = Enterobatteri carbapenemi+colistina R
COSPa = P.aeruginosa colistina R

Infezioni nosocomiali



MRSA trend italiano





CR-KP – the Italian epidemic

late 2008

early 2011

2014

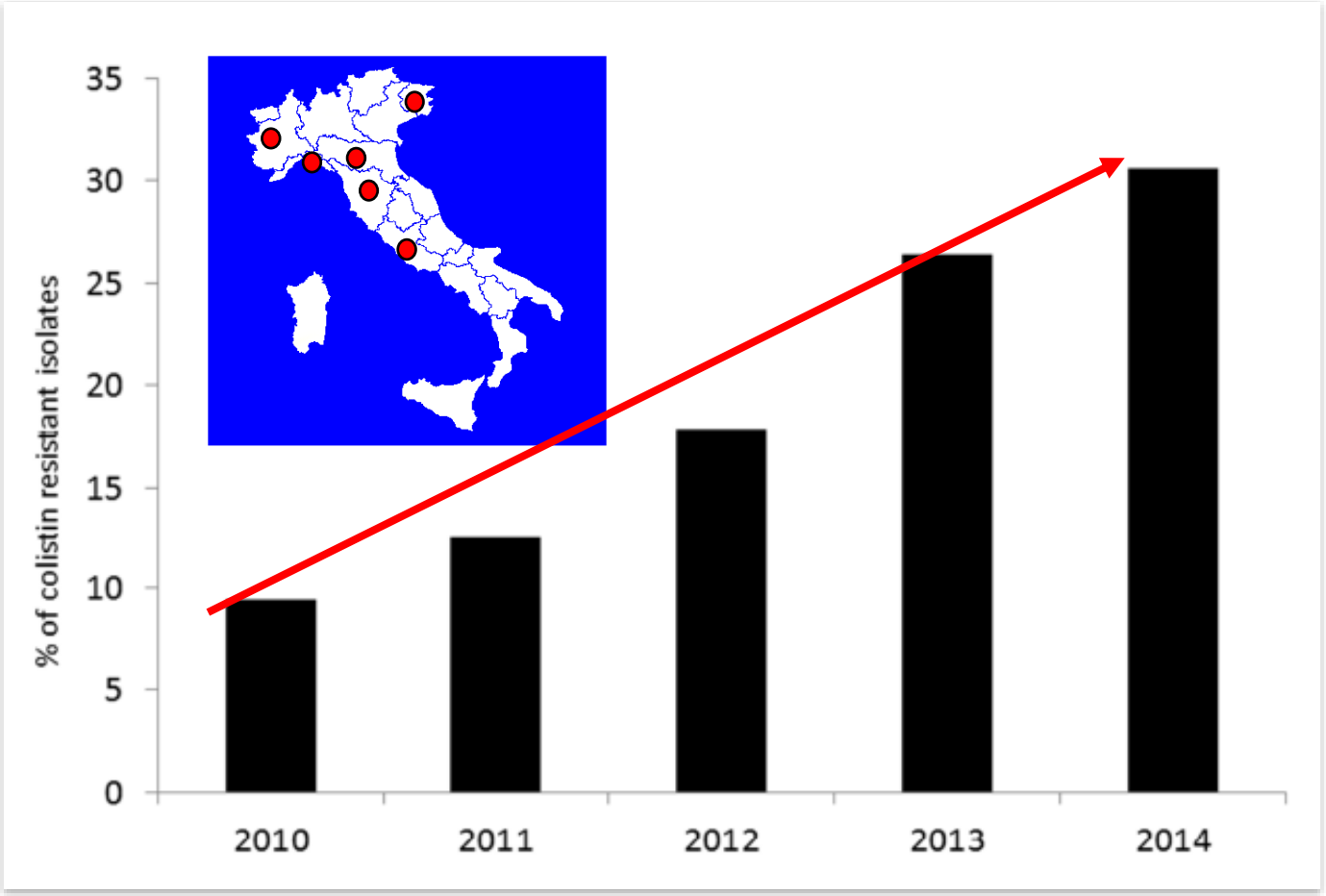
The first reported cases of CR-Kp

Giani *et al* – JCM 2009
Santoriello *et al* – unpublished

Fontana *et al* – BMC Res Notes 2010
Marchese *et al* – J Chemother 2010
Ambretti *et al* – New Microb 2010
Gaibani *et al* – Eurosurv 2011
Mezzatesta *et al* – CMI 2011
Agodi *et al* – JCM 2011
Richter *et al* – JCM 2011
Di Carlo *et al* – BMC Gastroenterol 2011
Rossolini GM – unpublished

Giani – Eurosurveillance 2013
ARISS – Euscape survey 2013

resistenza a colistina in KPC+ *K. pneumoniae* isolate da sangue Italia 2010-14



Giacobbe *et al* – Clin Microbiol Infect - 2015

New Drugs anti-CRE: coverage of strains with different R mechanisms

Ceftazidime Avibactam	**KPC**	**OXA-48**		
Imipenem Relebactam	**KPC**			
Carbavance	**KPC**			
ATM-AVI	**KPC**	**OXA-48**	**VIM**	**NDM**
Plazomicin	**KPC**	**OXA-48**	**VIM**	

Increasing importance of identification of the resistance mechanism

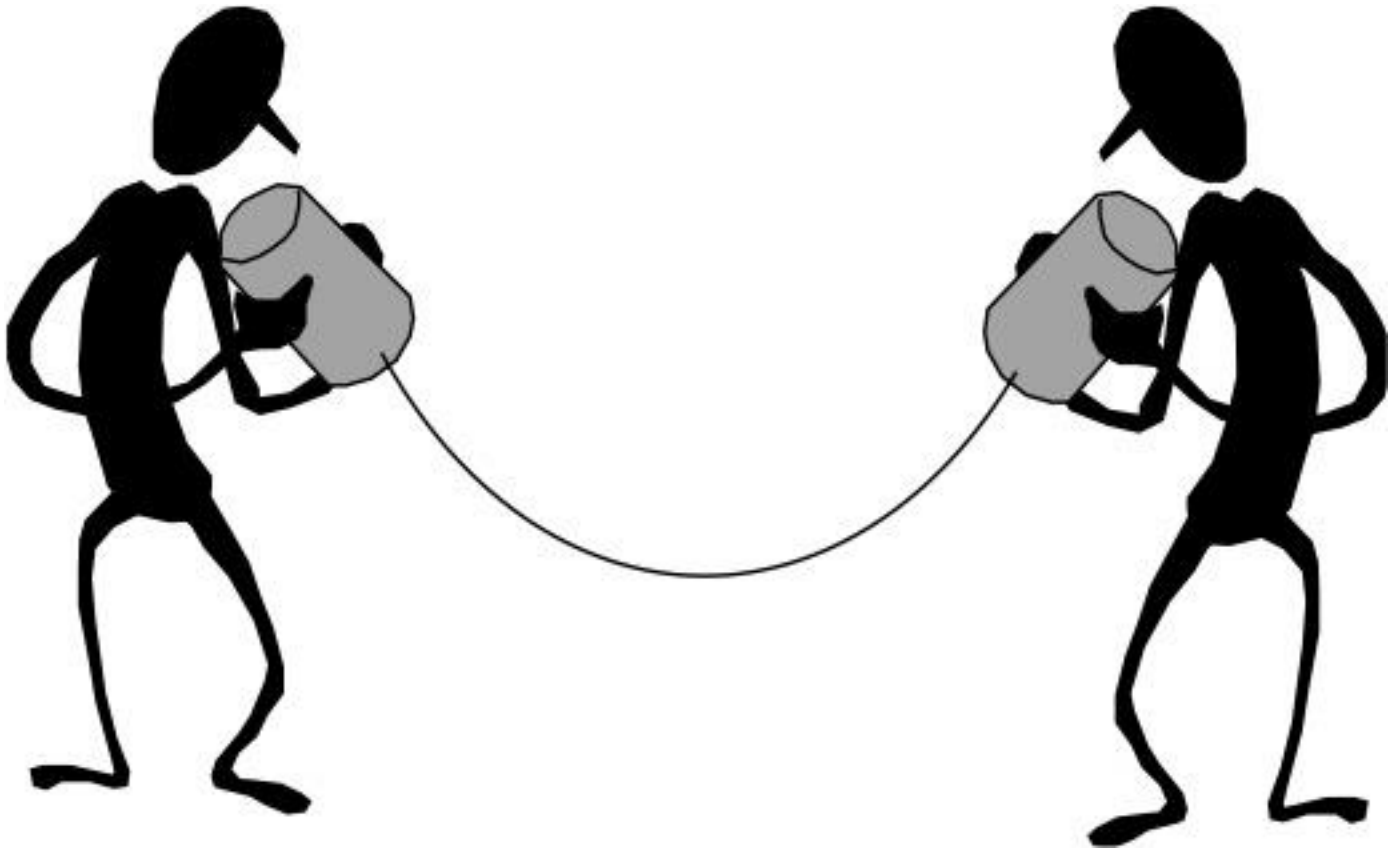
posizionamento tecnologia nella routine diagnostica

Selezione dei pazienti target

- ICU
- Oncoematologico, SCT, SOT
- Area critica se colonizzato da patogeni MDR

- Necessità di interventi organizzativi per favorire la **gestione dei fattori di rischio individuali a livello di reparto** e favorire una diagnosi e trattamento precoce attraverso strumenti per la diagnosi tempestiva (***early warning***)
- Favorire la **costituzione di percorsi multi-specialistici e multi-professionali** per la gestione di una patologia grave e complessa come la sepsi. Attivazione di progetti pilota per la definizione di procedure
- Favorire l'operatività di analisi microbiologiche per **terapie antibiotiche su infezioni locali**
- Disporre di dati epidemiologici e clinici sulla sepsi anche migliorando le attuali fonti informative **estendendo la sorveglianza microbiologica al livello di reparto** e inserendo indicatori di processo. Valutare periodicamente l'affidabilità degli indicatori disponibili (*patient safety*) e dei dati (Margherita)
- Promuovere la **sorveglianza attiva attraverso la corretta applicazione dei *bundle*** per la prevenzione delle infezioni (es. CVC e ventilazione meccanica) e valutazione (*compliance*, mortalità)
- Disporre di **dati sulle sensibilità antibiotica** e sul consumo di antibiotici (dati ECDC)

comunicazione

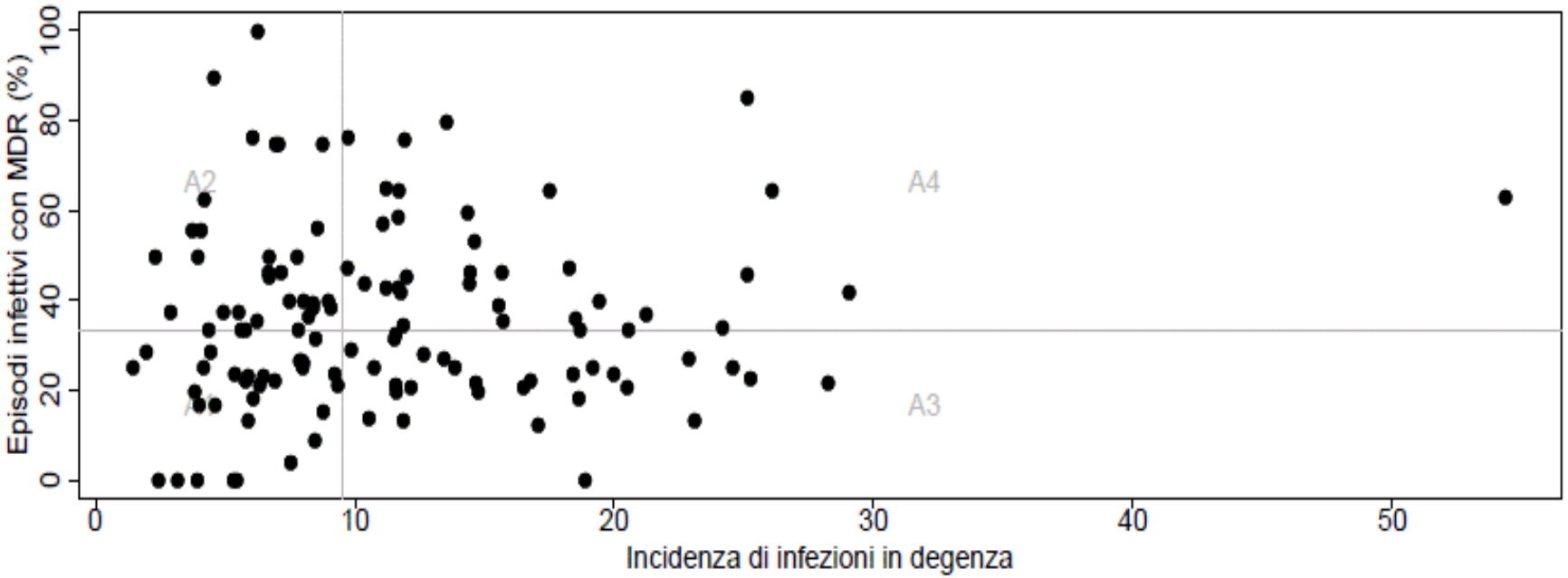


Infezione e sepsi: sviluppo e importanza della rete

Progetto PROSAFE - Petalo INFEZIONI

Report nazionale (124 TI) - **Anno 2016** [TI Polivalenti]

Pazienti infetti in degenza



Incidenza di infezioni in degenza

Il grafico sovrastante incrocia le variabili *Incidenza di infezioni in degenza* e *Percentuale di infezioni multiresistenti* (ad esclusione del germe S. Coagulasi negativo meticillina resistente). La nuvola nera di punti racchiude i dati delle TI nazionali. 2 linee grigie intersecano il grafico in corrispondenza dei valori mediani nazionali e delineano 4 aree. L'area **A1** identifica i centri che sembrano praticare un'efficace prevenzione delle infezioni e una buona gestione dell'antibiotico terapia. Per contro a cadere nell'area **A4** sono i centri che, osservando un'elevata incidenza di infezioni in degenza ed un'alta percentuale di multiresistenze, paiono non riuscire a controllare efficacemente i fenomeni. E' bene sottolineare che ad influire notevolmente su tali statistiche sono i case-mix delle TI. E' pertanto importante valutare con estrema cautela tale grafico e quella appena fornita è solo una delle tante possibili chiavi di lettura.

Fattori che individuano il potenziale di rischio infettivo

- Case-mix

-Tipologia (medico, chirurgico elettivo, trauma maggiore, ecc.)

-% pazienti con durata degenza < 24 h

-Degenza media per pazienti degenti > 24 h

-% pazienti in coma

-Gravità dei pazienti alla ammissione

- N. posti-letto
- Contesto ospedaliero

Tutti dati rilevabili a tavolino dal rapporto GiViTI

Quali pratiche verificare sul campo

- Struttura della T.I.
- Igiene delle mani
- Accesso visitatori
- Organizzazione del lavoro infermieristico
- Organizzazione del lavoro medico
- Prevenzione delle infezioni
- Diagnostica elle infezioni
- Trattamento delle infezioni
- Interventi specifici per la prevenzione delle infezioni procedura/correlate e per la prevenzione di insorgenza di MDR

Perché questa variabilità ? 3

Aspetti "**qualitativi**": come e perché si fa/non si fà

-Modelli organizzativi, leadership

-Processi decisionali e loro condivisione

-Stili e modelli di comunicazione tra il personale e circolazione dell'informazione

-Gestione del personale

-Turn-over del personale

-Cultura condivisa di reparto in tema di infezioni e MDR (come reagisce il reparto di fronte all'evento «infezione»)

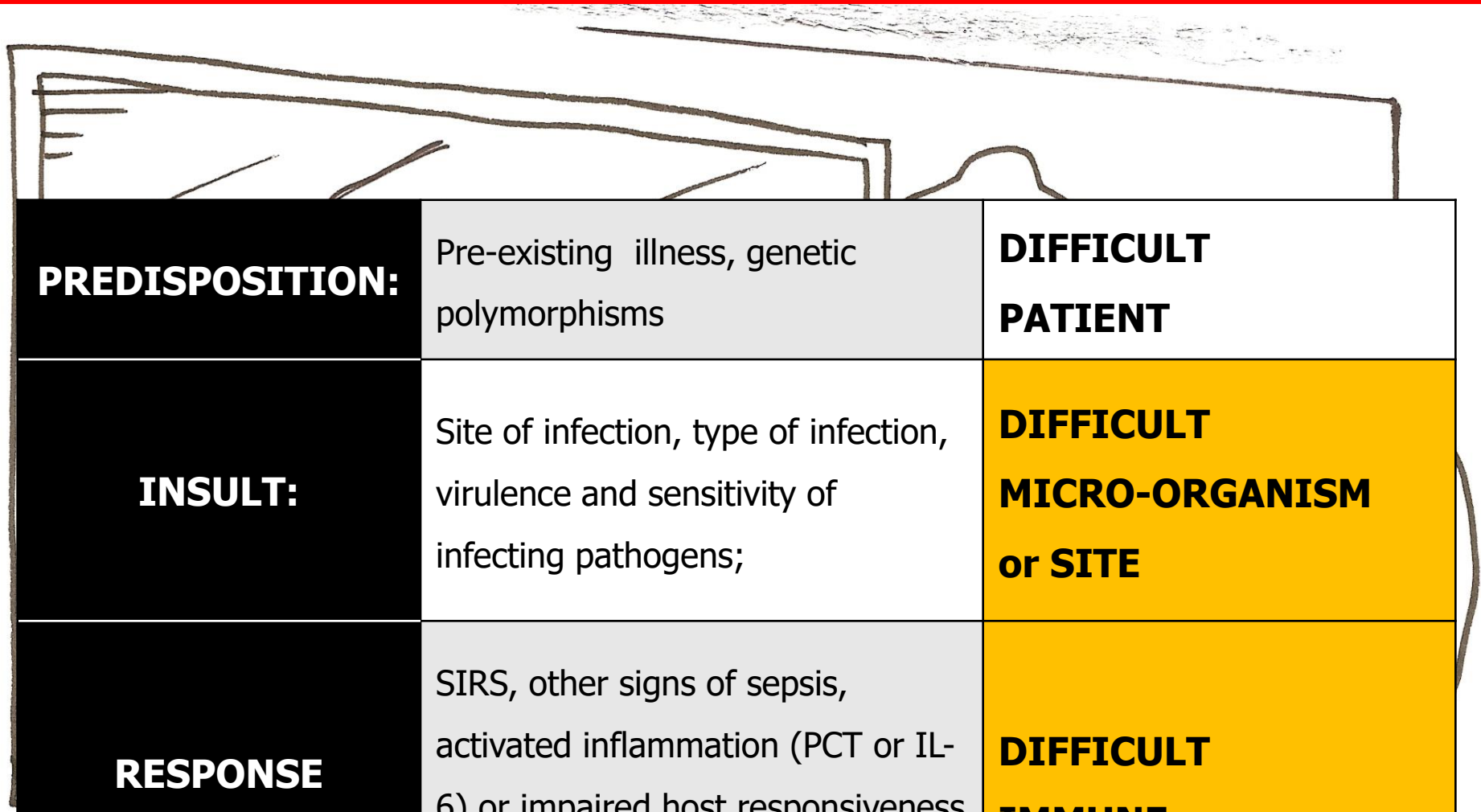
-Clima interno e dinamiche relazionali

"Come succede ciò che succede"

Risultati

- Diversità dei «modelli organizzativi»
- Diversità nel processo decisionale relativo alle infezioni
- Diversità nei processi comunicativi e di circolazione delle informazioni interne al reparto, tra medici, tra infermieri, tra medici e infermieri (la continuità)
- Diversità nella gestione dell' «anello debole» della catena
- Diversità nella gestione delle «criticità»

PATIENTS WITH SEPTIC SHOCK ARE REALLY HETEROGENEOUS



PREDISPOSITION:	Pre-existing illness, genetic polymorphisms	**DIFFICULT PATIENT**
INSULT:	Site of infection, type of infection, virulence and sensitivity of infecting pathogens;	**DIFFICULT MICRO-ORGANISM or SITE**
RESPONSE	SIRS, other signs of sepsis, activated inflammation (PCT or IL-6) or impaired host responsiveness (HLA-DR);	**DIFFICULT IMMUNE INFLAMMATORY RESPONSE**
ORGAN DYSFUNCTION	Time and number of failing organs	

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

B. SCREENING FOR SEPSIS AND PERFORMANCE IMPROVEMENT

1. **We recommend that hospitals and hospital systems have a performance improvement program for sepsis, including sepsis screening for acutely ill, high-risk patients (BPS).**

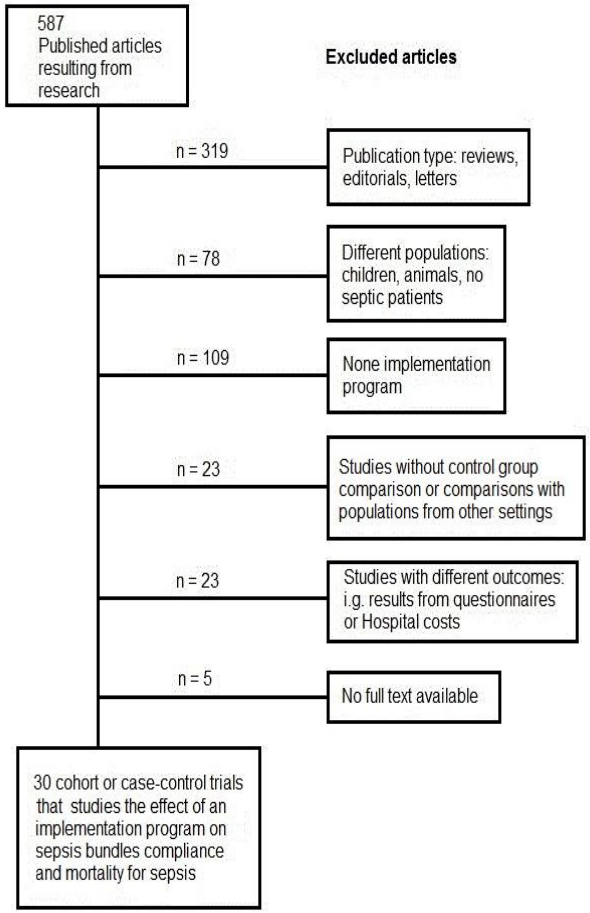
Rationale Performance improvement efforts for sepsis are associated with improved patient outcomes [40]. Sepsis performance improvement programs should anti

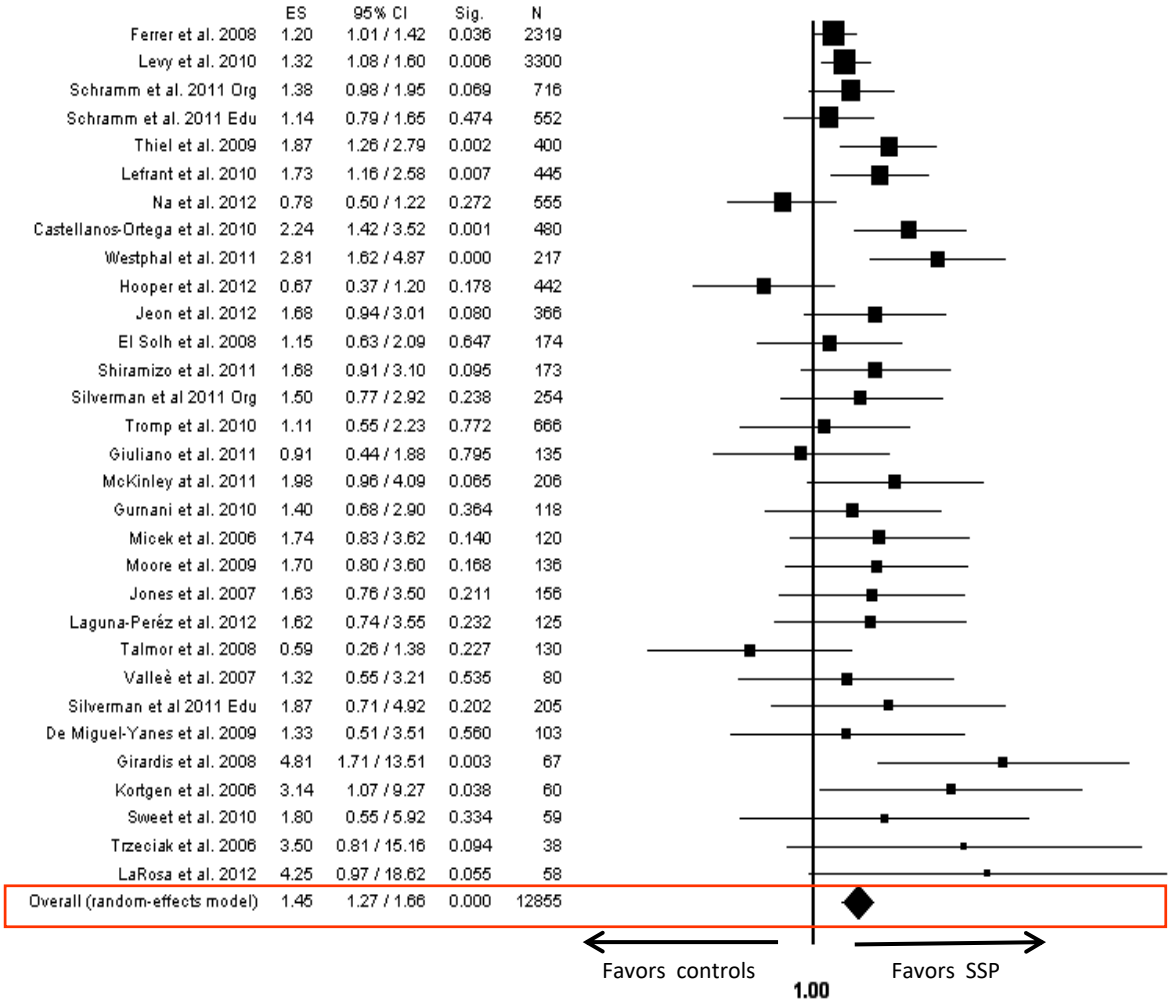
Effect of Performance Improvement Programs on Compliance with Sepsis Bundles and Mortality: A Systematic Review and Meta-Analysis of Observational Studies

PLOS ONE | DOI:10.1371/journal.pone.0125827 May 6, 2015

Elisa Damiani[1]*, Abele Donati[1], Giulia Serafini[2], Laura Rinaldi[2], Erica Adrario[1], Paolo Pelaia[1], Stefano Busani[2], Massimo Girardis[2]

SSP EFFECTIVENESS





SURVIVAL

SSP EFFECTIVENESS

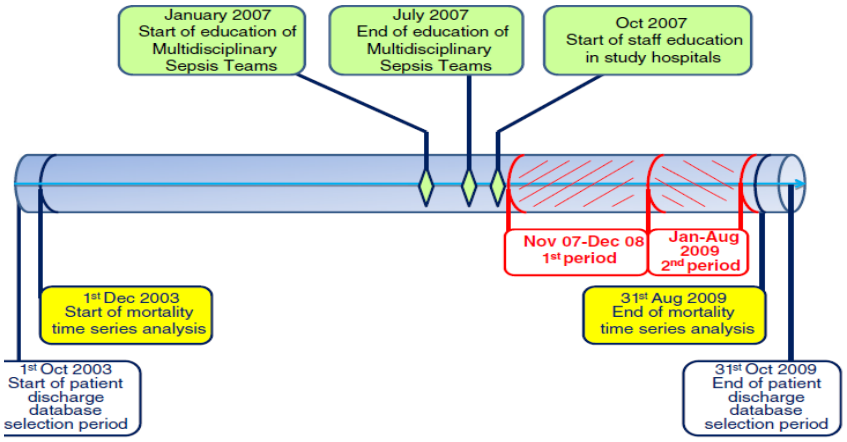
RESEARCH ARTICLE Open Access

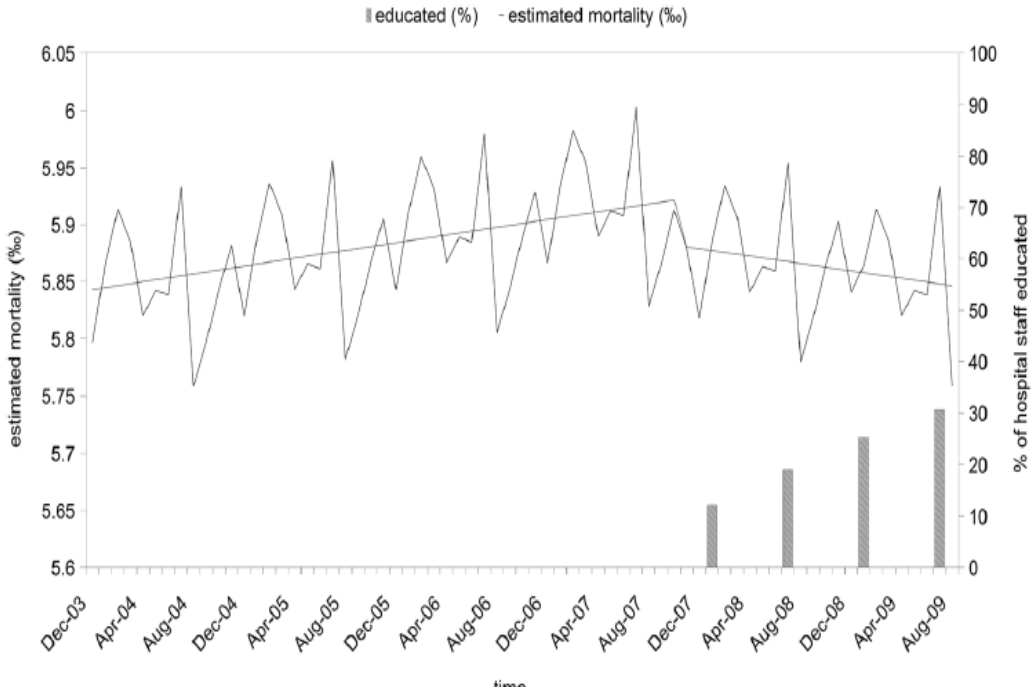
Hospital staff education on severe sepsis/septic shock and hospital mortality: an original hypothesis

Capuzzo *et al. BMC Anesthesiology* 2012, **12**:28

Background: Signs of serious clinical events overlap with those of sepsis. We hypothesised that any education on severe sepsis/septic shock may affect the outcome of all hospital patients. We designed this study to assess the trend of the mortality rate of adults admitted to hospital for at least one night in relationship with a hospital staff educational program dedicated to severe sepsis/septic shock.

Methods: This study was performed in six Italian hospitals in the same region. Multidisciplinary Sepsis Teams members were selected by each hospital management among senior staff. The education included the following



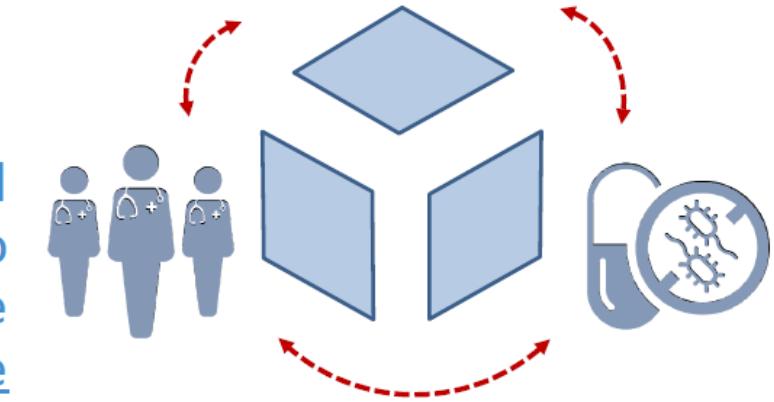


Conclusions

This study suggests that an educational program specifically devoted to severe sepsis/septic shock according to the Surviving Sepsis Campaign was associated with a decrease in the hospital mortality of the patients admitted to the hospital wards/units responsible for most of the cumulative hospital mortality. If this finding is con-

Piano (2017-2020) di Lotta della Regione Toscana

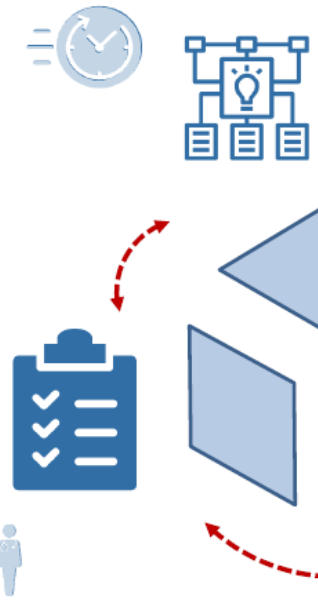
Tempi brevi e certi
i accesso alle cure:
rattamento entro **1h** dalla diagnosi



agnosi Rapida del
patogeno
responsabile
dell'infezione grave

Trattamento
appropriato e **mi**
con antibiotici spec
e terapia con fluidi
(SEPSIS 6)

Piano (2017-2020) di Lotta alla S[illegible] della Regione Toscana



Algoritmi per identificazione di sospetta infezione grave al PS e nei reparti

Formazione al personale sanitario inclusi (MMG, PLS, RSA) calata in ciascuna realtà

Raccolta dati e monitiraggio

Piano (2017-2020) di Lotta alla SEPSI della Regione Toscana

Attenzione all'infezione grave nel territorio e al 118

Accesso rapido alle cure per sospetta SEPSI

Riconoscimento e monitaggio dell'infezione grave

Diagnosi e trattamento entro 1 ora
colture, antibiotici, fluidi, controllo fonte infettiva

Diagnostica microbiologica rapida e terapia mirata

Percorso microbiologico integrato: PS ,TI, Microbiologia, reparti

Integrazione Sistemica basata sui **Fattori Umani**

Sepsis Puzzle