Problematiche infettivologiche del paziente in ICU

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Financial disclosure: fees for lectures by MSD, Pfizer

UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

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Intensive Care Med (2015) 41:551–552
DOI 10.1007/s00134-014-3598-8

Luciano Gattinoni
V. Marco Ranieri
Antonio Pesenti

Sepsis: needs for defining severity

Table 1 Clinical trials on severe sepsis/septic shock

Study	ALBIOS [1]	SEPSISPAM [2]	TRISS [3]	ProCESS [4]	ARISE [5]
Geographical area	Europe (Italy)	Europe (France)	Europe (Scandinavia)	USA	Australia/New Zealand (90 %)
Patients enrolled (*N*)	1,810	776	998	1,341	1,591
Death at 90 days, no./total (%)	754/1,781 (42.2 %)	334/776 (43.0 %)	439/998 (44.0 %)	396/1,232 (32.0 %)	297/1,588 (18.7 %)
Mechanical ventilation	1,446/1,810 (79.8 %)	594/776 (76.5 %)	695/998 (69.0 %)	188/1,341 (14 %)	243/1,591 (15.2 %)
Severity score	SAPS II ≈48	SAPS II ≈ 56.1–57.2	SAPS II ≈ 51–52	APACHE II ≈20–21	APACHE II ≈15–16
Expected hospital mortality	41 %[a]	60–62 %[a]	48–51 %[a]	38.1–41.6 %[a]	22.9–25.6 %[a]

FIRST

RECOGNITION

Clinical Review & Education

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

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

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

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

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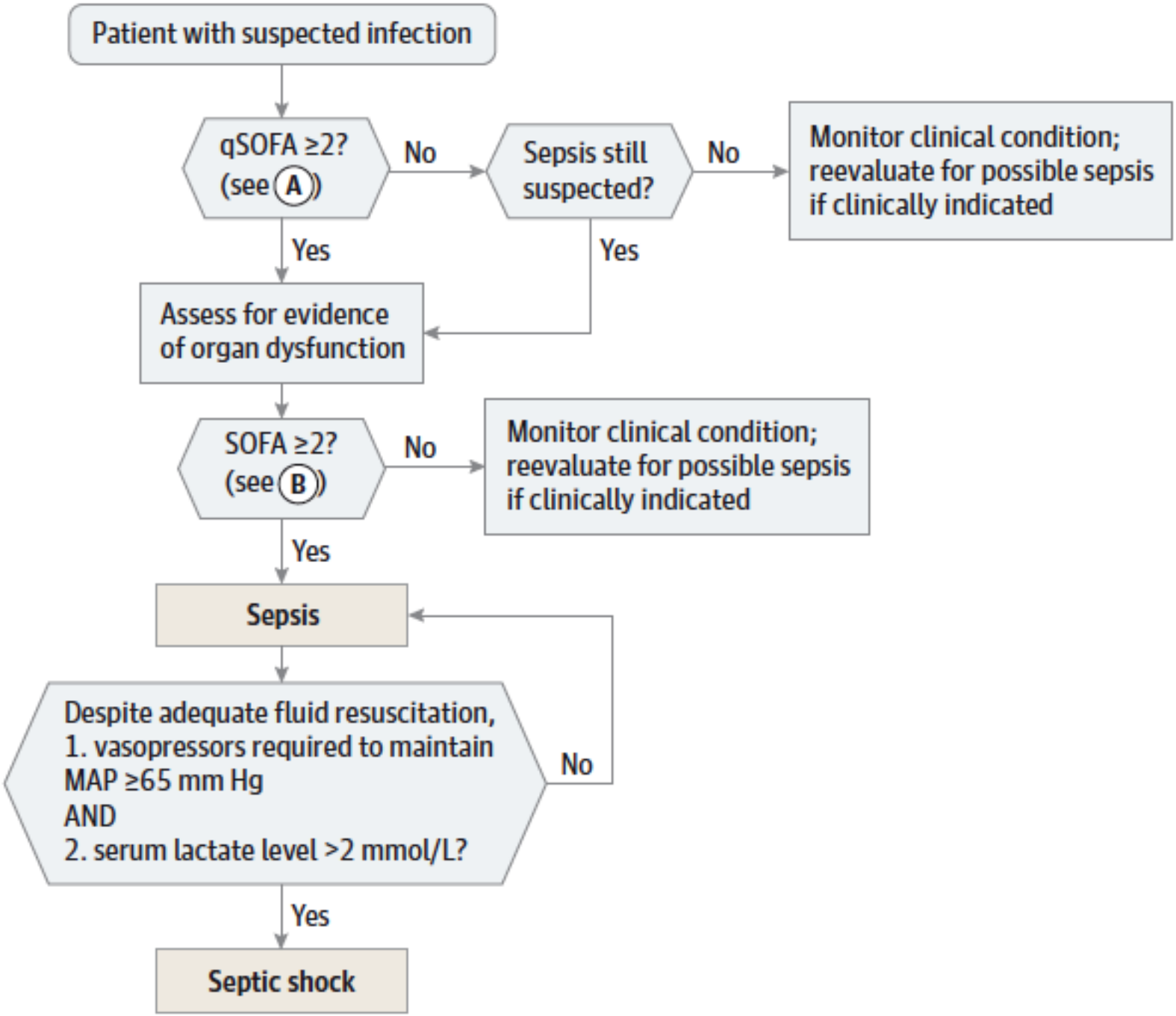
Box 4. qSOFA (Quick SOFA) Criteria

Respiratory rate ≥22/min

Altered mentation

Systolic blood pressure ≤100 mm Hg

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


Patient with suspected infection
qSOFA ≥2? (see A)
No
Sepsis still suspected?
No
Monitor clinical condition; reevaluate for possible sepsis if clinically indicated
Yes
Yes
Assess for evidence of organ dysfunction
SOFA ≥2? (see B)
No
Monitor clinical condition; reevaluate for possible sepsis if clinically indicated
Yes
Sepsis
Despite adequate fluid resuscitation,
1. vasopressors required to maintain MAP ≥65 mm Hg
AND
2. serum lactate level >2 mmol/L?
No
Yes
Septic shock

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(A) qSOFA Variables

- Respiratory rate
- Mental status
- Systolic blood pressure

(B) SOFA Variables

- PaO_2/FiO_2 ratio
- Glasgow Coma Scale score
- Mean arterial pressure
- Administration of vasopressors with type and dose rate of infusion
- Serum creatinine or urine output
- Bilirubin
- Platelet count

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

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Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

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

Source control+
samples+
TREATMENT

Which real evidence on sepsis management?

Treatment	
Prompt fluid bolus is recommended (500-1000 mL) with appropriate safety limits	Fluid therapy with balanced crystalloids vs albumin is suggested based on meta-analyses,[8,9] while specific fluid comparisons undergo additional randomized clinical trials
Norepinephrine is recommended as a first-line vasopressor	Vasopressin may spare norepinephrine at higher doses
Hydroxylethyl starch may cause harm	Increases mortality and worsens renal outcomes among survivors
Protocolized early goal-directed therapy is not superior to usual care in early septic shock	Tested among patients with prompt shock recognition, intravenous fluid boluses, and early antibiotics
Low-dose corticosteroids to be considered for vasopressor-dependent shock	Dosing regimen and timing of discontinuation remains controversial

Seymour C. et al., *JAMA. 2015*; 314 (7):708-717.

Guideline recommendations

- Administration of effective IV antimicrobials within the 1st hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C)
- Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (grade 1B)

Surviving Sepsis Campaign

Crit Care Med 2013;41:580-637

Early, appropriate antibiotics

- Early = within 1 hour after recognition of potential septic shock

- Appropriate = *in vitro* activity against pathogen
  - Route of administration
  - Dose and frequency
  - Penetration
  - Cidality

Surviving Sepsis Campaign

Crit Care Clin 2011;27:53-76

Empiric Antibiotic Treatment Reduces Mortality in Severe Sepsis and Septic Shock From the First Hour: Results From a Guideline-Based Performance Improvement Program*

Ricard Ferrer, MD, PhD[1]; Ignacio Martin-Loeches, MD, PhD[2]; Gary Phillips, MAS[3]; Tiffany M. Osborn, MD, MPH[4]; Sean Townsend, MD[5]; R. Phillip Dellinger, MD, FCCP, FCCM[6]; Antonio Artigas, MD, PhD[2]; Christa Schorr, RN, MSN[6]; Mitchell M. Levy, MD, FCCP, FCCM[7]

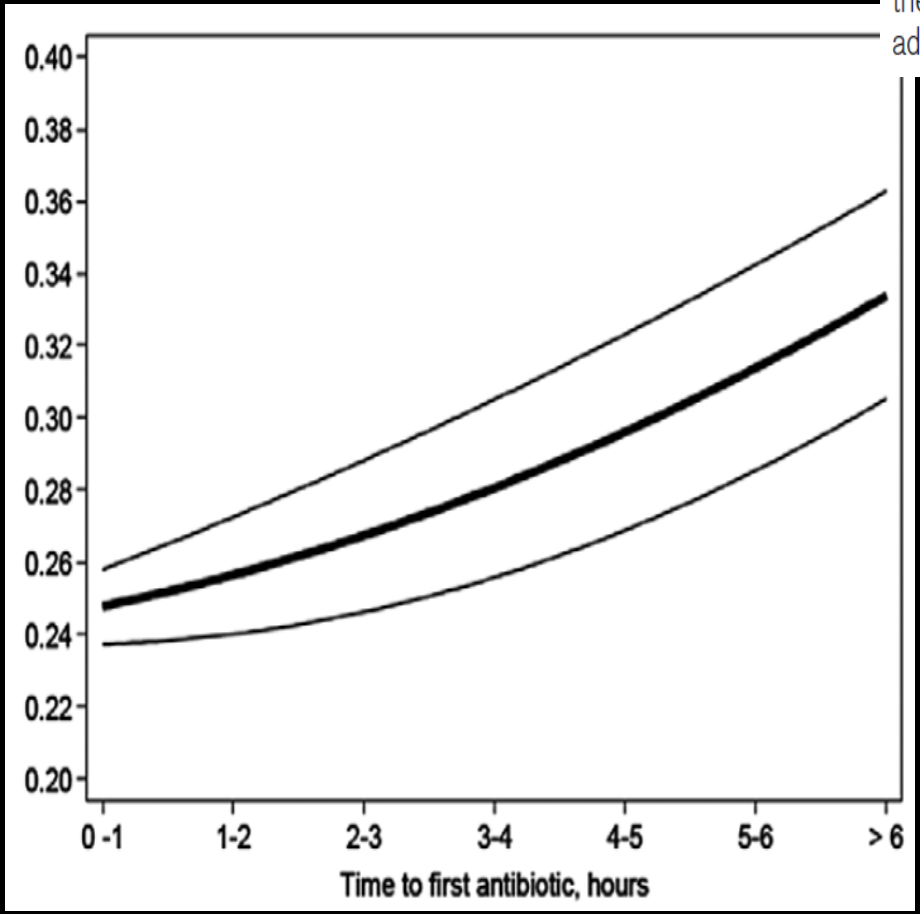

Figure 2. Predicted hospital mortality and the associated 95% CIs for time to first antibiotic administration. The results are adjusted by the sepsis severity score (SSS), ICU admission source (emergency department [ED], ward, vs ICU), and geographic region (Europe, United States, and South America). Probability of hospital mortality is based on the subject having the following specific characteristics: the patient is from the United States, admission source is the ED, and the SSS is 52 (median of all observations).

Right antibiotic therapy (in terms of timing and empiric coverage) still the only strong predictive variable for survival

(*Crit Care Med* 2014; 42:1749–1755)

Effect of timing on survival

The strong association persists
even when therapeutic factors such as the rapidity of fluid resuscitation are included, or non-therapeutic variables - that are typically predictive of survival - such as APACHE II, number of admission organ failures, the site of infection, and neutropenia were examined. This relationship held whether the infection was documented or suspected; whether source control was required; the pathogen isolated or not; and whether bacteremia was present or absent.

Surviving Sepsis Campaign

Adapted with permission from:
Crit Care Med 2006;34:1589-96

Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol*

Michael A. Puskarich, MD; Stephen Trzeciak, MD; Nathan I. Shapiro, MD; Ryan C. Arnold, MD; James M. Horton, MD; Jonathan R. Studnek, PhD; Jeffrey A. Kline, MD; Alan E. Jones, MD; on behalf of the Emergency Medicine Shock Research Network (EMSHOCKNET)

Surviving Sepsis Campaign

Crit Care Med 2011; 39:2066 –2071

Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol*

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Conclusion: In this large, prospective study of emergency department patients with septic shock, we found no increase in mortality with each hour delay to administration of antibiotics after triage. However, delay in antibiotics until after shock recognition was associated with increased mortality.

Surviving Sepsis Campaign

Crit Care Med 2011; 39:2066 –2071

Combination therapy vs. monotherapy for septic shock

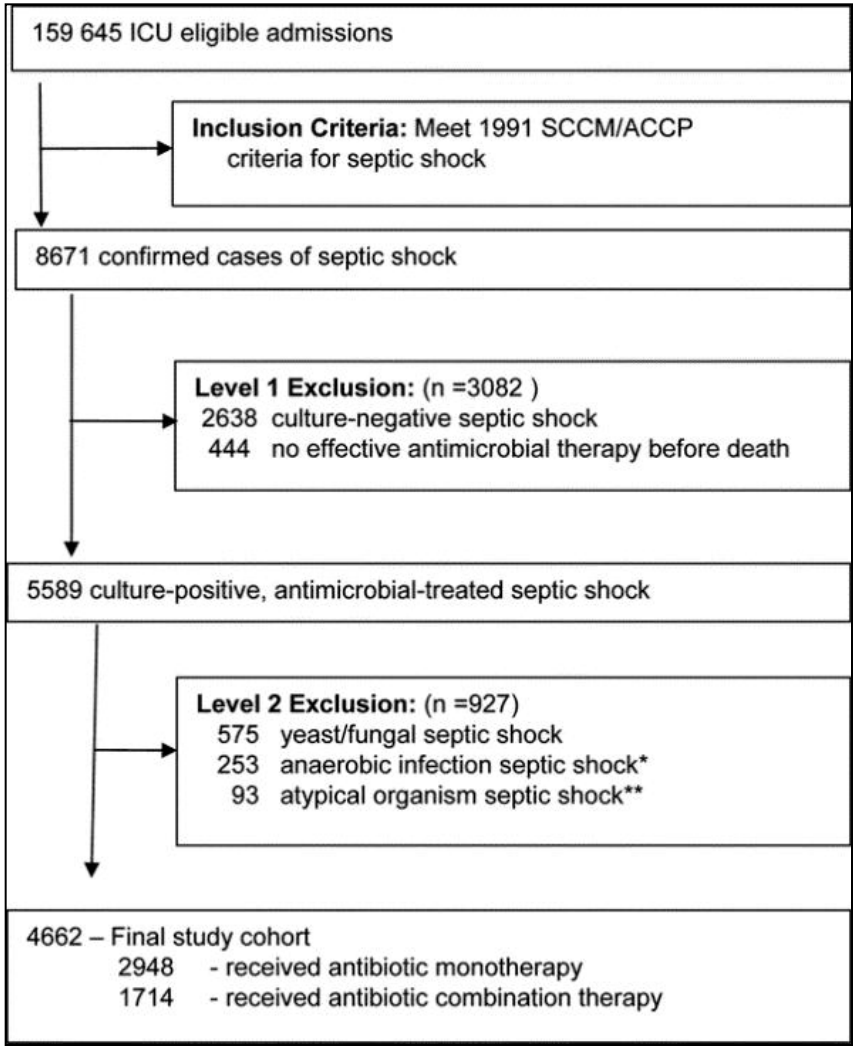
Mortality rate *			
	Monotherapy (n=1223)	Combination Rx (n=1223)	HR (95% CI)
28-Day, %	36.3	29	0.77 (0.67 – 0.88)
ICU, %	35.7	28.8	0.75 (0.63 – 0.88)
Hospital, %	47.8	37.4	0.69 (0.59 – 0.81)
# deaths			
All Gram + , %	39.9	30.7	0.73 (0.58 – 0.92)
All Gram - , %	34.5	28.2	0.79 (0.67 – 0.94)

* Propensity score adjusted

Surviving Sepsis Campaign

Crit Care Med 2010;38:1773-85

Figure 1.



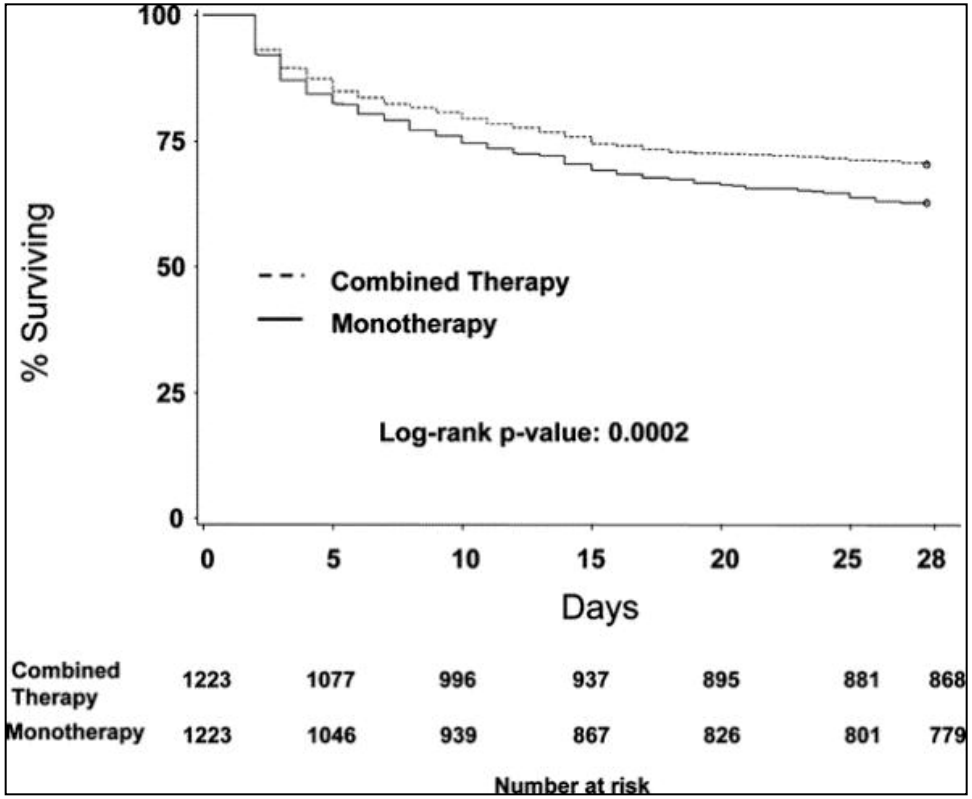
Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: A propensity-matched analysis *.

Kumar, Anand; Zarychanski, Ryan; Light, Bruce; Parrillo, Joseph; Maki, Dennis; Simon, Dave; Laporta, Denny; Lapinsky, Steve; Ellis, Paul; Mirzanejad, Yazdan; Martinka, Greg; Keenan, Sean; Wood, Gordon; Arabi, Yaseen; Feinstein, Daniel; Kumar, Aseem; Dodek, Peter; Kravetsky, Laura; Doucette, Steve

Critical Care Medicine. 38(9):1773-1785, September 2010.
DOI: 10.1097/CCM.0b013e3181eb3ccd

Figure 1. Subject selection flow diagram. SCCM, Society of Critical Care Medicine; ACCP, American College of Chest Physicians; ICU, intensive care unit. *Clostridia species, Bacteroides species, peptostreptococci, Clostridium difficile-associated septic shock, miscellaneous anaerobes. **Mycobacterium tuberculosis, Legionella species, Listeria, Bacillus species, Corynebacterium jeikeium.

Figure 2.



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Critical Care Medicine. 38(9):1773-1785, September 2010.
DOI: 10.1097/CCM.0b013e3181eb3ccd

Figure 2. Adjusted Cox proportional hazards of mortality associated with combination antibiotic therapy of septic shock.

Guideline recommendations

- Combination empirical therapy for the following patients (grade 2B):
  - Neutropenic with severe sepsis and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens (*Acinetobacter* or *Pseudomonas* bacteremia)
  - Severe infections associated with respiratory failure and septic shock (*Pseudomonas* bacteremia)
  - Septic shock from bacteremic *Streptococcus pneumoniae*

Surviving Sepsis Campaign

Crit Care Med 2013;41:580-637

IDENTIFICATION

Dati epidemiologici Niguarda

2010 -2017

2860-SAR

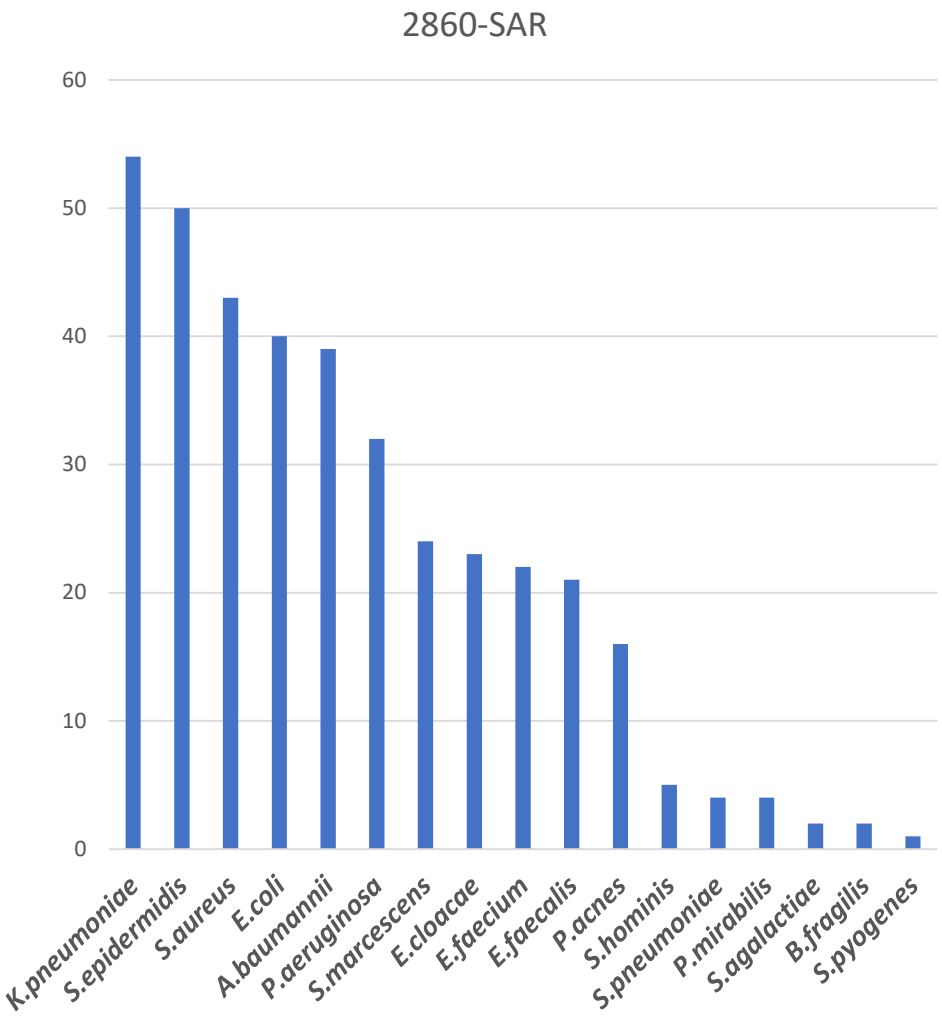
Emocolture

Pus Liquidi

Biopsie

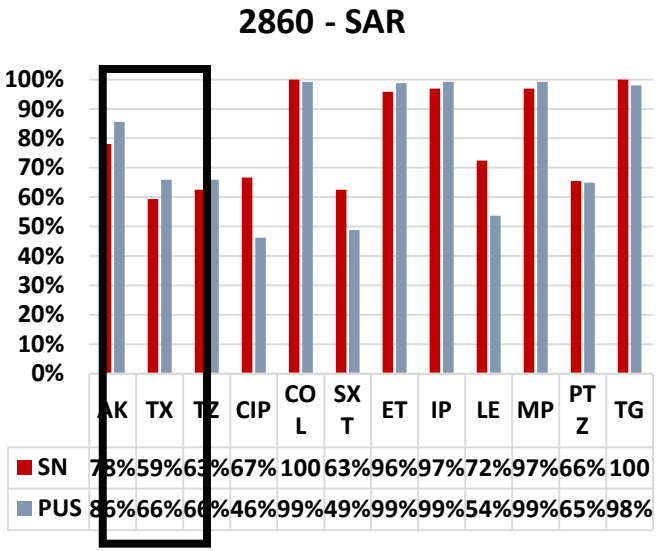
Microrganismi isolati
Sensibilità/Resistenza agli antibiotici

Sangue
numero isolati
2010-2017



E.coli

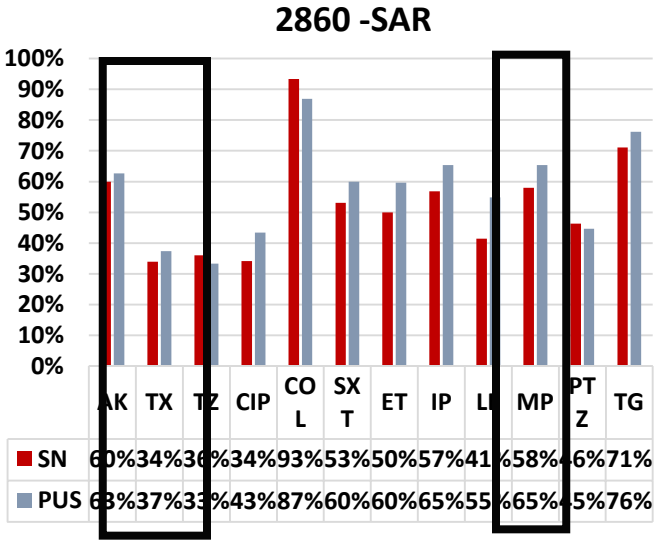
%S (2010-2017)



Amikacina	AK
Cefotaxime	TX
Ceftazidime	TZ
Ciprofloxacina	CIP
Colistina	COL
Cotrimoxazolo	SXT
Ertapenem	ET
Imipenem	IP
Levofloxacina	LE
Meropenem	MP
Piperacillina/Tz	PTZ
Tigeciclina	TG

K.pneumoniae

%S (2010-2017)



Amikacina	AK
Cefotaxime	TX
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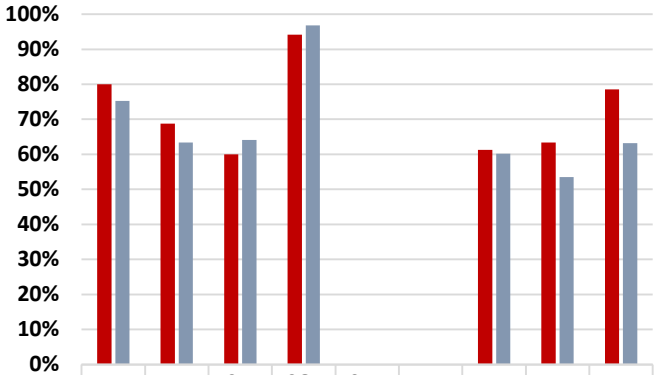
Imipenem	IP
Levofloxacina	LE
Meropenem	MP
Piperacillina/Tz	PTZ
Tigeciclina	TG

P.aeruginosa

%S (2010-2017)

2860 -SAR

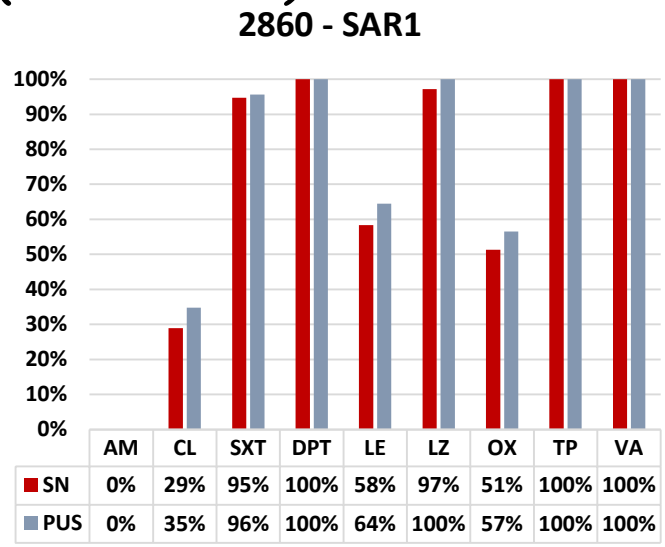


	AK	TZ	CIP	COL	SXT	ET	IP	MP	PTZ
SN	80%	69%	60%	94%	0%	0%	61%	63%	79%
PUS	75%	63%	64%	97%	0%	0%	60%	53%	63%

Amikacina	AK
Cefotaxime	TX
Ceftazidime	TZ
Ciprofloxacina	CIP
Colistina	COL
Cotrimoxazolo	SXT
Ertapenem	ET
Imipenem	IP
Levofloxacina	LE
Meropenem	MP
Piperacillina/Tz	PTZ
Tigeciclina	TG

S.aureus

%S (2010-2017)



	AM	CL	SXT	DPT	LE	LZ	OX	TP	VA
SN	0%	29%	95%	100%	58%	97%	51%	100%	100%
PUS	0%	35%	96%	100%	64%	100%	57%	100%	100%

Ampicillina	AM
Clindamicina	CL
Cotrimoxazolo	SXT
Daptomicina	DPT
Levofloxacina	LE
Linezolide	LZ
Oxacillina	OX
Teicoplanina	TP
Vancomicina	VA

Il progetto

Il progetto Margherita PROSAFE nasce come un progetto osservazionale per la raccolta continua, su supporto elettronico, dei dati relativi ai pazienti ricoverati in terapia intensiva (TI). Gli obiettivi sono quelli di:

- standardizzare le procedure di raccolta dei dati relativi ai pazienti ricoverati;
- analizzare l'attività svolta in termini sia di risultati clinici conseguiti, sia di risorse utilizzate;
- documentare la casistica raccolta per esigenze di ricerca e/o normale gestione clinica di reparto;
- favorire, con un dettagliato lavoro di ricerca epidemiologica, il confronto tra TI al fine di migliorare la qualità dell'assistenza fornita.

Figure 1. Flow chart of the study

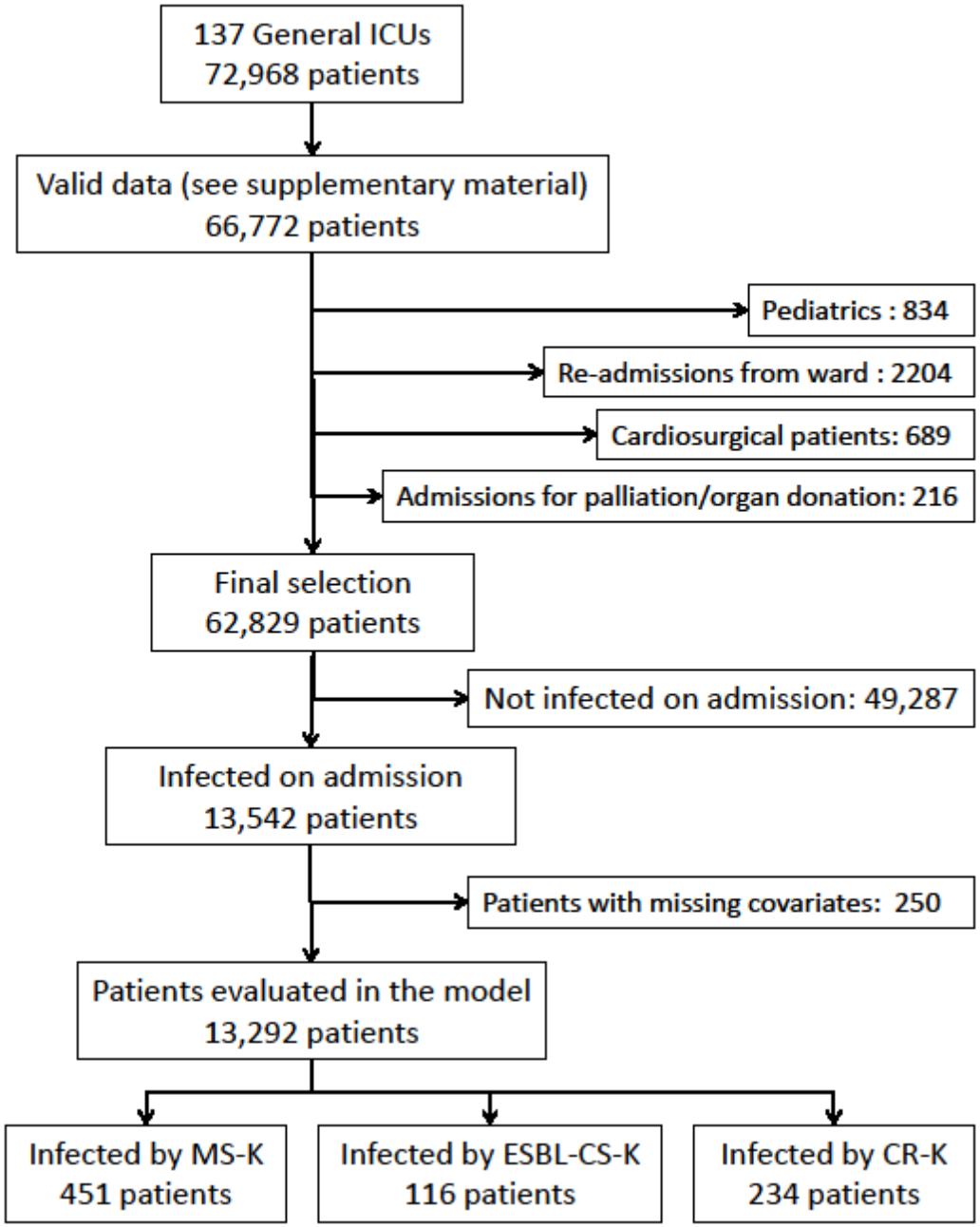


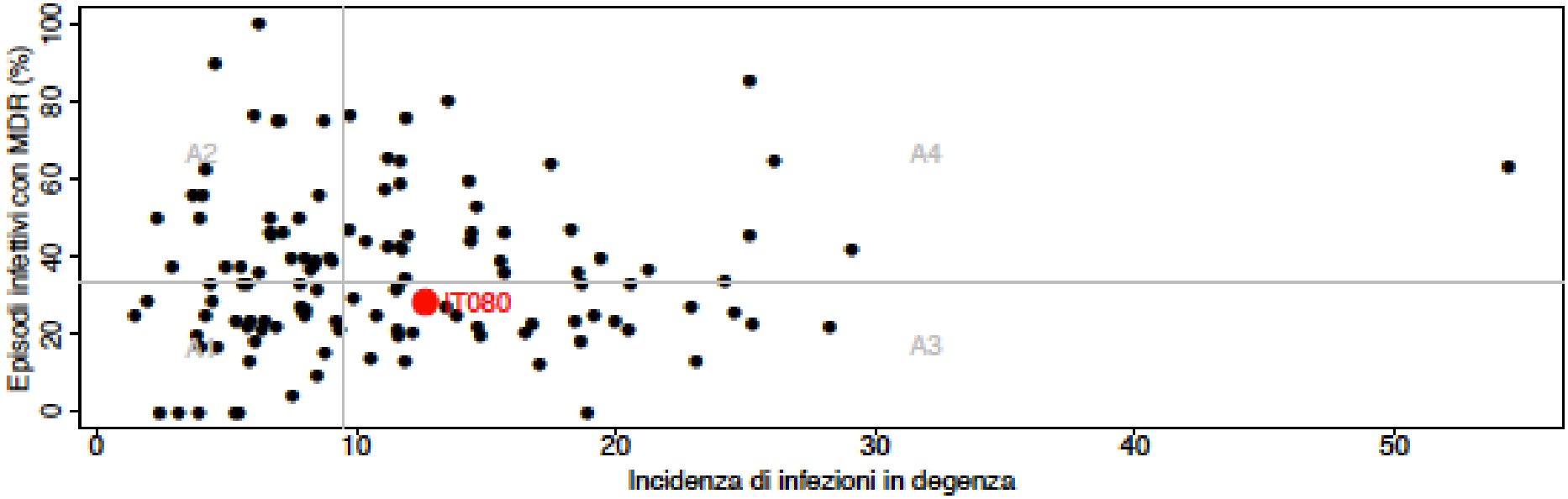
Figura 1

- 2 anni (2012-2013)
- 66.772 pazienti in 137 T.I. polivalenti
- 13.542 infetti alla ammissione eleggibili
- 13.292 valutati
- 842 con infezione da KBS
- 801 arruolati
- 451 Kbs sensibile
- 116 Kbs ESβL
- 234 Kbs CR

Figura 2: calibrazione

- K Sens Attesa 37,7% Oss 36,6%
- K ESβL Attesa 39,2 % Oss 39,7%
- K CR Attesa 44,7% Oss 53,4 %

Centro IT080 - Anno 2016
Pazienti infetti in degenza



Dati GIVITI 2016 Niguarda

Principles of Antibiotic Therapy

Empiric Therapy (85%)

- Infection not well defined ("best guess")
- Broad spectrum
- Multiple drugs
- Evidence usually only 2 randomized controlled trials
- More adverse reactions
- More expensive

Directed Therapy (15%)

- Infection well defined
- Narrow spectrum
- One, seldom two drugs
- Evidence usually stronger
- Less adverse reactions
- Less expensive

THE NEED FOR EARLY APPROPRIATE THERAPY CREATES PROBLEMS

- NEED FOR EARLY APPROPRIATE THERAPY CAN DRIVE AGGRESSIVE USE OF ANTIBIOTICS

BUT

- AGGRESSIVE USAGE MAY MEAN OVERUSE WHICH DRIVES MORE RESISTANCE AND INAPPROPRIATE THERAPY
- HOW DO WE BREAK THIS VICIOUS CYCLE ???

Treatment Duration?

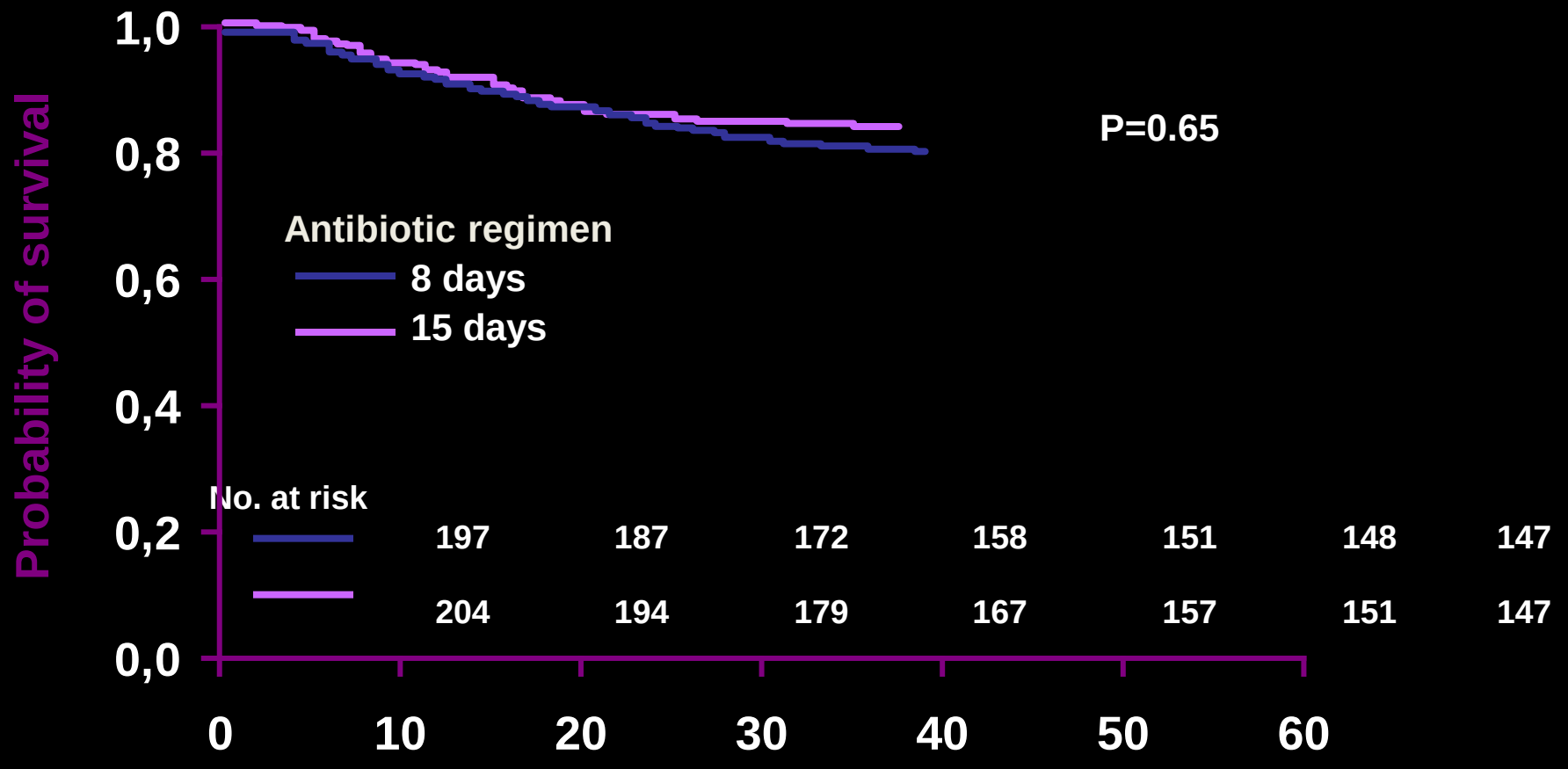
- Uncomplicated UTIs
  - Depends on antibiotic (Single dose: gatifloxacin; 3 days: ciprofloxacin, TMP/SMX; 7 days: nitrofurantoin, oral cephalosporins)
- Endocarditis (4- 6 weeks)
- Osteomyelitis (4-6 weeks)
- Catheter-related infections? Depends on organism
  - S. epidermidis and line removed: 5-7 days, line not removed, 10-14 days
  - S. aureus: 14 days +/- TEE

Treatment Duration

- Pneumonia
  - Hospital/healthcare-associated with good clinical response: 8 days (unless etiologic pathogen is P. aeruginosa, ~10-14 days)
  - Assumes active therapy administered initially

8 vs 15 Day Treatment of VAP

No difference in outcome except if P. aeruginosa involved



JAMA 2003 290:2588

CHEST®
Official publication of the American College of Chest Physicians

ONLINE FIRST

Short- versus long-duration antibiotic regimens for ventilator-associated pneumonia: a systematic review and meta-analysis

George Dimopoulos MD, PhD, [1], Garyphallia Poulakou, MD, PhD [2], Ioannis A. Pneumatikos, MD, PhD [3], Apostolos Armaganidis, MD, PhD [1], Marin H. Kollef, MD [4], Dimitrios K. Matthaiou MD [1]

Treatment Duration

- Meningitis (Tunkel et al. Clin Infect Dis 2004;39:1267-84)
  - Neisseria meningitidis (7days)
  - Haemophilus influenzae (7 days)
  - Streptococcus pneumoniae (10-14 days)
  - Streptococcus agalactiae (14-21 days)
  - Aerobic gram negative bacilli (21 days)
  - Listeria monocytogenes (□21 days)

Quenot *et al. Annals of Intensive Care* 2013, **3**:21
http://www.annalsofintensivecare.com/content/3/1/21

Annals of Intensive Care
a SpringerOpen Journal

REVIEW Open Access

Role of biomarkers in the management of antibiotic therapy: an expert panel review II: clinical use of biomarkers for initiation or discontinuation of antibiotic therapy

Pancreatitis
LRTI
Meningitis
Sepsis

Quenot *et al. Annals of Intensive Care* 2013, **3**:21
http://www.annalsofintensivecare.com/content/3/1/21

Annals of Intensive Care
a SpringerOpen Journal

REVIEW **Open Access**

Role of biomarkers in the management of antibiotic therapy: an expert panel review II: clinical use of biomarkers for initiation or discontinuation of antibiotic therapy

It seems reasonable to recommend using the algorithm tested on the largest number of patients, i.e., as in the ProVAP et Prorata studies, where stopping therapy was strongly encouraged when the serum PCT level was <0.5 ng/mL at 3 days or more after initiating antibiotics, or an >80% decrease from the maximal serum PCT value was recorded.

Quenot *et al. Annals of Intensive Care* 2013, **3**:21
http://www.annalsofintensivecare.com/content/3/1/21

Annals of Intensive Care
a SpringerOpen Journal

REVIEW **Open Access**

Role of biomarkers in the management of antibiotic therapy: an expert panel review II: clinical use of biomarkers for initiation or discontinuation of antibiotic therapy

In summary, we suggest withholding antibiotic therapy in adult patients suspected of community-acquired LRTI and having a serum PCT level <0.25 ng/mL; if clinical suspicion is high, it is however recommended to repeat the PCT measurement at a 6-h interval and reassess the therapeutic approach, accounting for new clinical findings.

Quenot *et al. Annals of Intensive Care* 2013, **3**:21
http://www.annalsofintensivecare.com/content/3/1/21

Annals of Intensive Care
a SpringerOpen Journal

REVIEW Open Access

Role of biomarkers in the management of antibiotic therapy: an expert panel review II: clinical use of biomarkers for initiation or discontinuation of antibiotic therapy

It should be noted that patients having infective endocarditis, bone and joint infection, acute mediastinitis, intracerebral or intraabdominal abscess were excluded from the above studies.

Therefore, PCT-based algorithms cannot be used in these patients for discontinuing antibiotics.

Using procalcitonin-guided algorithms to improve antimicrobial therapy in ICU patients with respiratory infections and sepsis

Philipp Schuetz[a], *Issam Raad*[b], *and Devendra N. Amin*[c]

Table 2. Outcomes associated with PCT monitoring in ICU studies (adapted from [42])

Parameter	PCT group	Control group	Adjusted[a] OR or absolute difference (95% CI)[a]	*P*
Initiation of antibiotics, *n* (%)	286 (100%)	311 (100%)	–	–
Duration[b] of antibiotics (days), median (IQR)	8 (5–15)	12 (8–18)	–3.17 (–4.28, –2.06)	<0.0001
Total exposure[c] of antibiotics (days), median (IQR)	8 (5–15)	12 (8–18)	–3.21 (–4.32, –2.10)	<0.0001
Mortality, *n* (%)	57 (19.9%)	74 (23.8%)	0.84 (0.54, 1.31)	0.443
ICU length-of-stay, median (IQR)	12 (6–23)	12 (6–22)	1.01 (–1.26, 3.28)	0.385
Hospital length-of-stay, median (IQR)	21 (11–38)	24 (14–38)	–1.36 (–4.5, 1.77)	0.393

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SYSTEMATIC REVIEW

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An ESICM systematic review and meta-analysis of procalcitonin-guided antibiotic therapy algorithms in adult critically ill patients

results. *Conclusions:* Procalcitonin-guided antibiotic therapy algorithms could help in reducing the duration of antimicrobial administration without having a negative impact on survival.

Reduce Inappropriate Initial Antimicrobial Therapy

- Guidelines and goal directed protocols
- Broad spectrum and combination antibiotics
- ID consultation
- More selective and sensitive diagnostic methods

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