ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

«ΛΟΙΜΩΞΙΟΛΟΓΙΑ»

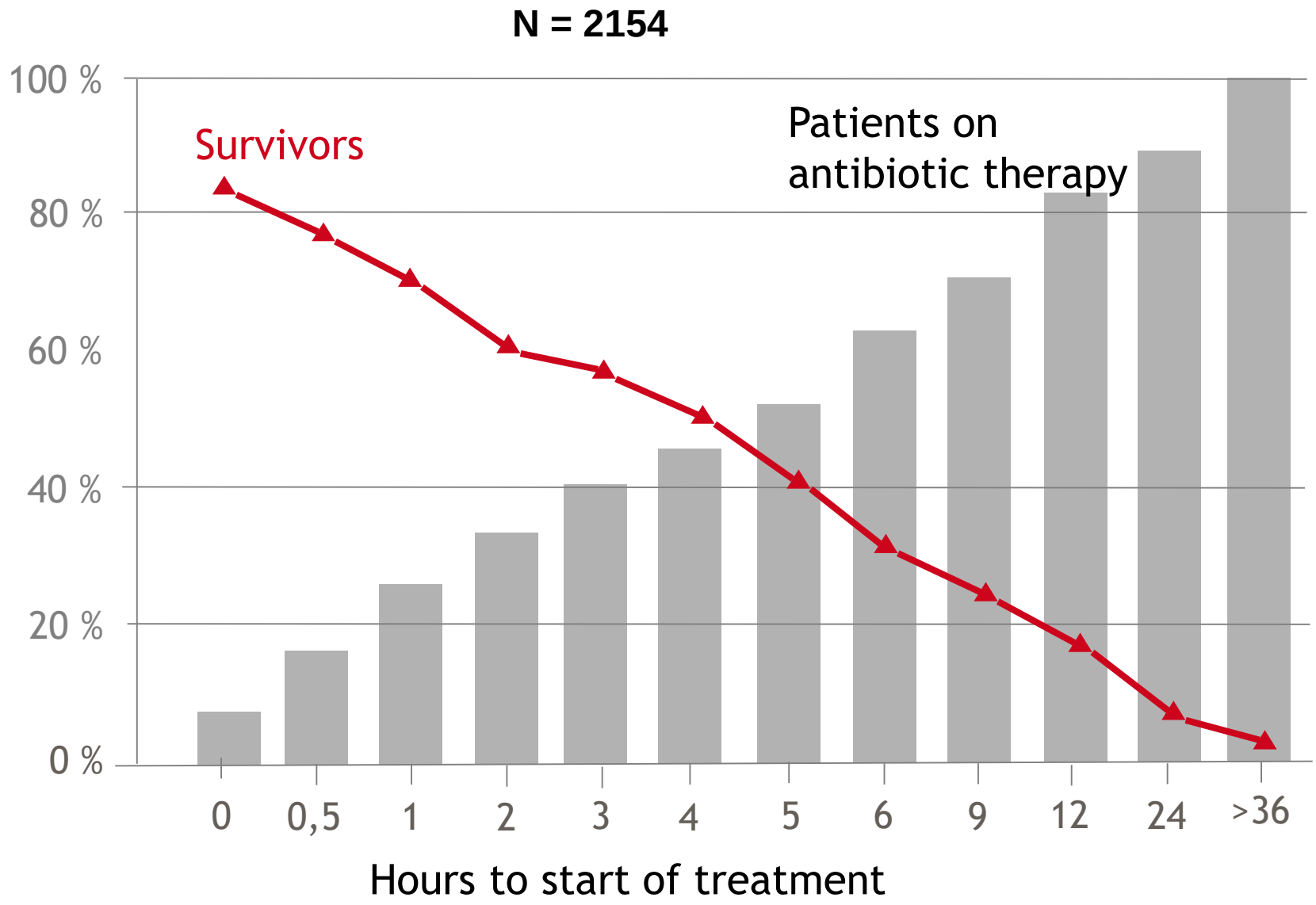
Καθορισμός διάρκειας θεραπείας με βιοδείκτες

Ηρακλής Τσαγκάρης

Αναπληρωτής Καθηγητής ΕΚΠΑ

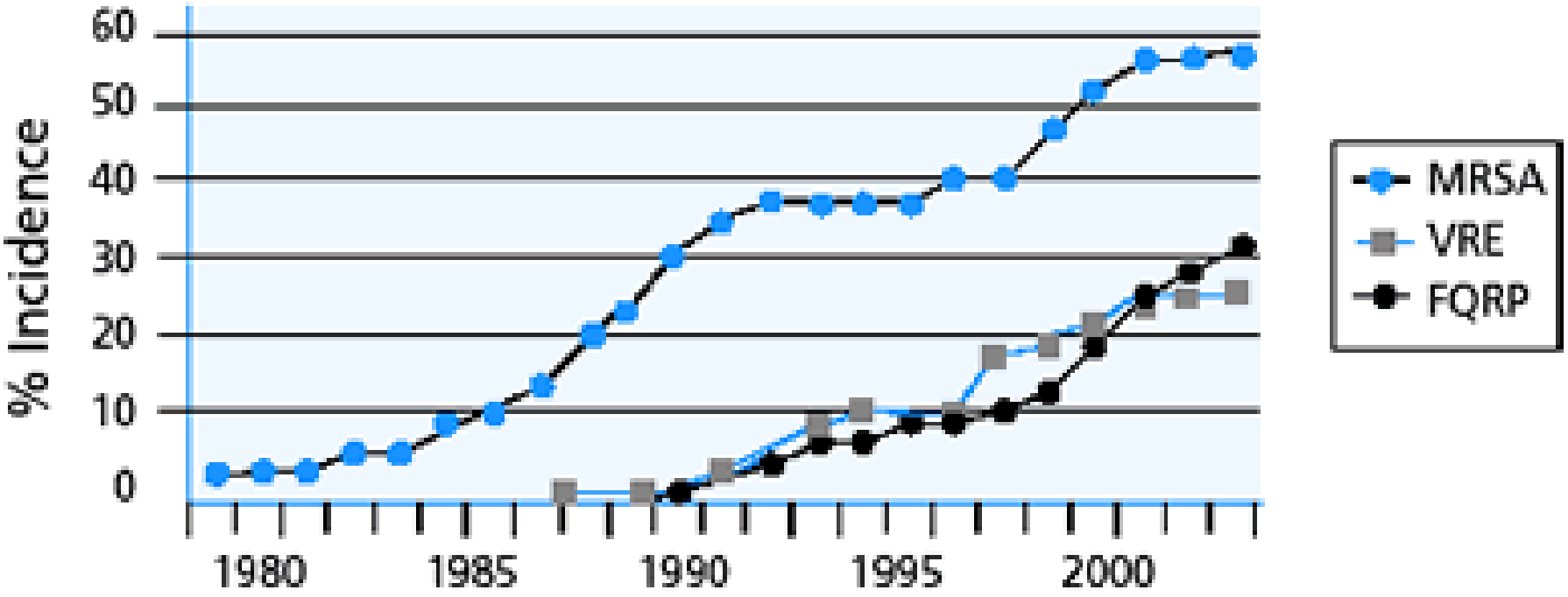
Νοσοκομείο ΑΤΤΙΚΟΝ

Septic Shock is often diagnosed and treated too late



Kumar et al. CCM 2006; 34: 1589-96.

Resistant Strains Spread Rapidly



Source: Centers for Disease Control and Prevention

MRSA = Methicillin-resistant *Staphylococcus Aureus*
VRE = Vancomycin-resistantant Enterococci
FQRP = Floroquinolone-resistant *Pseudomonas aeruginosa*

Guidelines

- Most currently used guidelines are not able to clearly stratify patients according to their individual response to therapy, because most of the guidelines provide recommendations for a maximum duration of antibiotic therapy only in order to cover the worst-case scenario, which could result due to medico-legal reasons and non-availability of good documentable criteria for the progress of source control and treatment of systemic inflammation.

Meissner, Ann Lab Med, 2014

What motivates YOU stopping antibiotics?

- „We said 8 days“
- „Patient is stable“
- „Patient has no more fever“
- „Patient goes home“
- „Patient develops a rash“
- „Patient sits on toilet with diarrhea“
- „Renal function is deteriorating“
- The fellow (attending) is changing
- Cultures came back negative
- **… pick your choice or add another…**

EDITORIAL

Dear SIRS, what is your biomarker level?

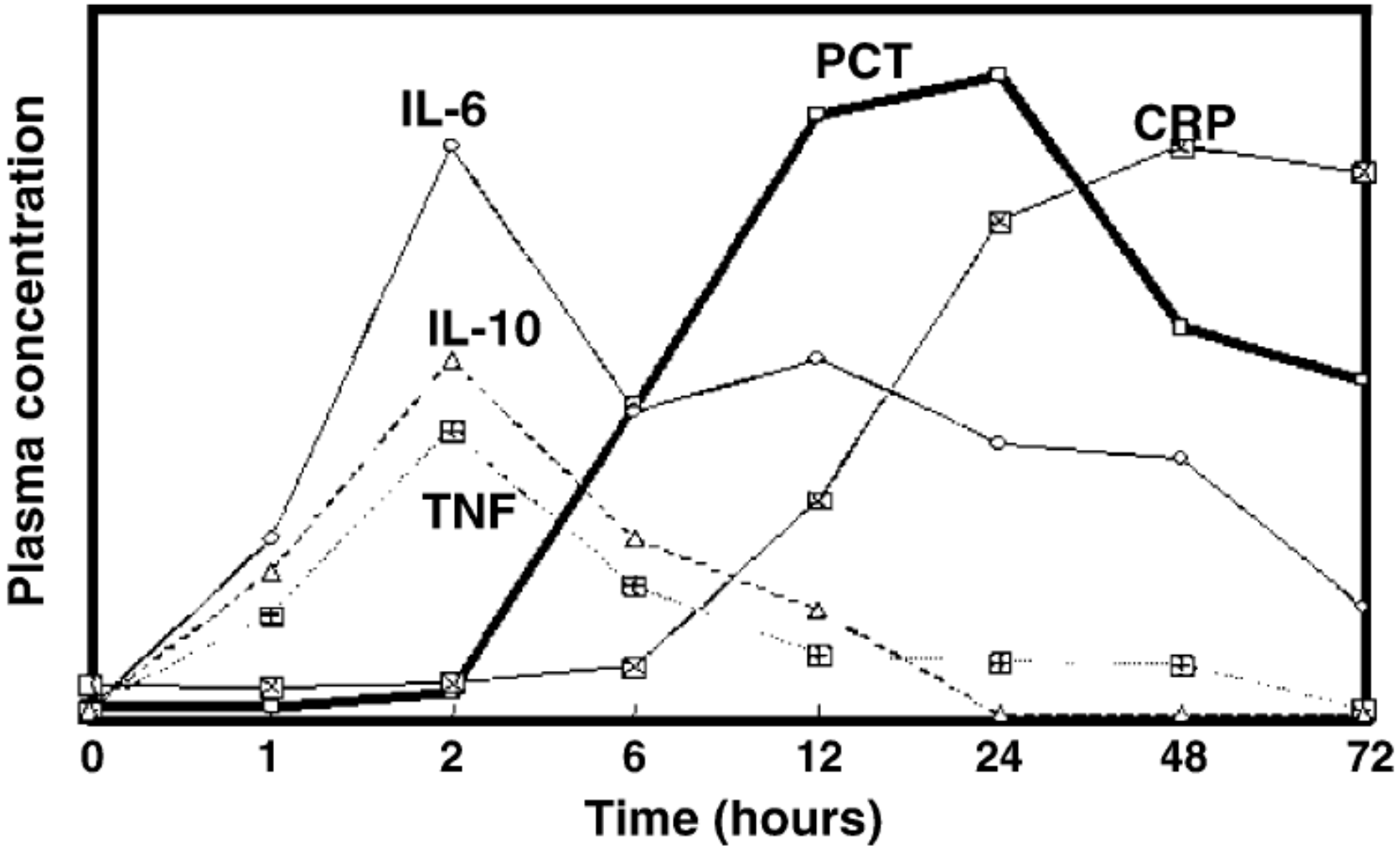
J.L. Vincent
D. Mercan

"*The diagnosis of infection, particularly in critically ill patients, is far from simple, and (…) biomarkers levels, are merely a sign of host response to the infectious event. They may be of use in conjunction with full clinical assessment including the presence of signs of sepsis, bacteriological data, and organ function evaluation, but on their own are of little value. As in many other facets of medicine, oversimplification of the septic process, both in terms of definitions and diagnosis, can be a negative and harmful concept."*

Intensive Care Med (2000) 26: 1170-1171

Doi 10.1007/s001340000605

Procalcitonin (PCT)



Reinhart K, et al. Crit Care Clin 2006;22;503-519

PCT: what do we expect

- Diagnosis of severe bacterial infection
- Evaluation of sepsis severity
- Assessment of the appropriateness of therapy (antibiotics or surgery/drainage), and
- Tailoring of antibiotic prescription (indication and duration)

Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis

Benjamin M P Tang, Guy D Eslick, Jonathan C Craig, Anthony S McLean

Lancet Infect Dis 2007; 7: 210–17

Department of Intensive Care Medicine, Nepean Hospital, Penrith, New South Wales, Australia (B M P Tang MD, A S McLean MD); School of Public Health, University of Sydney, Sydney, New South Wales (B M P Tang, G D Eslick PhD, J C Craig MD); and Department of Medicine, University of Sydney, Nepean Hospital, Penrith (G D Eslick)

Procalcitonin is widely reported as a useful biochemical marker to differentiate sepsis from other non-infectious causes of systemic inflammatory response syndrome. In this systematic review, we estimated the diagnostic accuracy of procalcitonin in sepsis diagnosis in critically ill patients. 18 studies were included in the review. Overall, the diagnostic performance of procalcitonin was low, with mean values of both sensitivity and specificity being 71% (95% CI 67–76) and an area under the summary receiver operator characteristic curve of 0·78 (95% CI 0·73–0·83). Studies were grouped into phase 2 studies (n=14) and phase 3 studies (n=4) by use of Sackett and Haynes' classification. Phase 2 studies had a low pooled diagnostic odds ratio of 7·79 (95% CI 5·86–10·35). Phase 3 studies showed significant heterogeneity because of variability in sample size (meta-regression coefficient –0·592, p=0·017), with diagnostic performance upwardly biased in smaller studies, but moving towards a null effect in larger studies. Procalcitonin cannot reliably differentiate sepsis from other non-infectious causes of systemic inflammatory response syndrome in critically ill adult patients. The findings from this study do not lend support to the widespread use of the procalcitonin test in critical care settings.

Procalcitonin (PCT)

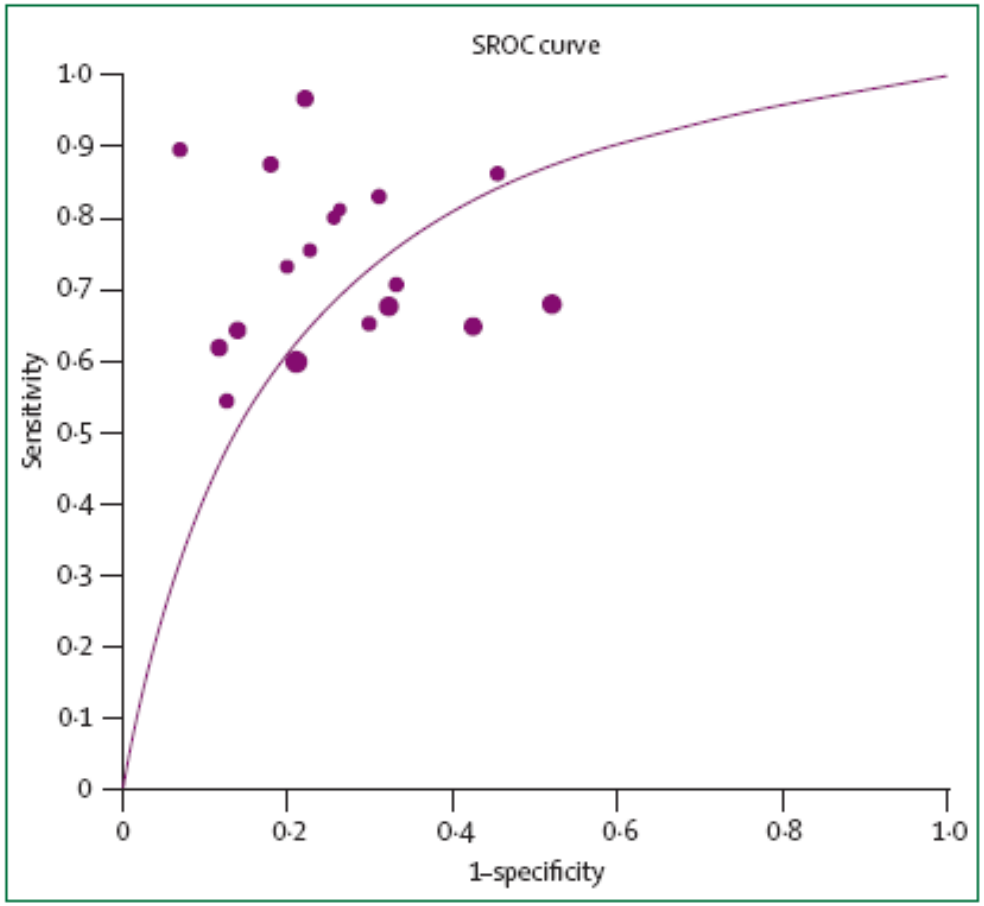


Figure 3: Summary receiver operator characteristic (SROC) curve of all studies

Circles indicate individual study estimates of sensitivity and 1–specificity. Size of circles is proportional to inverse variance of each study.

The diagnostic performance of procalcitonin was low, with mean values of both sensitivity and specificity being 71% (95% CI 67–76) and an area under the summary receiver operator characteristic curve of 0.78 (95% CI 0·73–0·83)

❖ **Procalcitonin cannot reliably differentiate sepsis from other non-infectious causes of SIRS in critically ill adult patients**

Conclusions

"…Procalcitonin cannot reliably differentiate sepsis from other non-infectious causes of systemic inflammatory response syndrome in critically ill adult patients.

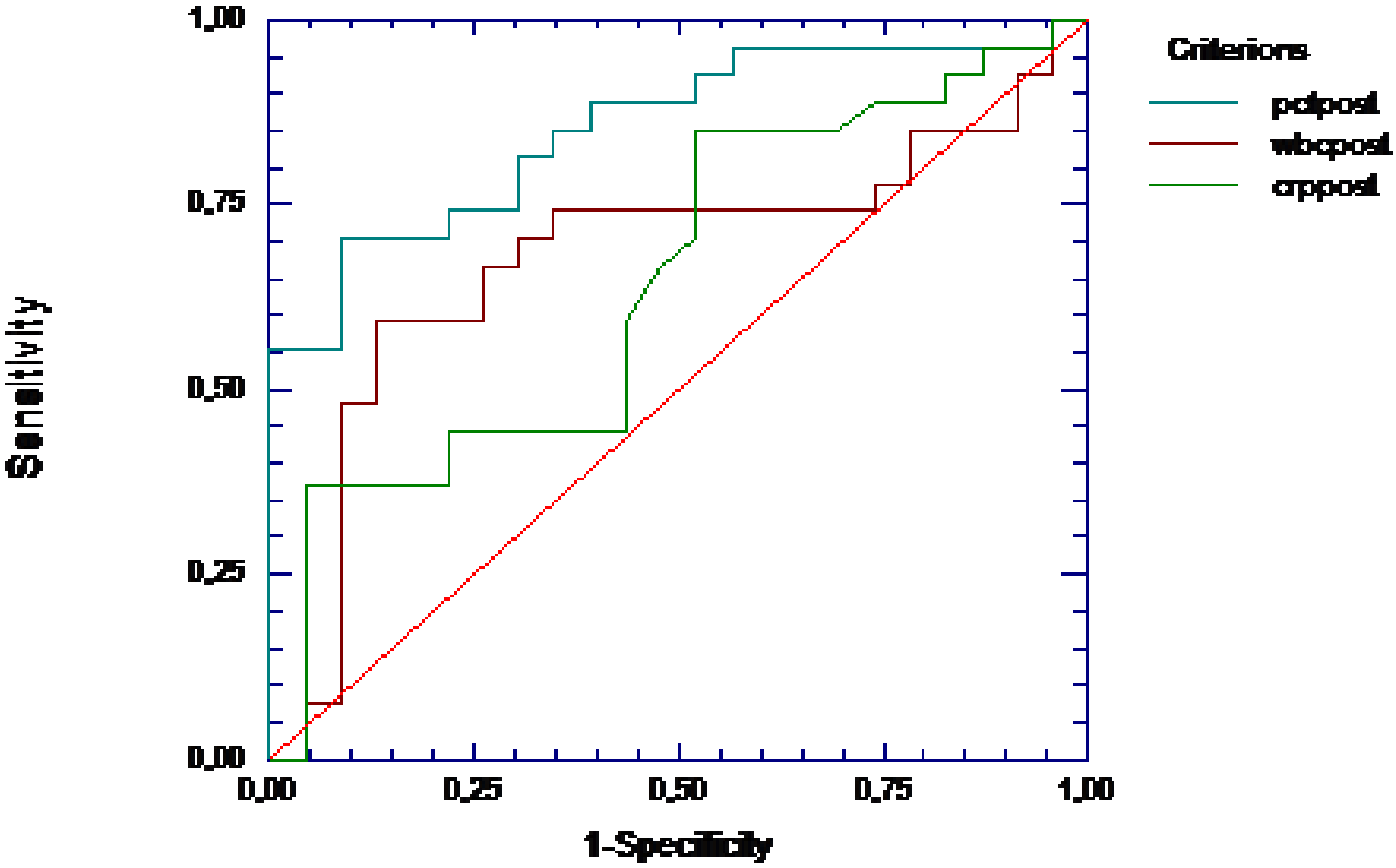
The findings from this study do not lend support to the widespread use of the procalcitonin test in critical care settings…"

Tang, Lancet Infect Dis, 2007

Can PCT rule in/out bacterial infection?

- NO…..at least not entirely
  - But what has better ROC's?
  - Nonetheless, PCT will not replace clinical judgment

But what has better ROC's?



Tsangaris, *et al. BMC Infectious Diseases* 2009 **9**:213

Reasons for discrepant conclusions on PCT as a marker of infection

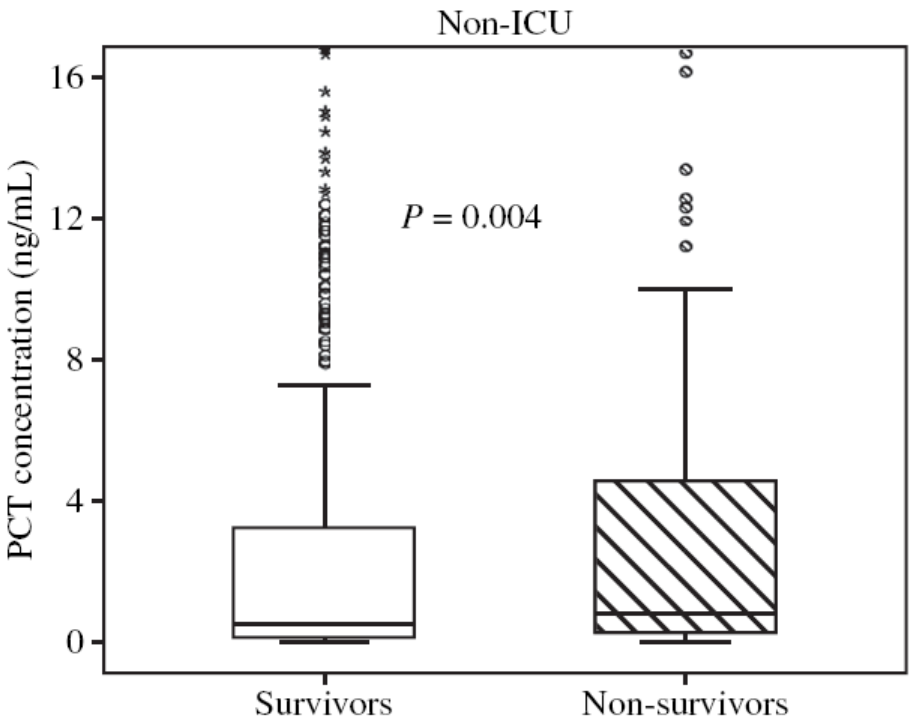
- ✓ Different assays
- ✓ Cut-off range depends on:
  - Clinical setting and type of infection
  - Pretest probabilities
- ✓ Poor study design of many studies
- ✓ Single PCT measurements of limited value
- ✓ False positives and negatives (10%)

PCT: what do we expect

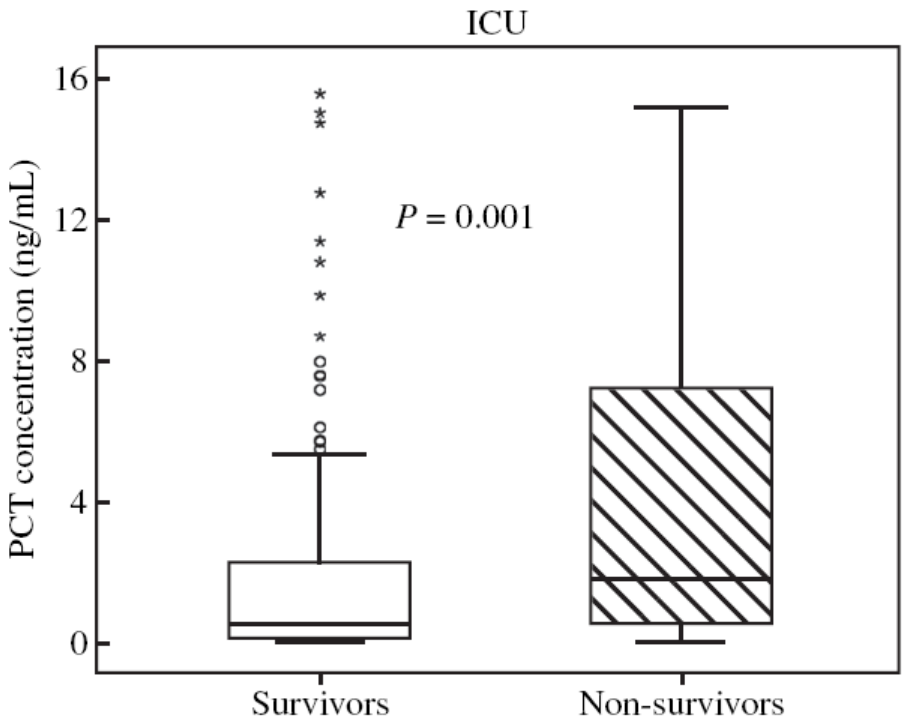
- Diagnosis of bacterial infection
- Evaluation of sepsis severity
- Assessment of the appropriateness of therapy (antibiotics or surgery/drainage), and
- Tailoring of antibiotic prescription (indication and duration)

PCT and survival

922 pts

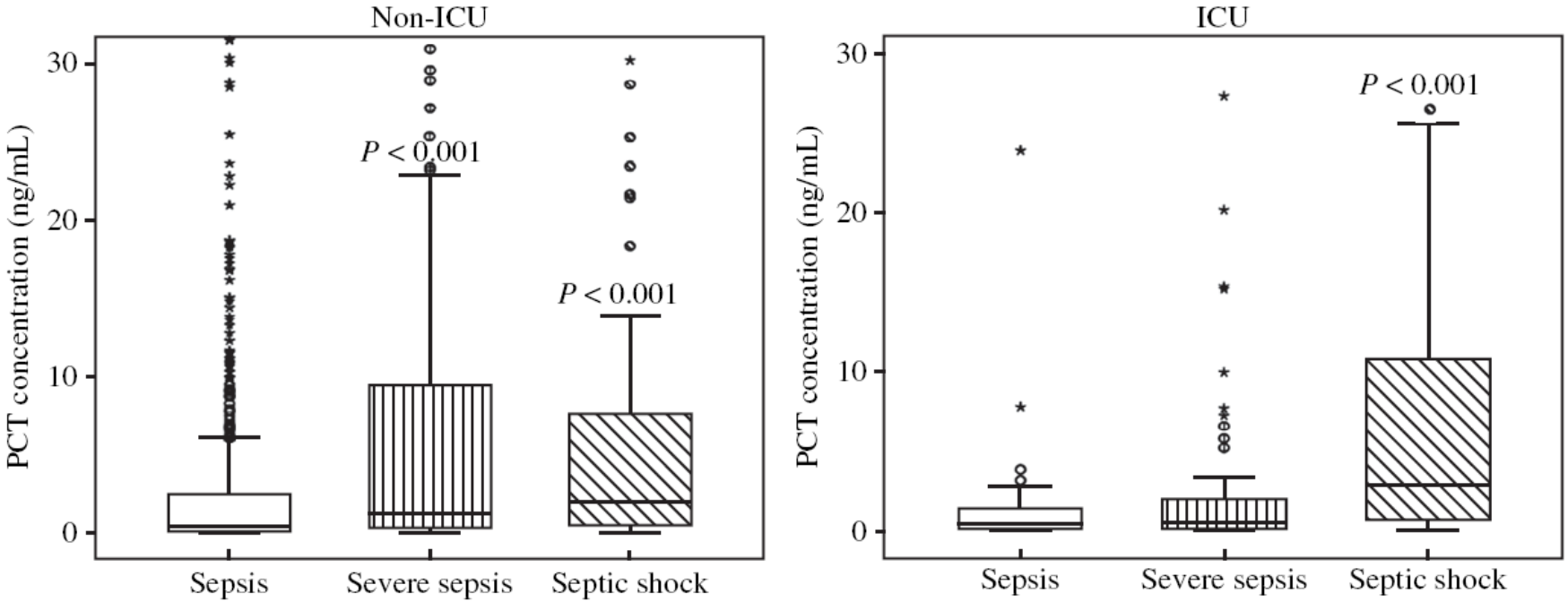


234 pts



Giamarellos-Bourboulis, Tsangaris, et al. J Hosp Infect 2011; 77: 58-63

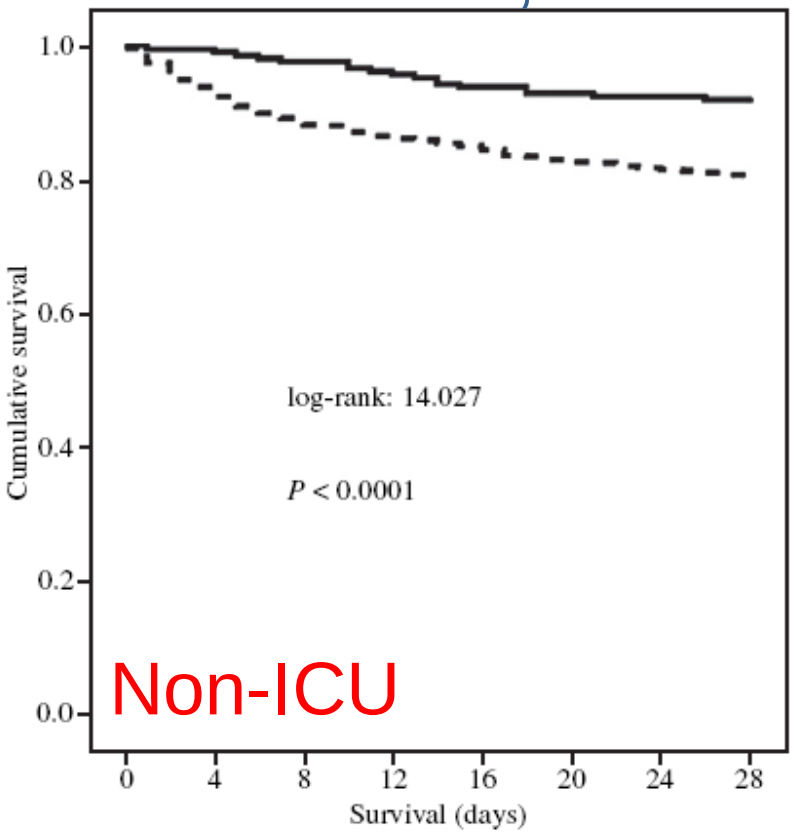
PCT and sepsis severity



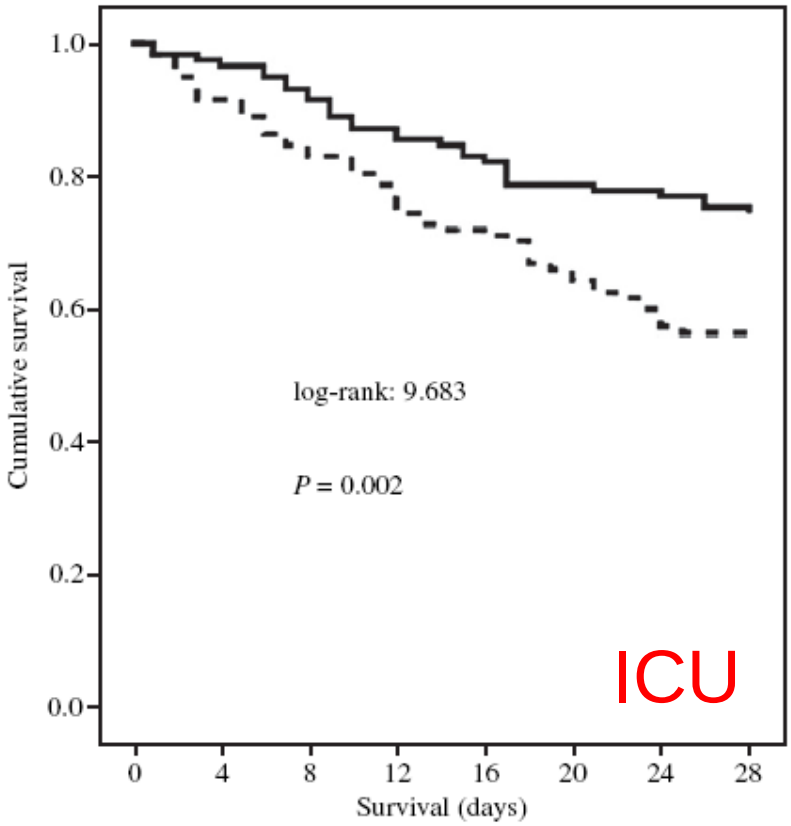
Giamarellos-Bourboulis, Tsangaris, et al. J Hosp Infect 2011; 77: 58-63

PCT threshold

PCT 0,12



PCT 0,85



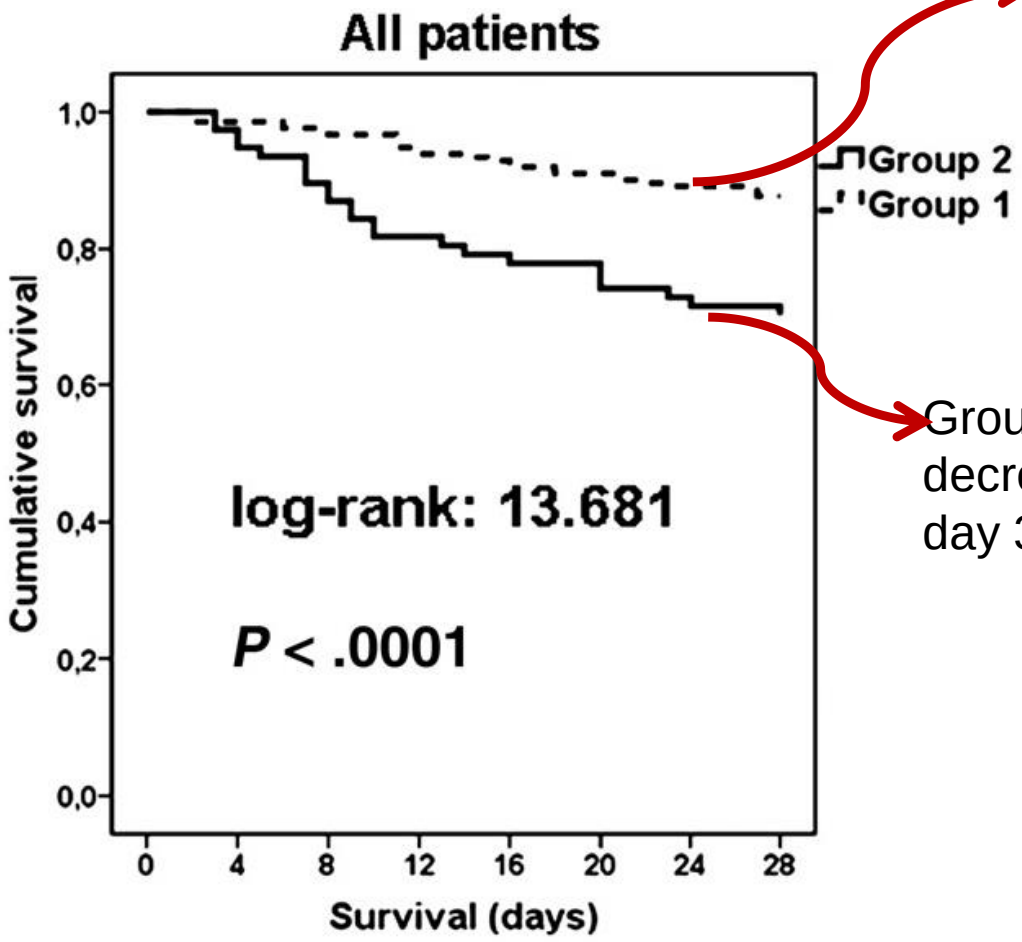
Giamarellos-Bourboulis, Tsangaris, Kanni, et al. J Hosp Infect 2011; 77: 58-63

PCT: what do we expect

- Diagnosis of severe bacterial infection
- Evaluation of sepsis severity
- Assessment of the appropriateness of therapy (antibiotics or surgery/drainage), and
- Tailoring of antibiotic prescription (indication and duration)

Does PCT carry a prognostic role?

289 pts

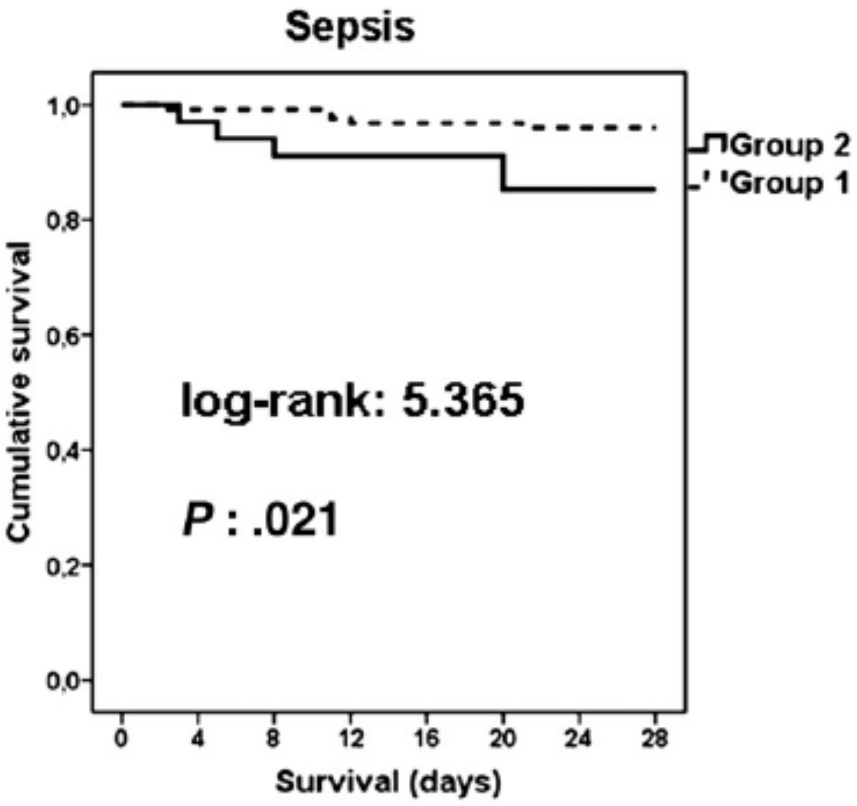


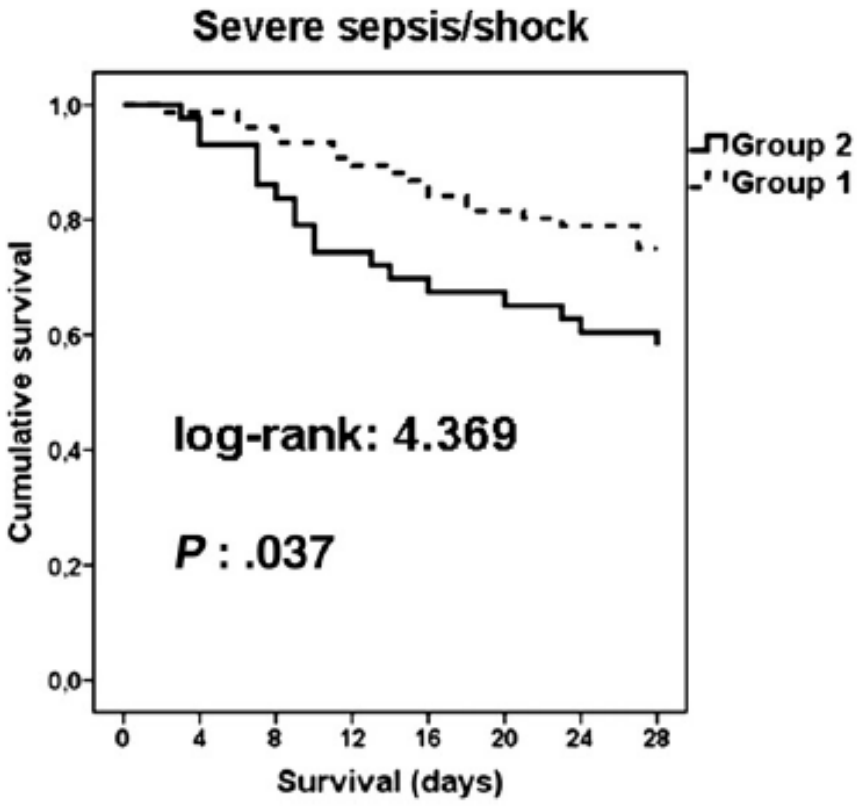
Group 1: ↓PCT on day 3 by >30% or PCT on day 3 <0.25 ng/mL

Group 2: ↑ PCT or decrease of PCT on day 3 by <30%.

Georgopoulou, J Crit Care, 2011

Does PCT carry a prognostic role?





Georgopoulou, J Crit Care, 2011

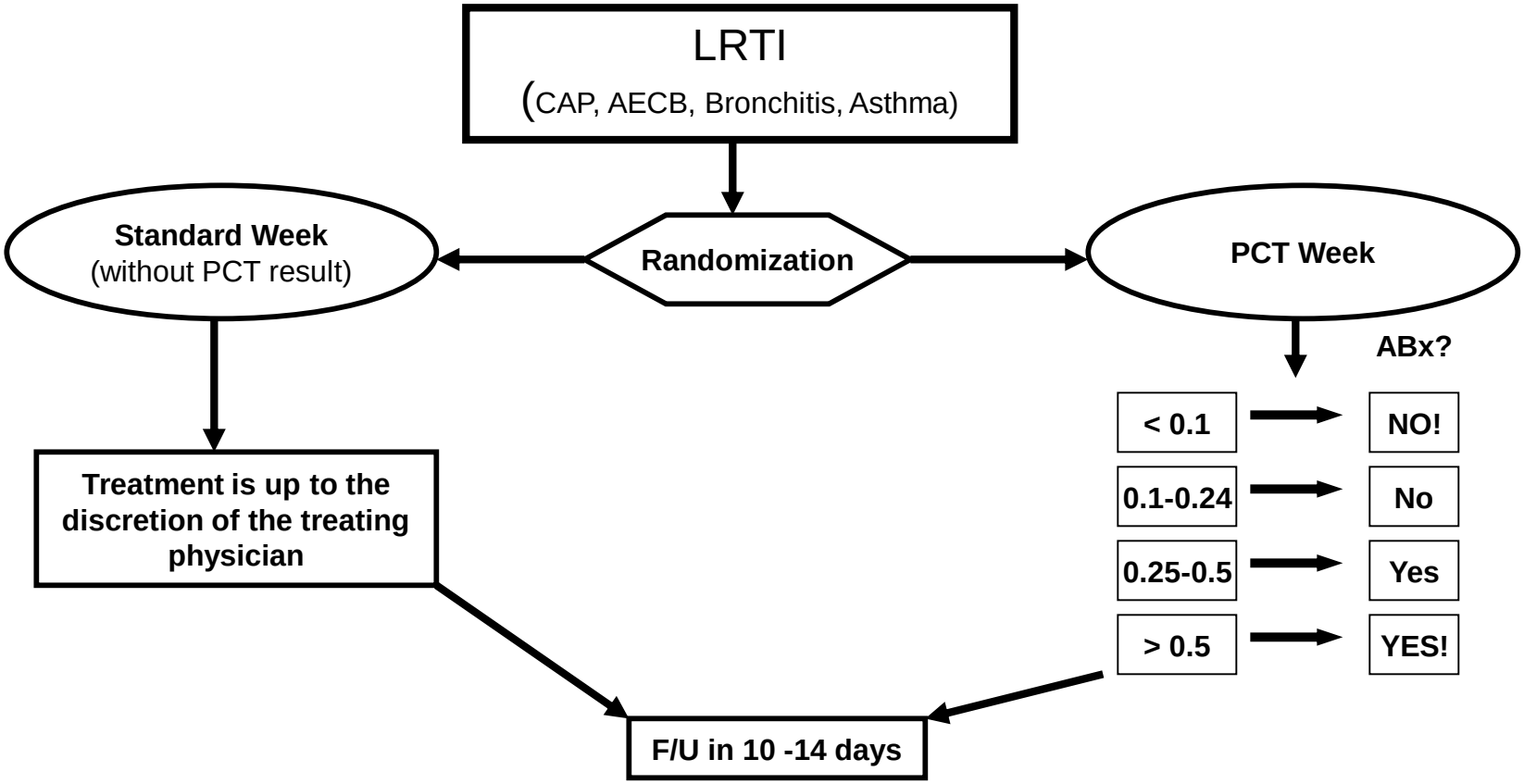
PCT: what do we expect

- Diagnosis of severe bacterial infection
- Evaluation of sepsis severity
- Assessment of the appropriateness of therapy (antibiotics or surgery/drainage), and
- Tailoring of antibiotic prescription (indication and duration)

- Infections of the respiratory tract, including bronchitis, community-acquired pneumonia (CAP), and acute exacerbated chronic obstructive pulmonary disease (AECOPD), are the most important drivers for antibiotic (over-) treatment and thereby contribute to the increasing rate of antibiotic multi-resistance.

ProResp:

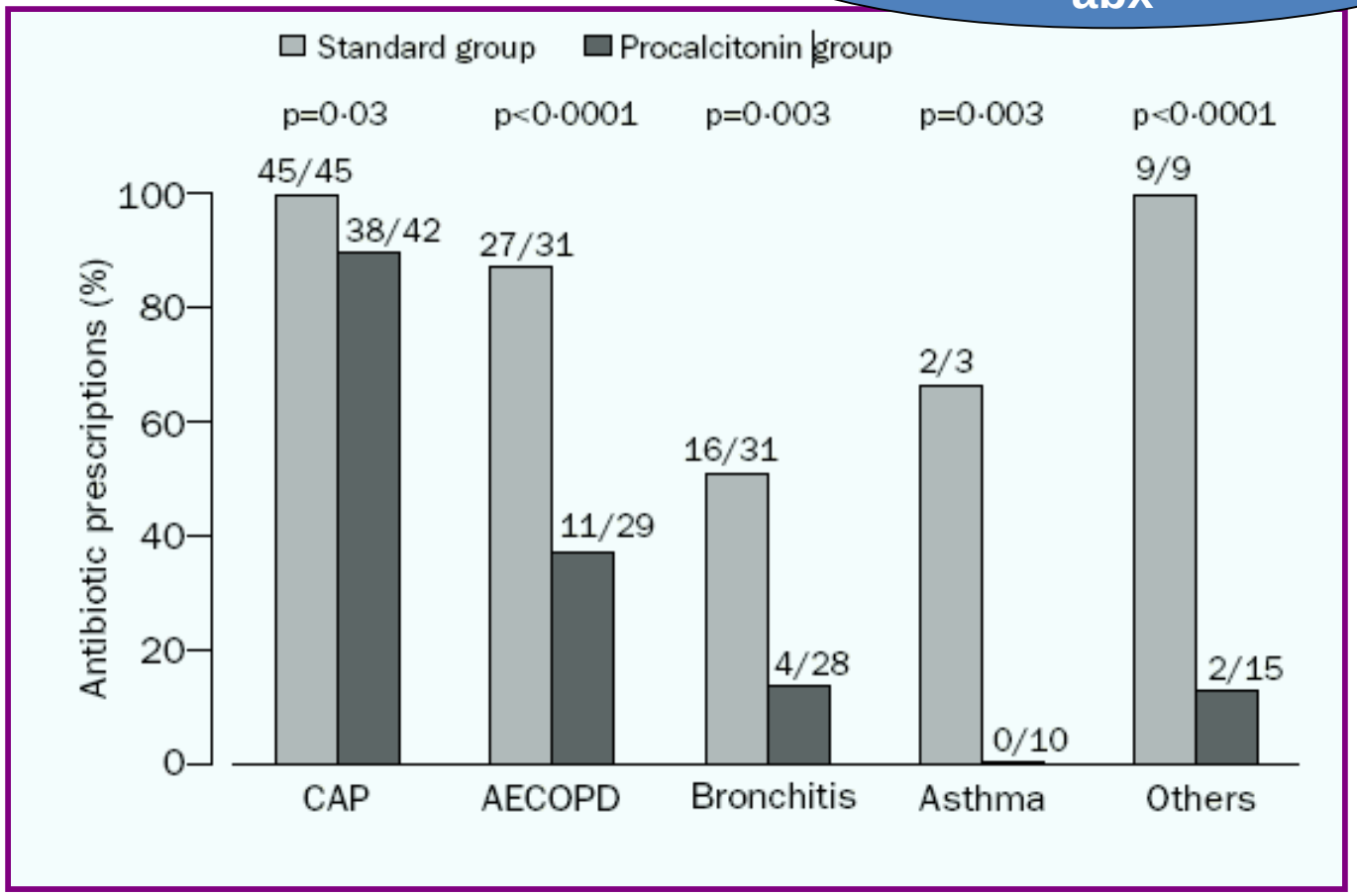
Study Design



Christ-Crain M, Lancet 2004; 363; 600-607

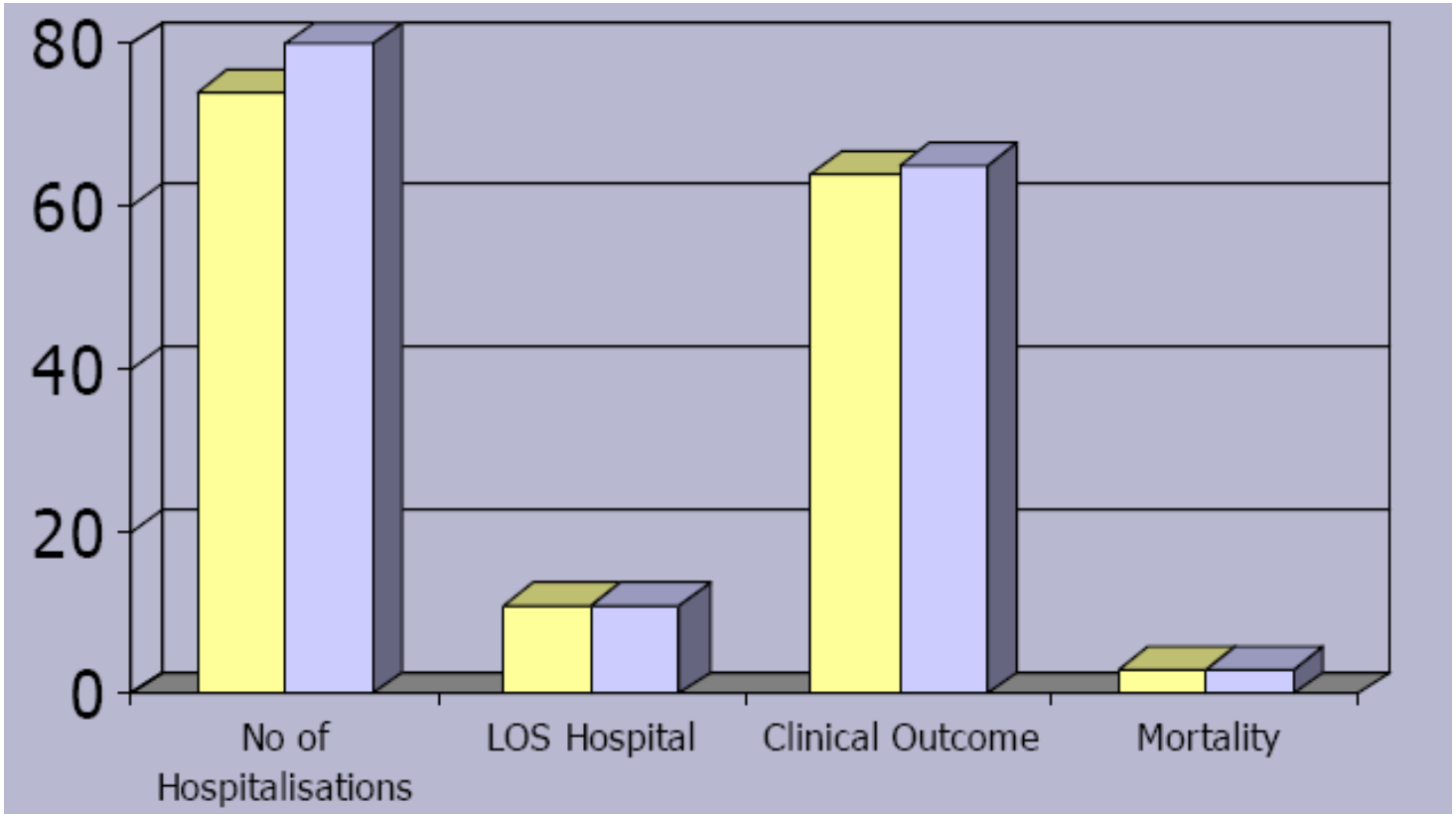
LRTI's

Overall, 50% reduction in use of abx



Christ-Crain M, Lancet 2004; 363; 600-607

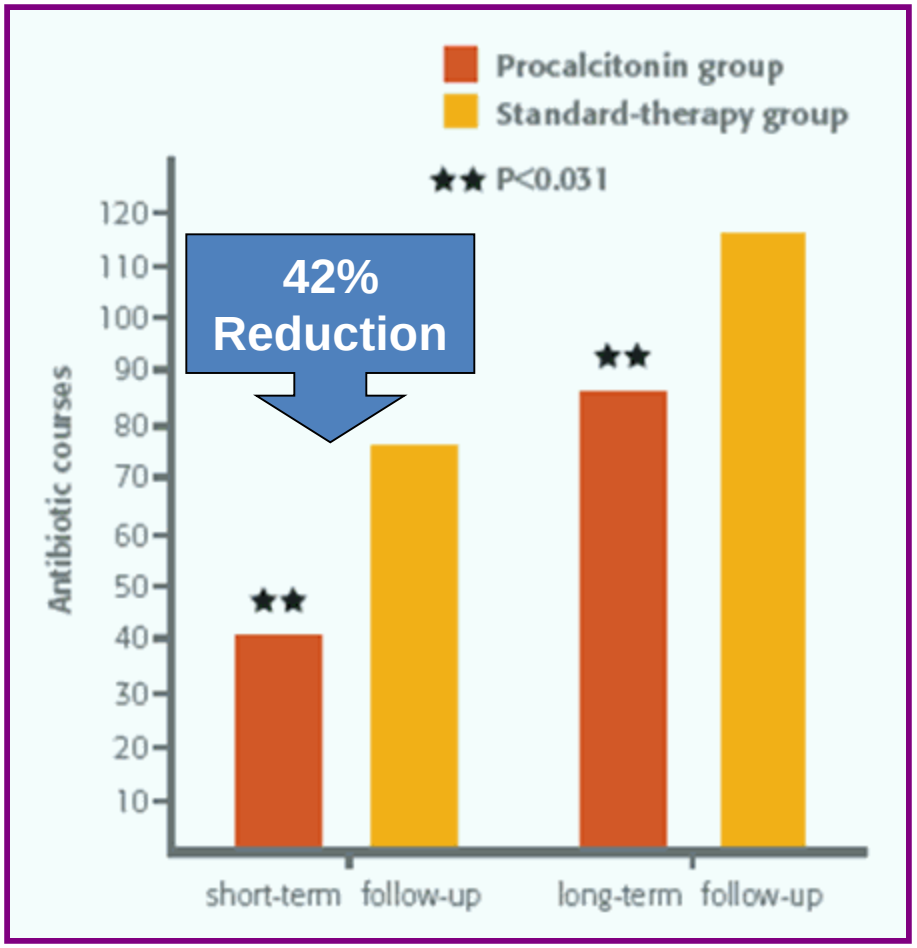
No worse outcomes

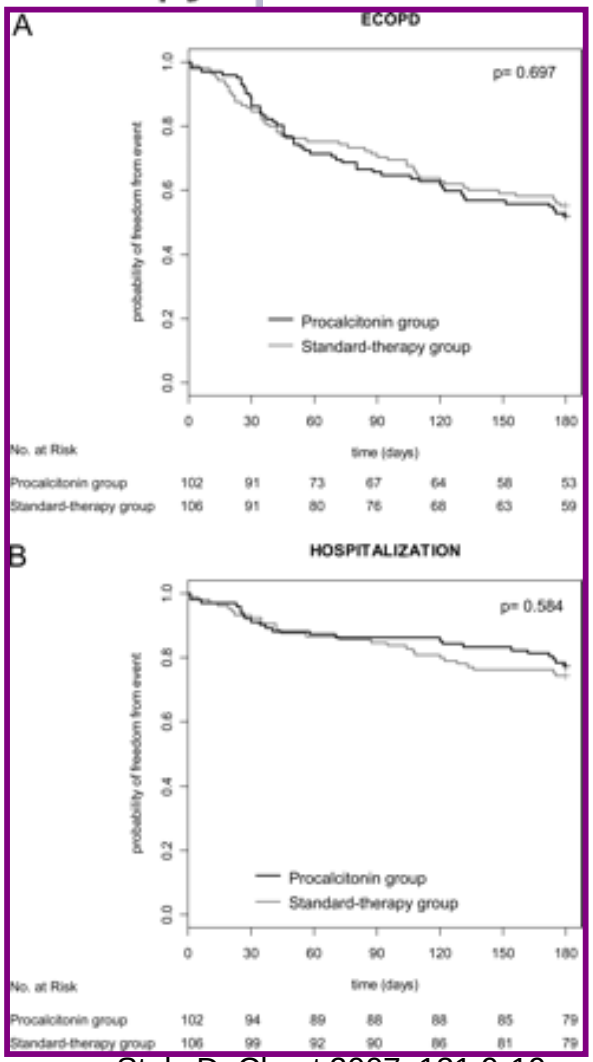


Christ-Crain M, Lancet 2004; 363; 600-607

Antibiotic Treatment of Exacerbations of COPD*

A Randomized, Controlled Trial Comparing Procalcitonin-Guidance With Standard Therapy

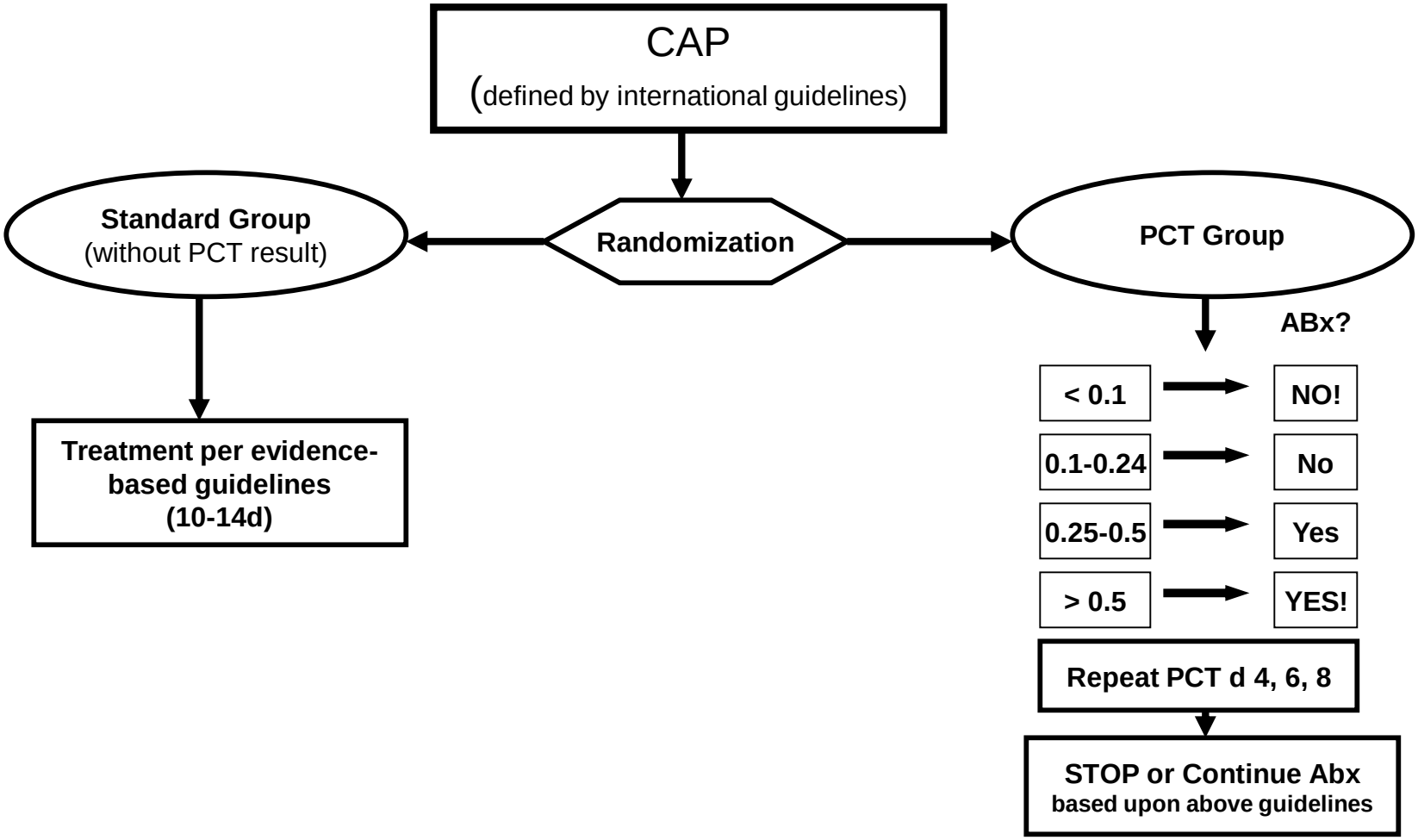




Stolz D, Chest 2007; 131:9-19.

ProCAP:

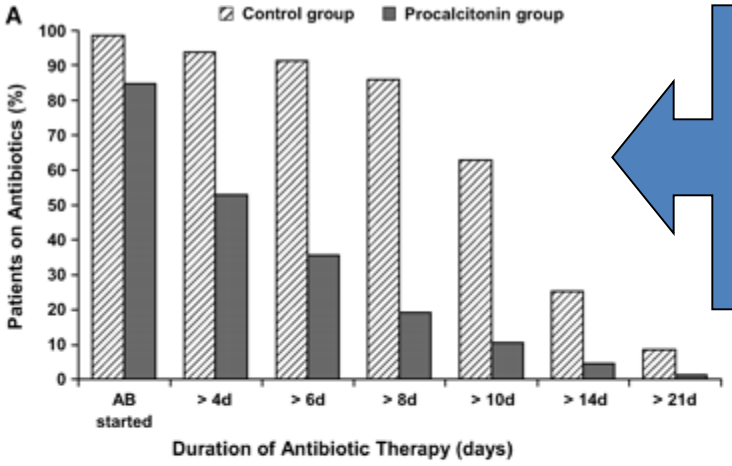
Study Design



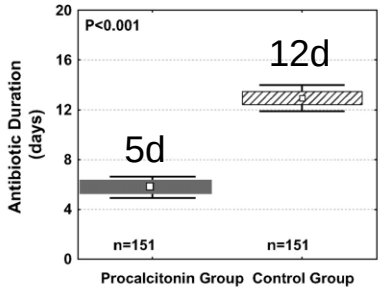
Christ-Crain M, AJRCCM 2006; 174: 84-93

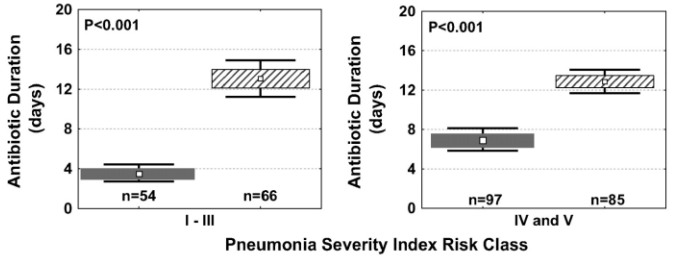
ProCAP:

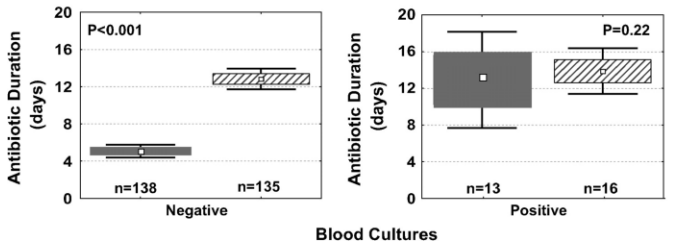
Results

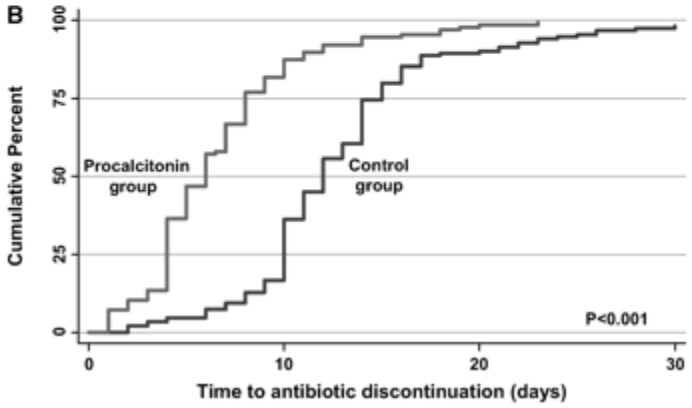


Overall 48% Reduction in Abx









Christ-Crain M, Crit Care 2005; 9:166

Use of Procalcitonin to Shorten Antibiotic Treatment Duration in Septic Patients

A Randomized Trial

Vandack Nobre[1], Stephan Harbarth[2], Jean-Daniel Graf[3], Peter Rohner[4], and Jérôme Pugin[1]

[1]Intensive Care, [2]Infection Control Program, [3]Central Chemistry Laboratory, and [4]Microbiology Laboratory, University Hospitals of Geneva, Faculty of Medicine, University of Geneva, Geneva, Switzerland

At a glance commentary

Scientific Knowledge on the Subject

The duration of antibiotic therapy in critically ill patients with sepsis is based on empirical rules, which may lead to antibiotic overuse and selection pressure.

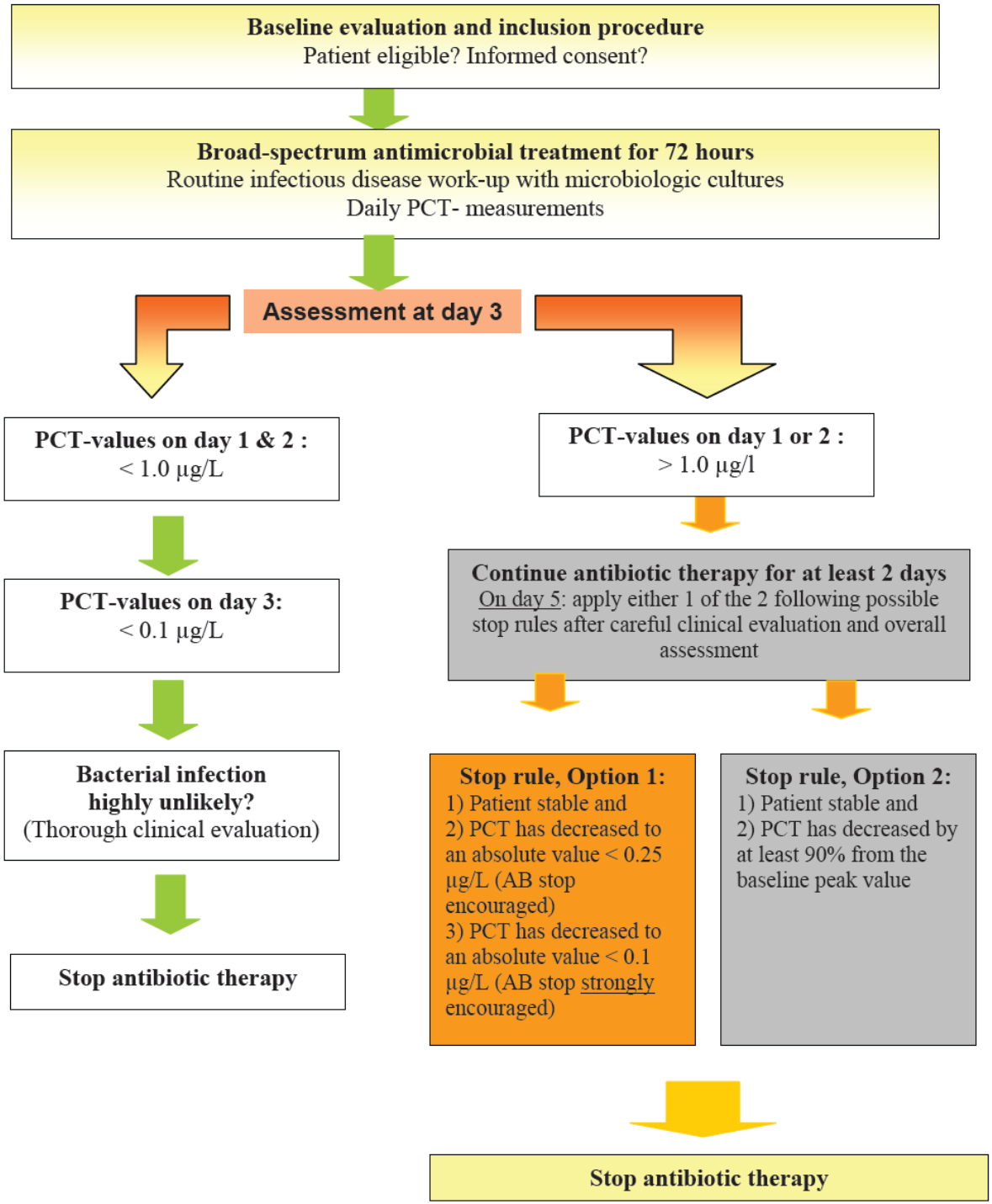
What This Study Adds to the Field

The application of a decision algorithm based on the relative decrease of plasma procalcitonin levels over time allows to significantly shorten the duration of antibiotic therapy and ICU stay, without apparent harm to patients with severe sepsis and septic shock.

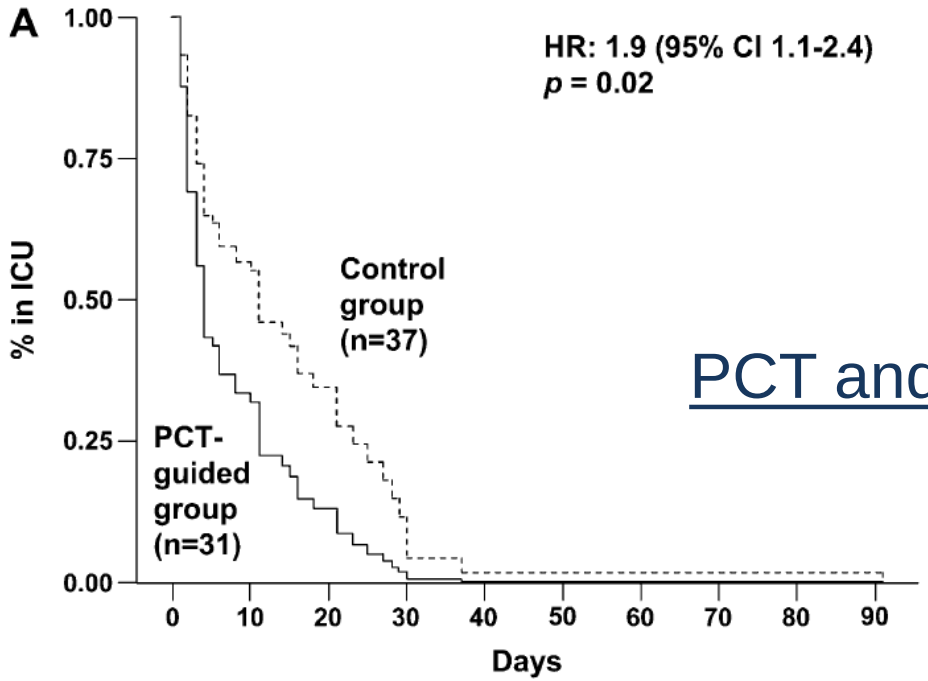
AJRCCM, Mar 2008

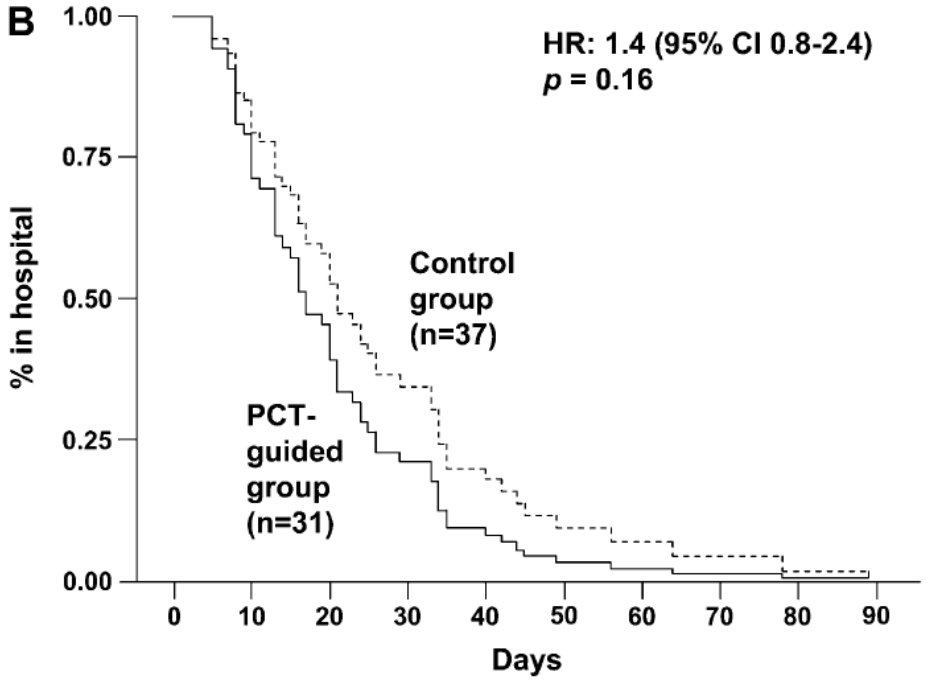
Did not refer to…

- Microbiologically documented infections caused by Pseudomonas aeruginosa, Acinetobacter baumanni, Listeria spp., Legionella pneumophila, Pneumocystis jiroveci, or Mycobacterium tuberculosis, for which a prolonged duration of antibiotic therapy is standard-of-care
- Infectious conditions requiring prolonged antibiotic therapy (e.g., bacterial endocarditis, brain abscess, deep abscesses)
- Antibiotic therapy started 48 hours or more before enrollment
- Chronic, localized infections (e.g.,chronic osteomyelitis)
- Severely immunocompromised patients


Baseline evaluation and inclusion procedure
Patient eligible? Informed consent?
Broad-spectrum antimicrobial treatment for 72 hours
Routine infectious disease work-up with microbiologic cultures
Daily PCT- measurements
Assessment at day 3
PCT-values on day 1 & 2 :
< 1.0 µg/L
PCT-values on day 3:
< 0.1 µg/L
Bacterial infection highly unlikely?
(Thorough clinical evaluation)
Stop antibiotic therapy
PCT-values on day 1 or 2 :
> 1.0 µg/l
Continue antibiotic therapy for at least 2 days
On day 5: apply either 1 of the 2 following possible stop rules after careful clinical evaluation and overall assessment
Stop rule, Option 1:
1) Patient stable and
2) PCT has decreased to an absolute value < 0.25 µg/L (AB stop encouraged)
3) PCT has decreased to an absolute value < 0.1 µg/L (AB stop strongly encouraged)
Stop rule, Option 2:
1) Patient stable and
2) PCT has decreased by at least 90% from the baseline peak value
Stop antibiotic therapy

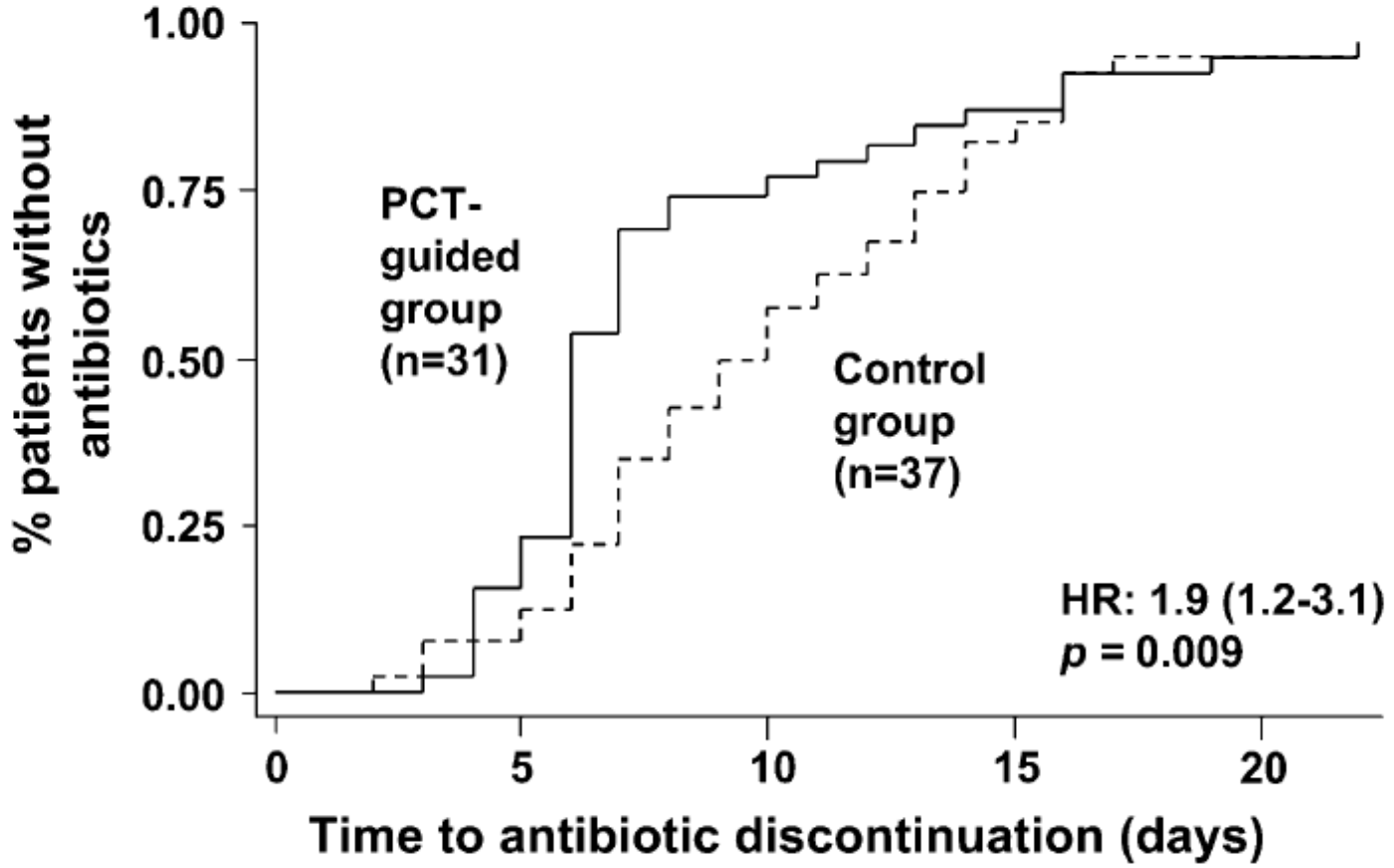
PCT and LOS





Nobre, AJRCCM, 2008

PCT and duration of antibiotic treatment



Nobre, AJRCCM, 2008

Does a PCT based algorithm affect outcome?

Per-Protocol Analysis	Control Group ($n = 37$)	PCT Group ($n = 31$)	RR (95% CI)	*P* Value
Primary outcomes				
Duration of antibiotic therapy, first episode of infection, median d (range)	10 (3–33)	6 (4–16)	Mean difference: 3.2 (1.1 to 5.4)	0.003
Total antibiotic exposure days/1,000 d	655	504	1.3 (1.1 to 1.5)*	0.0002
Days alive without antibiotics, mean ± SD	13.6 ± 7.6	17.4 ± 7.6	Mean difference: 3.8 (0.1 to 7.5)	0.04
Secondary outcomes				
Clinical cure, n (%)	31 (83.8)	28 (90.3)	0.8 (0.5 to 1.3)	0.48
28-d mortality, n (%)	6 (16.2)	5 (16.1)	1.0 (0.5 to 1.8)	0.74
In-hospital mortality, n (%)	7 (18.9)	6 (19.4)	0.9 (0.6 to 1.7)	0.79
Sepsis-related death, n (%)	1/6 (16.6)	3/5 (60)	0.3 (0.1 to 2.0)	0.44
Primary infection relapse rate, n (%)	1 (2.7)	1 (3.2)	0.9 (0.9 to 3.7)	0.70
ICU length of stay, median d (range)	5 (1–30)	3 (1–18)	Mean difference: 4.3 (0.4 to 8.3)	0.03
Hospital length of stay, median d (range)	21 (5–89)	14 (5–64)	Mean difference: 2.2 (−1.9 to 6.3)	0.16

Nobre, AJRCCM, 2008

JAMA®
The Journal of the American Medical Association

ORIGINAL CONTRIBUTION

Effect of Procalcitonin-Based Guidelines vs Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections

The ProHOSP Randomized Controlled Trial

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Stefanie Neidert, MD
Thomas Fricker, MD
Claudine Blum, MD
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Ronald Schoenenberger, MD
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Thomas Bregenzer, MD
Claus Hoess, MD
Martin Krause, MD
Heiner C. Bucher, MD
Werner Zimmerli, MD
Beat Mueller, MD
for the ProHOSP Study Group

Context In previous smaller trials, a procalcitonin (PCT) algorithm reduced antibiotic use in patients with lower respiratory tract infections (LRTIs).

Objective To examine whether a PCT algorithm can reduce antibiotic exposure without increasing the risk for serious adverse outcomes.

Design, Setting, and Patients A multicenter, noninferiority, randomized controlled trial in emergency departments of 6 tertiary care hospitals in Switzerland with an open intervention of 1359 patients with mostly severe LRTIs randomized between October 2006 and March 2008.

Intervention Patients were randomized to administration of antibiotics based on a PCT algorithm with predefined cutoff ranges for initiating or stopping antibiotics (PCT group) or according to standard guidelines (control group). Serum PCT was measured locally in each hospital and instructions were Web-based.

Main Outcome Measures Noninferiority of the composite adverse outcomes of death, intensive care unit admission, disease-specific complications, or recurrent infection requiring antibiotic treatment within 30 days, with a predefined noninferiority boundary of 7.5%; and antibiotic exposure and adverse effects from antibiotics.

Results The rate of overall adverse outcomes was similar in the PCT and control groups (15.4% [n=103] vs 18.9% [n=130]; difference, −3.5%; 95% CI, −7.6% to 0.4%). The mean duration of antibiotics exposure in the PCT vs control groups was lower in all patients (5.7 vs 8.7 days; relative change, −34.8%; 95% CI, −40.3% to −28.7%) and in the subgroups of patients with community-acquired pneumonia (n=925, 7.2 vs 10.7 days; −32.4%; 95% CI, −37.6% to −26.9%), exacerbation of chronic obstructive pulmonary disease (n=228, 2.5 vs 5.1 days; −50.4%; 95% CI, −64.0% to −34.0%), and acute bronchitis (n=151, 1.0 vs 2.8 days; −65.0%; 95% CI, −84.7% to −37.5%). Antibiotic-associated adverse effects were less frequent in the PCT group (19.8% [n=133] vs 28.1% [n=193]; difference, −8.2%; 95% CI, −12.7% to −3.7%).

Conclusion In patients with LRTIs, a strategy of PCT guidance compared with standard guidelines resulted in similar rates of adverse outcomes, as well as lower rates of antibiotic exposure and antibiotic-associated adverse effects.

Trial Registration isrctn.org Identifier: ISRCTN95122877

JAMA. 2009;302(10):1059-1066 www.jama.com

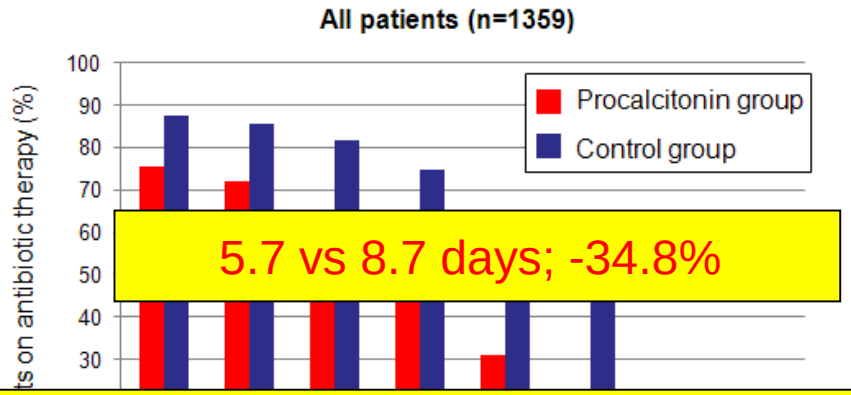
UNNECESSARY ANTIBIOTIC USE importantly contributes to increasing bacterial resistance and increases medical costs and the risks of drug-related adverse events.[1-3] The most frequent indication for antibiotic prescriptions in the northwestern hemisphere is lower respiratory tract infections (LRTIs), which range in severity from self-limited acute bronchitis to severe acute exacerbation of chronic obstructive pulmonary disease (COPD), and to life-threatening bacterial community-acquired pneumonia (CAP).[4] Clinical signs and symptoms, as well as commonly used laboratory markers, are unreliable in distinguishing viral from bacterial LRTI.[5-7] As many as 75% of patients with LRTI are treated with antibiotics, despite the predominantly viral origin of their infection.[8]

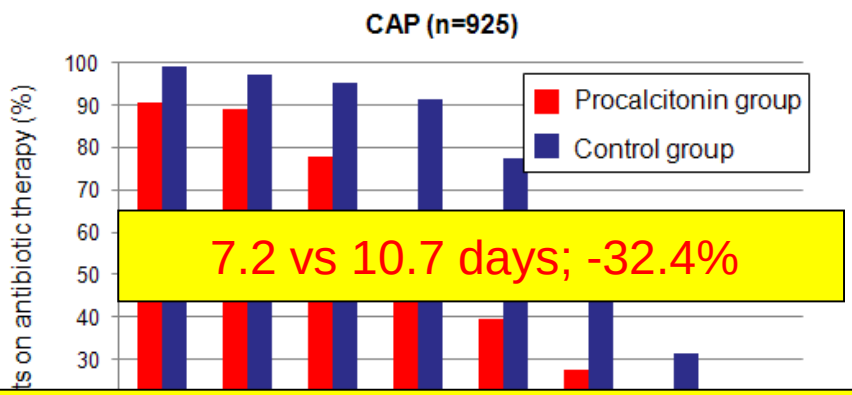
An approach to estimate the probability of bacterial origin in LRTI is the measurement of serum procalcitonin (PCT).

For editorial comment see p 1115.

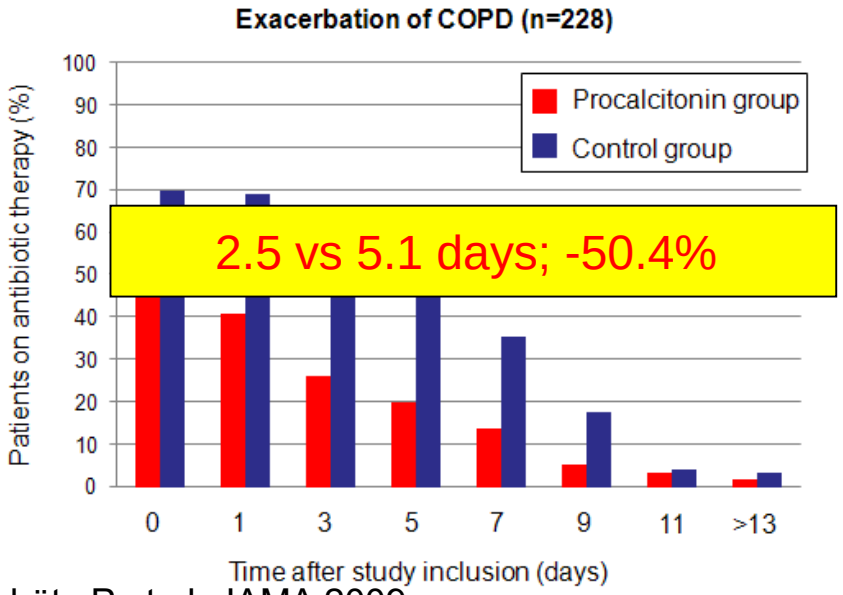
Author Affiliations and Members of the ProHOSP Study Group are listed at the end of this article.
Corresponding Author: Beat Mueller, MD, Department of Internal Medicine, Kantonsspital Aarau, Tellstrasse, CH-5001 Aarau, Switzerland (happy.mueller@unibas.ch).

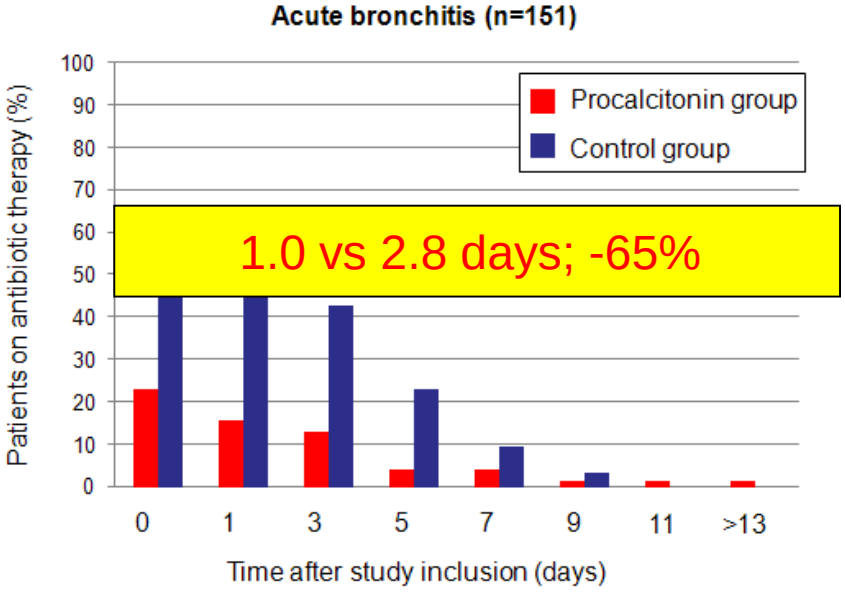
Marked Reduction in Antibiotic Use





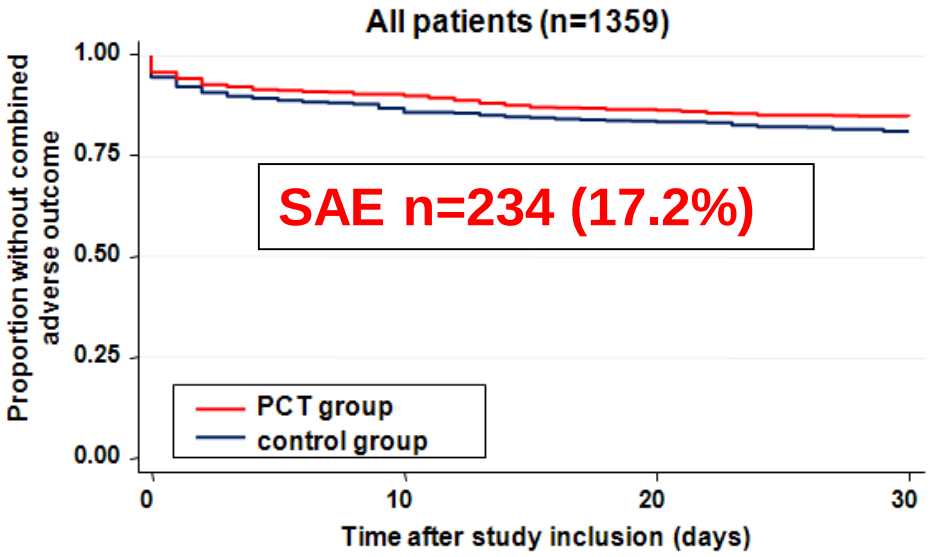
30% less antibiotic-related side effects !
(19.8% vs. 28.1%; p<0.001)

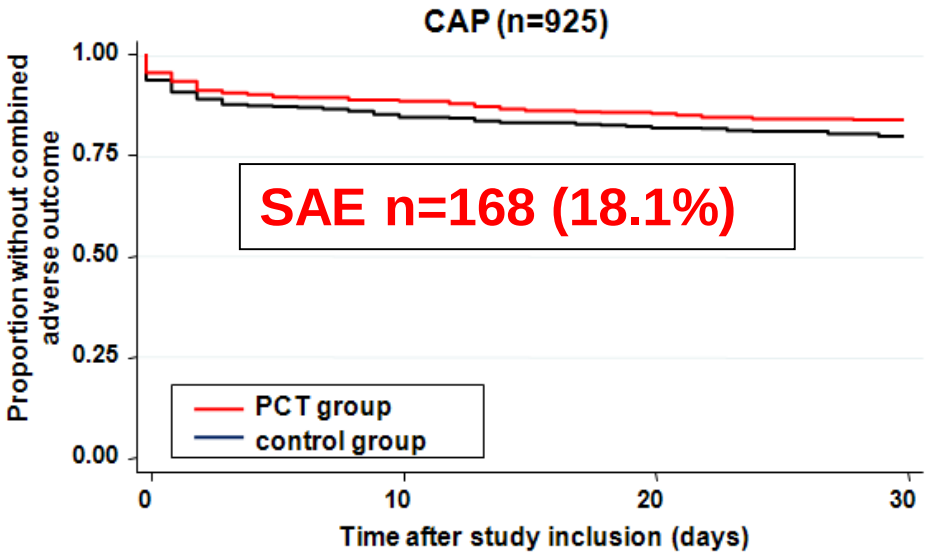


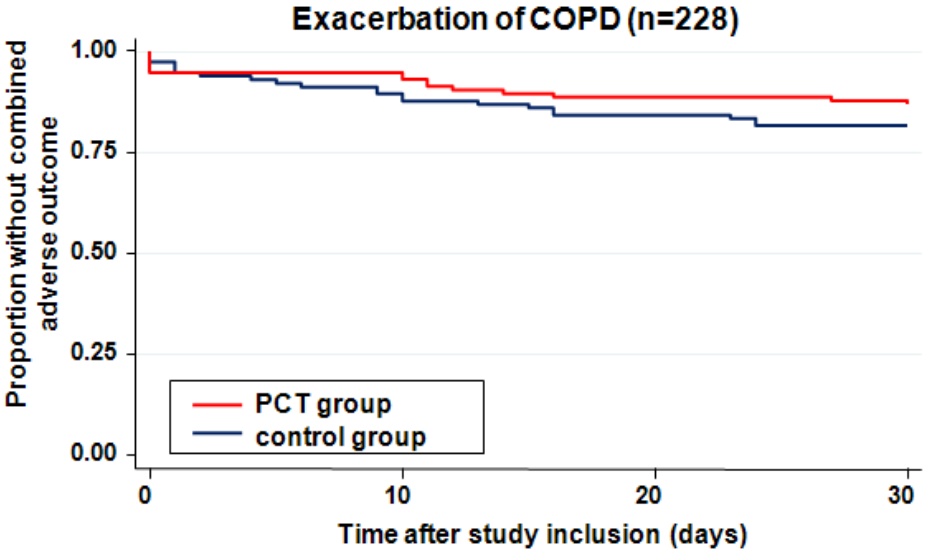


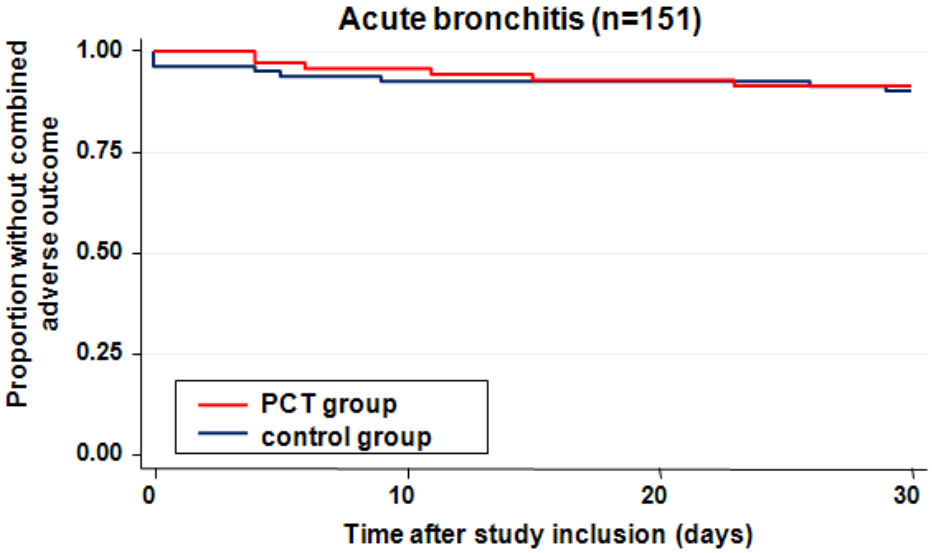
Schütz P et al. JAMA 2009

Safety of PCT guided antibiotic stewardship









Schütz P, ProHOSP, n=1359, JAMA 2009

Procalcitonin to Reduce Antibiotic Exposure in the Medical ICU - The ProRata-Trial

Demonstrate that a strategy including PCT kinetics in the management of the infection in the ICU :

1. Leads to a increase of AB free days during the 28 days
2. Without any impact on mortality at day 28 and day 60

Boudama L, et al. Lancet 2010;375:463-475

Guidelines for initiating antibiotics according to PCT value.
Except any situation requiring immediate therapy ...

PCT ...			
< 0.25 ng/mL	0.25 - 0.5 ng/mL	0.5 ng/mL < 1ng/mL	>= 1 ng/mL
Antibiotics strongly discouraged	Antibiotics discouraged	Antibiotics encouraged	Antibiotics strongly encouraged

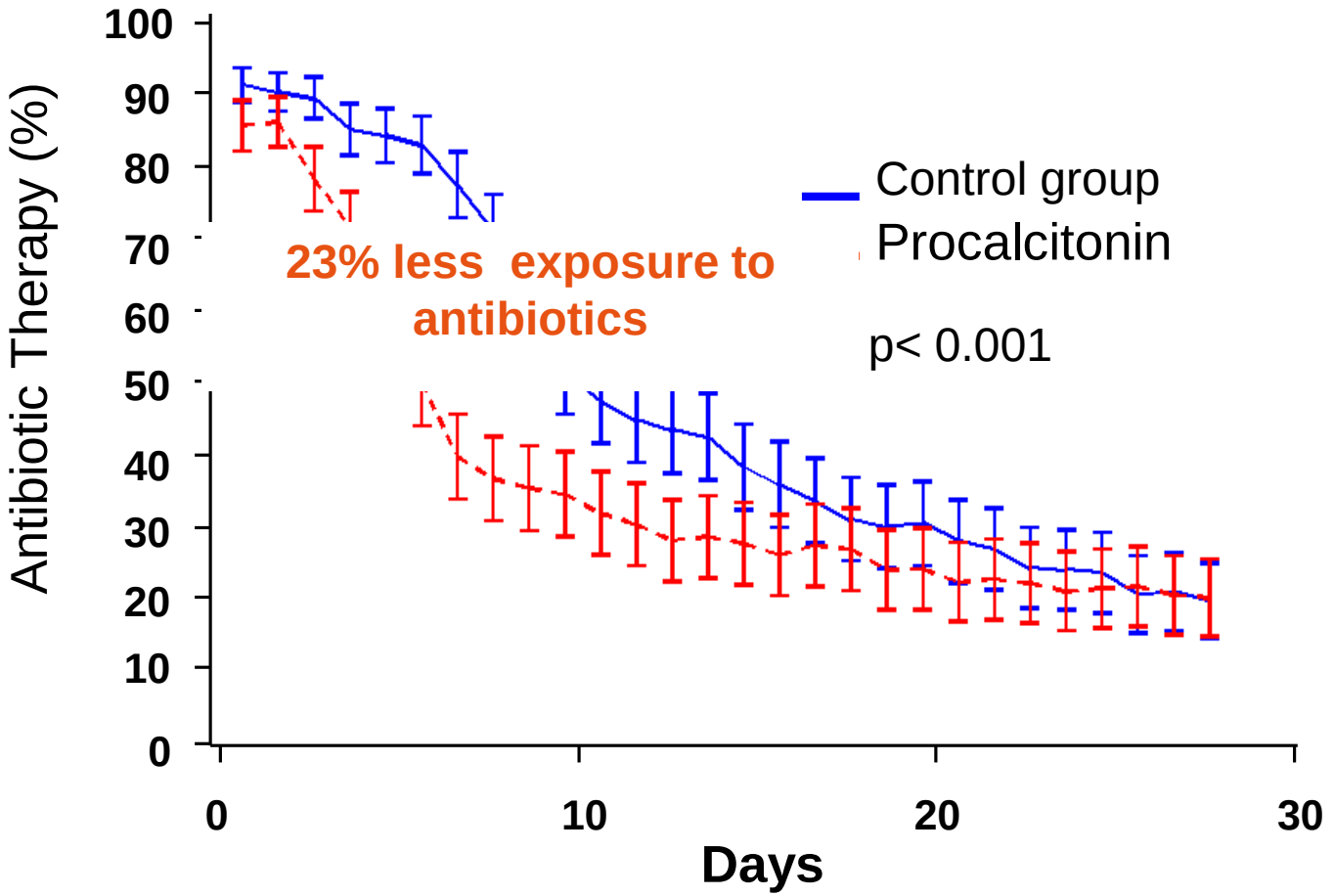
---

Guidelines for stopping, continuing or changing antibiotics according to daily measured PCT value.

PCT ...			
< 0.25 ng/mL	Decline more than 80% or 80% of peak (maximum) value or ≥ 0.25 to <0.5 ng/mL	Decline of PCT less than 80% of peak value and PCT ≥ 0.5 ng/mL	Increase of PCT above previous and PCT ≥ 0.5 ng/mL
Stopping antibiotics strongly discouraged	Stopping antibiotics encouraged	Continuing antibiotics encouraged	Changing antibiotics strongly encouraged

Boudama L, et al. Lancet 2010;375:463-475

Exposure to antibiotics within 28 days



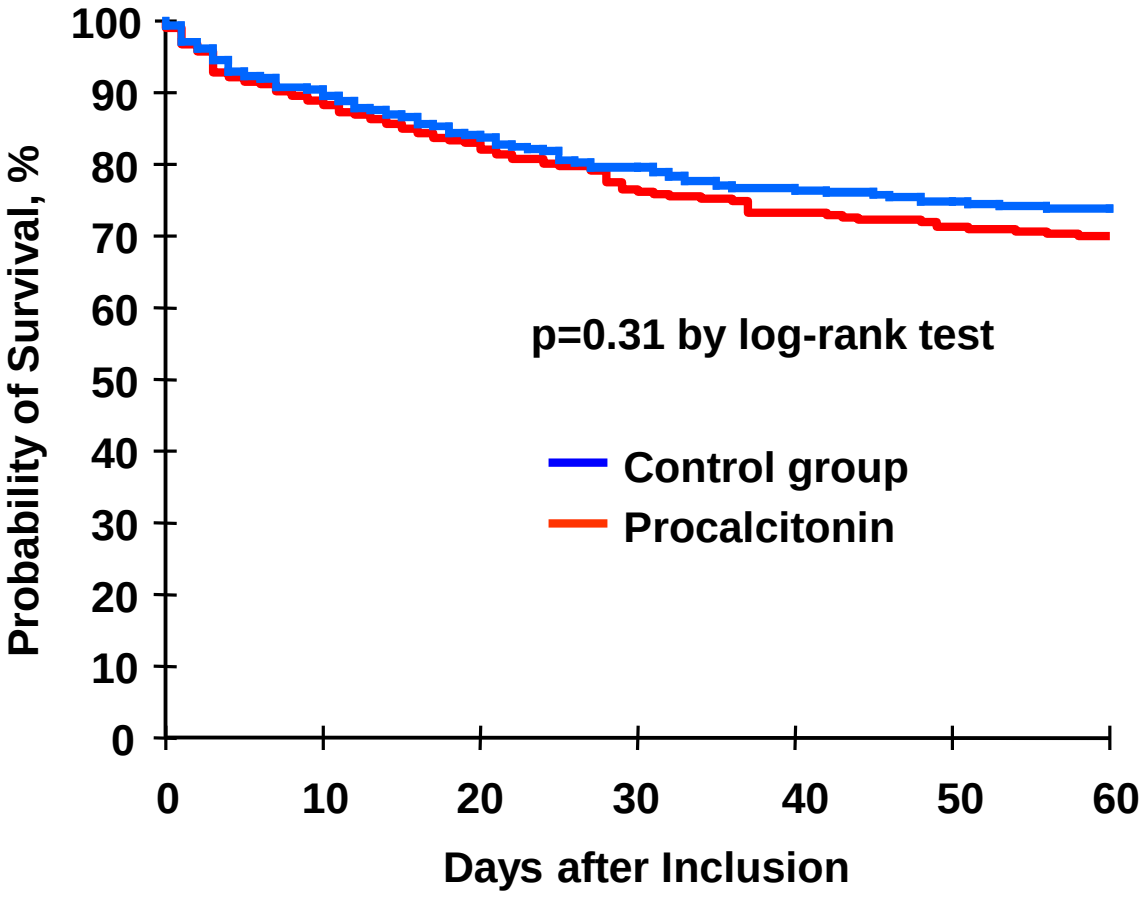
Boudama L, et al. Lancet 2010;375:463-475

Duration of treatment

	PCT	Controls	Δ (95% CI)
ALL	6.1±0	9.9±7.1	–3.8 (4.8–2.7)
CAP	5.5±4.0	10.5±6.4	–5.0 (6.6–3.4)
VAP	7.3±5.3	9.4±5.7	–2.1 (4.0–0.3)
Abdominal Infections	8.1±7.7	10.8±6.7	–2.7 (7.7-2.4)
Urinary Tract Infections	7.4±6.3	14.5±9.3	–7.1 (11.9–2.2)
Blood Cultures +	9.8±7.7	12.8±8.1	–3.0 (6.0-0.1)

Boudama L, et al. Lancet 2010;375:463-475

Patients alive at day 28 and day 60



Boudama L, et al. Lancet 2010;375:463-475

Did clinicians strictly follow the Algorithm?

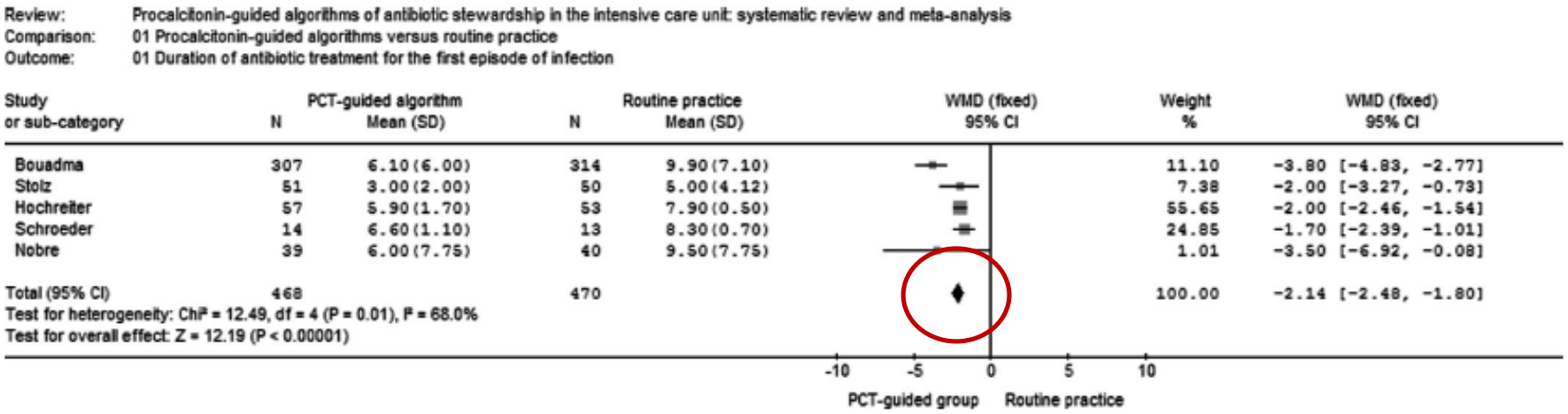
Guidelines were not followed in 219 episodes (53%)

- 65 patients did receive ABX despite PCT< 0,5
- 4 patients did not receive ABX despite PCT> 0,5
- In 39 patients ABX were discontinued despite PCT> 0,5
- In 79 patients ABX were discontinued despite PCT < 0,5

PCT aced as a guide, not as a rule

Procalcitonin-guided algorithms of antibiotic therapy in the intensive care unit: A systematic review and meta-analysis of randomized controlled trials

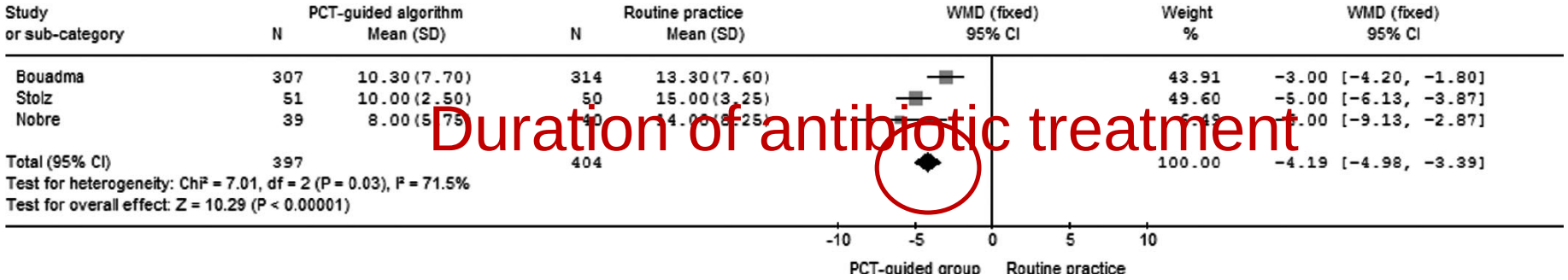
Petros Kopterides, MD; Ilias I. Siempos, MD; Iraklis Tsangaris, MD; Argirios Tsantes, MD; Apostolos Armaganidis, MD



Duration of antibiotic treatment for the first episode of infection

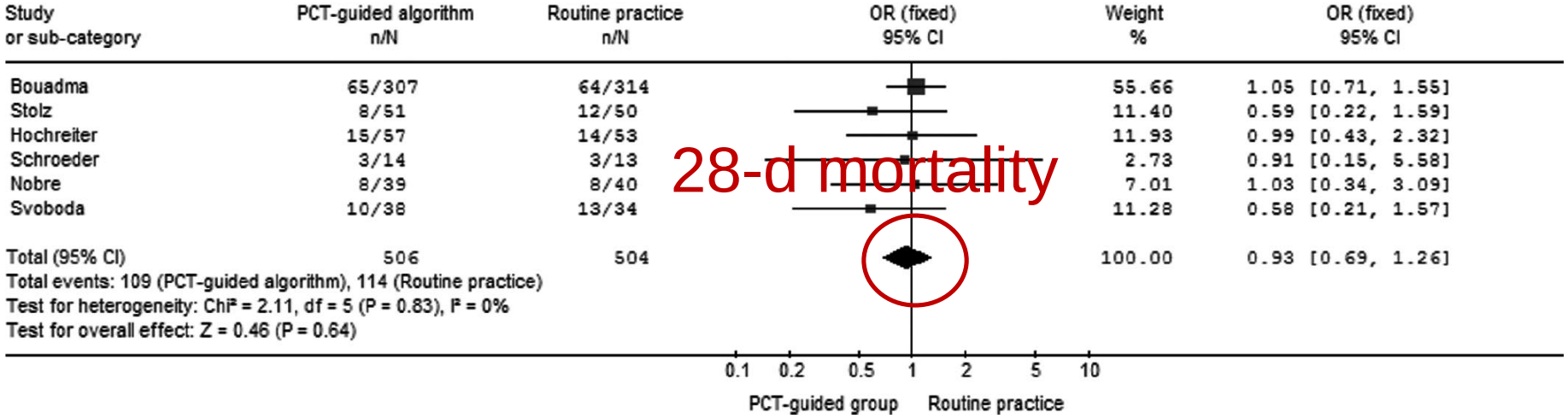
CCM 2010;38:2229-2241

Review: Procalcitonin-guided algorithms of antibiotic stewardship in the intensive care unit: systematic review and meta-analysis
Comparison: 01 Procalcitonin-guided algorithms versus routine practice
Outcome: 02 Total duration of antibiotic treatment



Duration of antibiotic treatment

Review: Procalcitonin-guided algorithms of antibiotic stewardship in the intensive care unit: systematic review and meta-analysis
Comparison: 01 Procalcitonin-guided algorithms versus routine practice
Outcome: 04 28-day mortality



28-d mortality

Kopterides, Siempos, Tsangaris, et al. CCM 2010;38:2229-2241

- We also found that the rates of relapsed/persistent infection did not differ between the comparator groups.
- This is comforting and adds robustness to the statement that PCT-based schemes seem to be safe in the ICU setting, although it should be underscored that only three studies reported on this outcome using different definitions and using ill-defined data collection strategies

Based on these studies, respiratory infection guidelines state that

- "… biomarkers can guide treatment duration by the application of predefined stopping rules for antibiotics. It has been shown that such rules work even in most severe cases, including pneumonia with septic shock …"

Woodhead M, Blasi F, Ewig S, Garau J, Huchon M, Leven M, Ortqvist A, Schaberg T, Torres A, Read R, et al. Guidelines for the management of adult lower respiratory tract infections. Clin Microbiol Infect. 2011;17 Suppl 6:E1–E59.

Procalcitonin levels to guide antibiotic therapy in adults with non-microbiologically proven apparent severe sepsis: a randomised controlled trial

Djillali Annane,[1] Virginie Maxime,[1] Jean Pierre Faller,[2] Chaouki Mezher,[3] Christophe Clec'h,[4] Patricia Martel,[5] Hélène Gonzales,[6] Marc Feissel,[2] Yves Cohen,[4] Gilles Capellier,[7] Miloud Gharbi,[1] Olivier Nardi[1]

- In intensive care unit patients with the phenotype of severe sepsis or septic shock and without an overt source of infection or a known pathogen, the current study was unable to confirm that a procalcitonin-based algorithm may influence antibiotic exposure.

BMJ Open 2013;**3**:e002186.

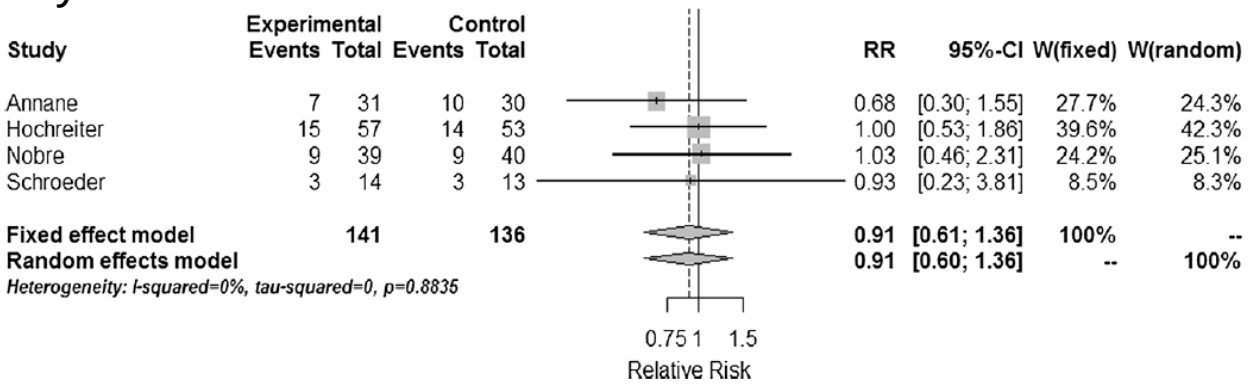
Regimen in the PCT group	Regimen in the control group
Medical patients:	Antibiotic treatment at the discretion of the patient's physician
PCT <0.25 ng/mL: antibiotics not initiated or stopped	
PCT ≥ 0.25 and < 0.5 ng/mL: Antibiotics strongly discouraged	
PCT ≥0.5 and <5 ng/mL: antibiotics recommended	
PCT ≥5 ng/mL: antibiotics strongly recommended	
Surgical patients:	
PCT <4 ng/mL: antibiotics not initiated or stopped	
PCT ≥4 and <9 ng/mL: antibiotics recommended	
PCT ≥9 ng/mL: antibiotics strongly recommended	

BMJ Open 2013;**3**:e002186.

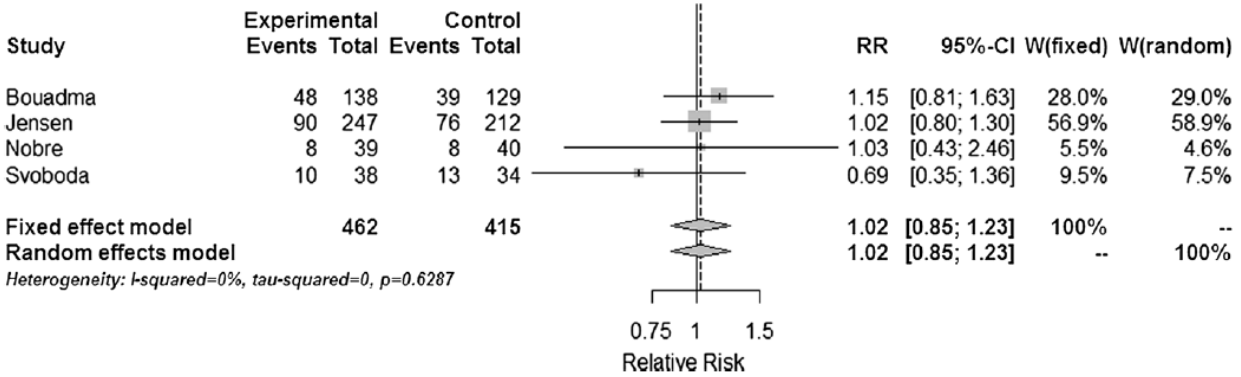
Procalcitonin-guided therapy in intensive care unit patients with severe sepsis and septic shock – a systematic review and meta-analysis

Anna Prkno[1,2], Christina Wacker[1,2], Frank M Brunkhorst[2,3†] and Peter Schlattmann[1,2*†]

Hospital mortality



28-d mortality

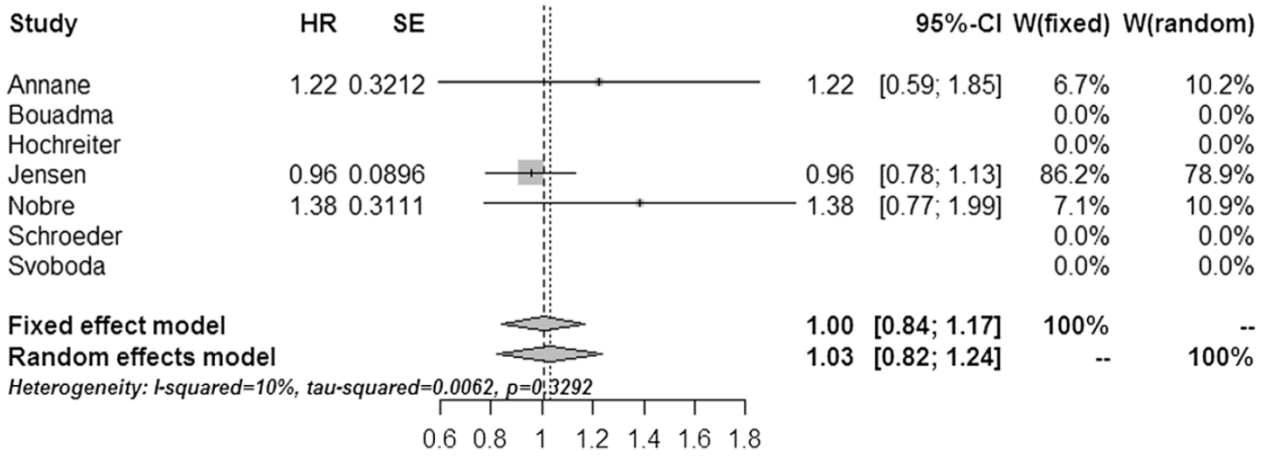


Critical Care 2013, **17**:R291

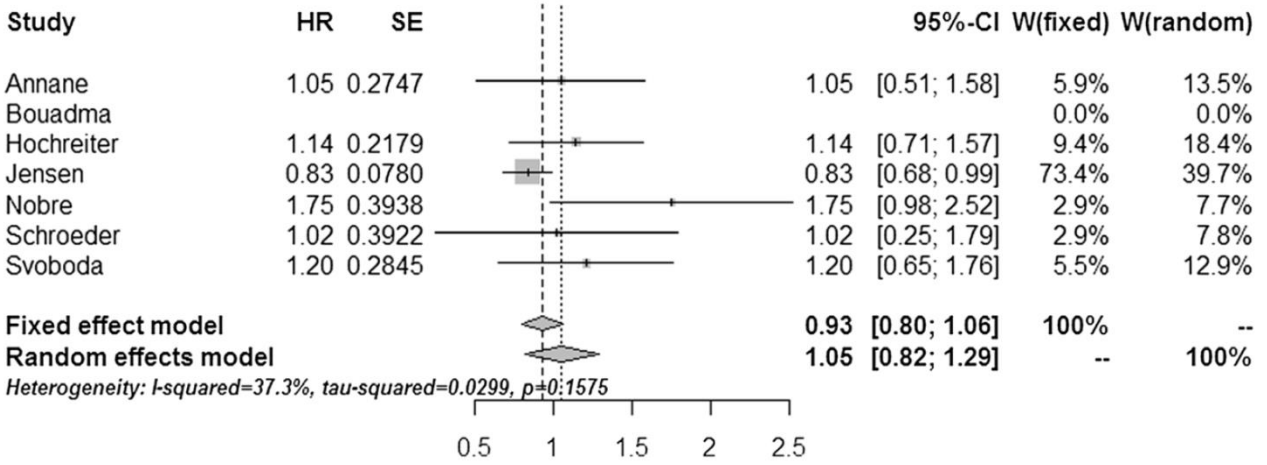
Procalcitonin-guided therapy in intensive care unit patients with severe sepsis and septic shock – a systematic review and meta-analysis

Anna Prkno[1,2], Christina Wacker[1,2], Frank M Brunkhorst[2,3†] and Peter Schlattmann[1,2*†]

Hospital LOS



ICU LOS



Critical Care 2013, **17**:R291

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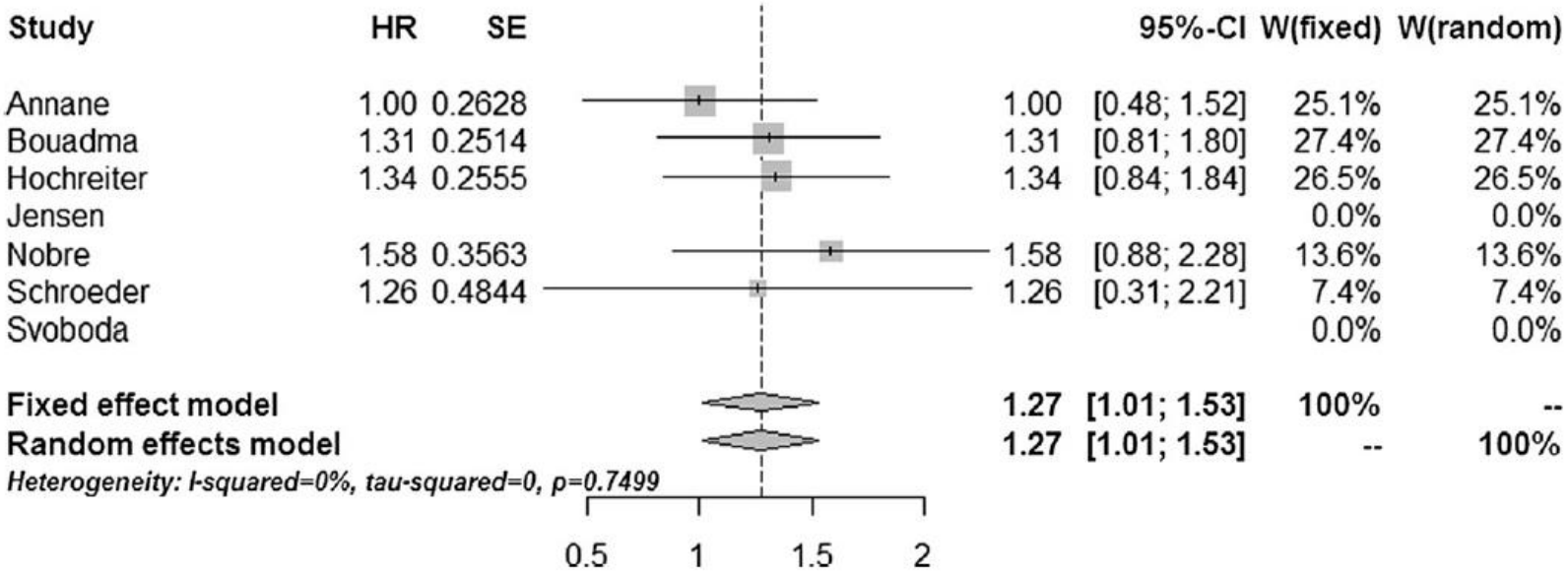
Anna Prkno[1,2], Christina Wacker[1,2], Frank M Brunkhorst[2,3†] and Peter Schlattmann[1,2*†]

Duration of antimicrobial therapy

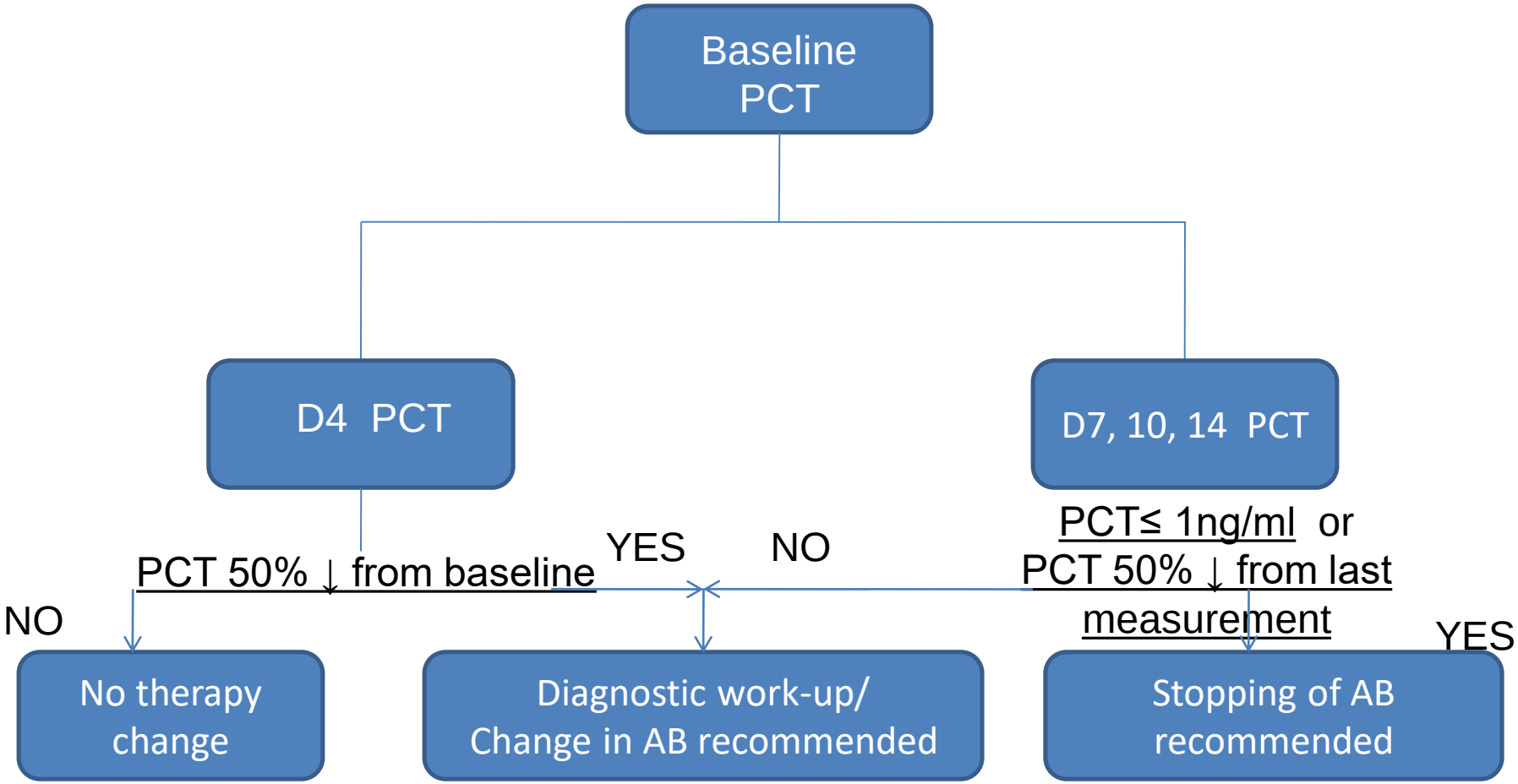


Critical Care 2013, **17**:R291

The SISPCT trial

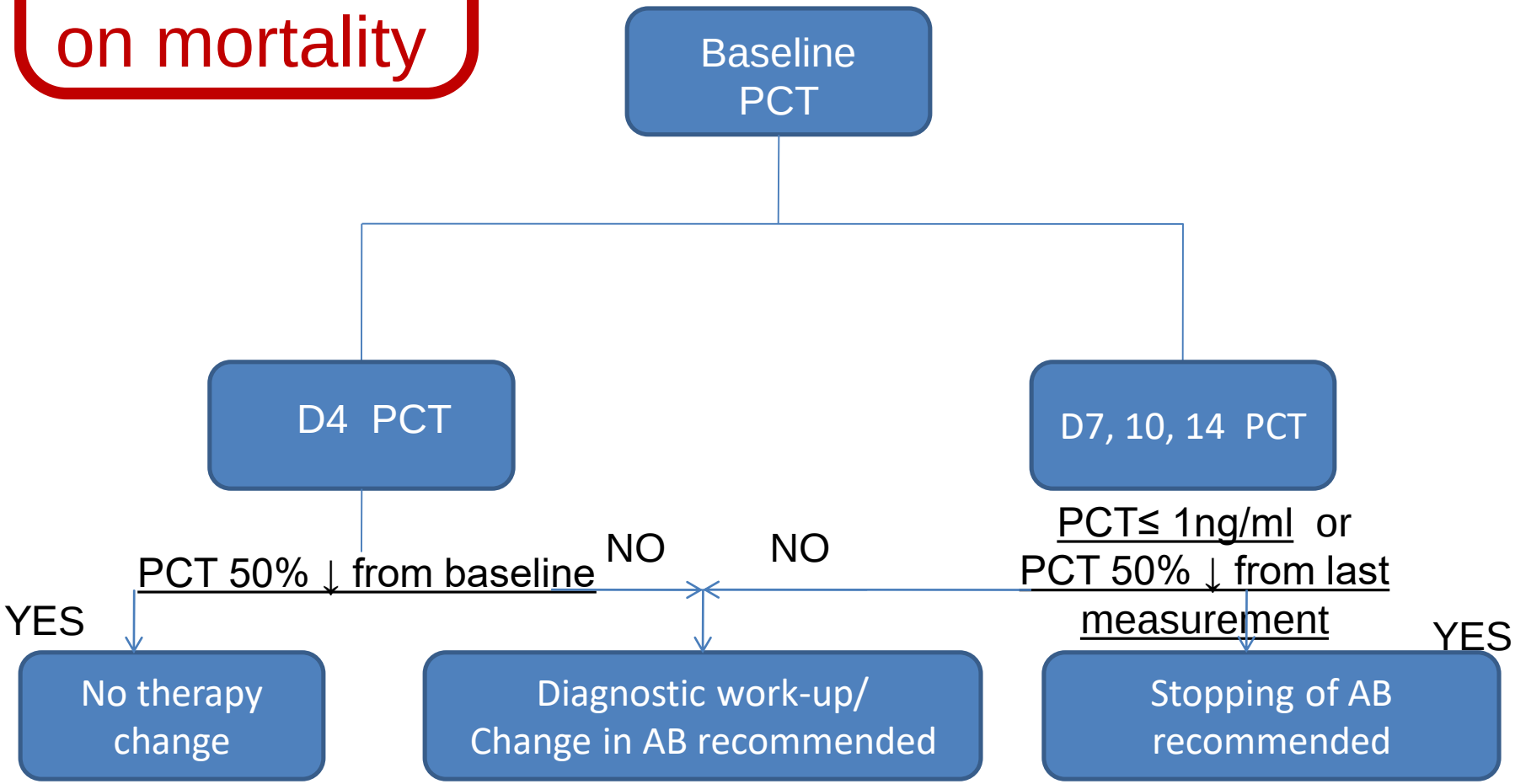
- German prospective, randomized, multicenter, bi-factorial, double-blind (selenium), open (PCT), 4-arm trial
- Presented by Prof. Reinhart at 27th annual ESICM congress (9/14)
- Hypothesis: PCT guided (D0, D4, D7, D10) sepsis therapy resulting in reduction of 28-d all cause mortality?

PCT algorithm



>1000pts
NO EFFECT
on mortality

PCT algorithm



No difference

- For 90-d mortality
- ICU/hospital LOS
- Clinical and microbial cure of infection

- According to

Site of infection

Severity

Organ failures

Sepsis stage

Medical or surgical pts

Significant difference in duration of antimicrobial therapy

PCT algorithm not followed

- D4: 25%

  fever 37%

  microbiological assesment 37%

  WBC 31%

- D10: 54%

  microbiological assesment 37%

  WBC 36%

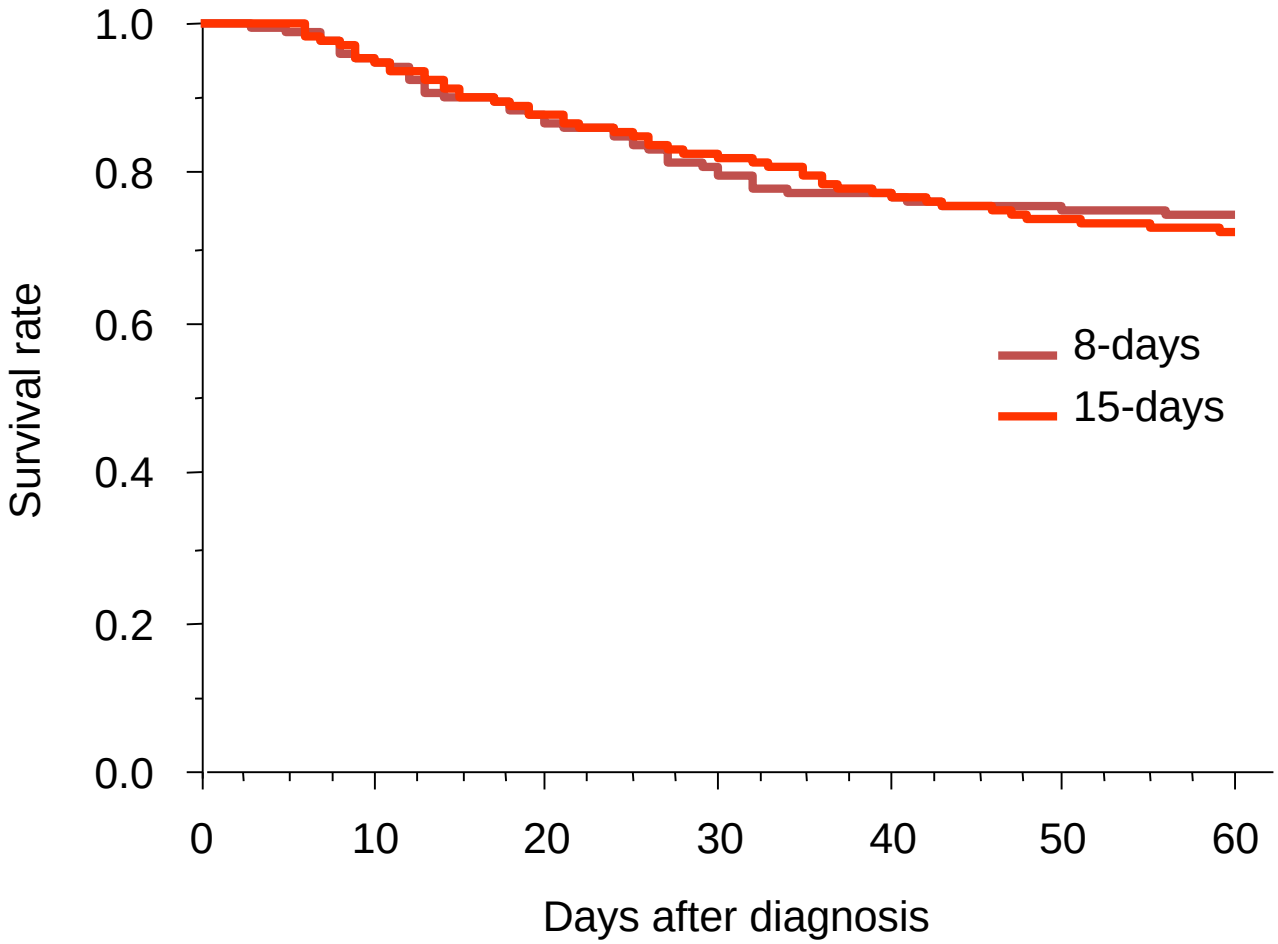
Safe extrapolation to the clinical decision-making process?

- High rate of patient exclusion (reaching >80% in the Svoboda, or >90% in Annane)
- High rate of algorithm overruling (PRORATA > 50%)
- Disregard the impact of renal failure, as well as renal replacement therapy on PCT levels
- Different algorithms
- Heterogeneity of duration of antibiotic therapy in the controls

Antibiotic duration and PCT protocol

Author	Infection	PCT (days)	Controls (days)
Crist-Crain	LRTI	10,9	12,8
Crist- Crain	CAP	5,8	12,9
Briel	LRTI	6,2	7,1
Schuetz	LRTI	5	9
Kristoffersen	LRTI	5,1	6,8
Nobre	SS/CS	6	10
Hochreiter	SS	5,9	7,9
Bouadma	ICU infections	6,1	9,9
Stolz	VAP	10	15

8 vs 15 days antibiotic therapy in VAP



Chastre P et al. JAMA 2003; 290: 2588-98

Procalcitonin versus C-reactive protein for guiding antibiotic therapy in sepsis: a randomized trial.

- Brazilian, two center study, 94 pts
- Both groups at least 7d of antibiotic in pts with SOFA>10 and/or bacteremia at inclusion, and pts with evident resolution stopped antibiotics after 7 days, despite biomarkers levels.
- Overruling 13%
- PCT 7d vs CRP 6d

Oliveira, CCM, 2013

	Type of infection	New studies since 2010?	Study design	PCT cut-off (µg/L)	Benefit of PCT use?	Main conclusions	Selected references since 2012
Pulmonary	AECOPD	yes	RCT (N = 120), meta-analysis	<0.25	++	PCT reduces initiation of antibiotic treatment in the ED without adverse outcomes	[7, 12]
	Asthma	yes	RCT (N = 216)	<0.1–0.25	++	PCT reduces initiation of antibiotic treatment in the ED without adverse outcomes	[89]
	Bronchitis	yes (Registry)	RCT, real-life (Registry)	<0.1–0.25	++	PCT reduces initiation of antibiotic treatment in the ED without adverse outcomes	[42]
	Community-acquired pneumonia	yes	RCT, meta-analysis (N = 4467) real-life (Registry)	<0.1–0.25; 80–90% decrease	+++	PCT shortens length of antibiotic therapy in the ED and hospital ward without adverse outcomes	[7]
	Pulmonary fibrosis	yes	RCT (N = 78)	<0.25	++	PCT reduces initiation of antibiotic treatment in the ED without adverse outcomes	[15]
	Upper respiratory tract infections	no	RCT (N = 458, 702)	<0.1–0.25	+++	PCT reduces initiation of antibiotic treatment in primary care without adverse outcomes (non-inferiority)	[90, 91]

	Type of infection	New studies since 2010?	Study design	PCT cut-off (μg/L)	Benefit of PCT use?	Main conclusions	Selected references since 2012
Abdominal	Abdominal infections with peritonitis	yes	Observational	<0.5; 80% decrease	++	PCT-guided therapy was associated with lower antibiotic exposure with no difference in mortality	[66]
	Appendicitis	yes	Observational, meta-analysis	NR	+	PCT is a marker of complicated appendicitis, low value for diagnosing appendicitis	[92]
	Pancreatitis	yes	RCT (N = 71)	<0.5	++	PCT reduces antibiotic exposure compared to prophylactic antibiotic treatment without adverse outcomes	[65]
	Urinary tract infections	yes	RCT (N = 125)	<0.25	++	PCT reduces antibiotic exposure without adverse effects	[47]
Blood	Blood stream infection	yes	Observational	<0.25–1.47	++	PCT levels correlate with risk for positive blood cultures	[19, 27]
	Neutropenia	yes	RCT (N = 62)	NR	–	PCT is not useful to manage antibiotic therapy, but PCT was a marker of bacteremia	[93]
	Severe sepsis/ shock	yes	RCT (N = 1575)	<0.5; 80% decrease	+++	PCT reduces antibiotic exposure and 3 month mortality in the ICU	[30]

	Type of infection	New studies since 2010?	Study design	PCT cut-off (μg/L)	Benefit of PCT use?	Main conclusions	Selected references since 2012
Postoperative	Postoperative abdominal infection	yes	Observational, meta-analysis	NR	+	Low PCT post-surgical ensure safe discharge, PCT is similar to CRP	[58, 59]
	Postoperative infections	yes	RCTs, Observational	<0.5–2.0	++	Low PCT suggests absence of perioperative infection and enables early discharge	
Other	Arthritis	yes	Observational	<0.5	+	PCT identifies infection in patients with rheumatoid arthritis	[94]
	Erysipelas	yes	Observational	<0.1	+	PCT differentiates erysipelas from DVT	[81]
	Meningitis	no	RCT, meta-analysis (N = 2058)	<0.5	+++	PCT reduces AB treatment during viral outbreak; serum PCT with CSF lactate reliably identifies bacterial meningitis	[72, 74]

		Patients			Effect on antibiotic exposure of PCT vs. control	Mortality
		PCT	Control	Type of infection		PCT vs. control
Nobre *et al.* [14]	2008	31	37	Severe sepsis/ septic shock	4-day reduction in median duration of antibiotic therapy	No difference in mortality
Boudama *et al.* [35] (PRORATA)	2010	307	314	Suspected infection/sepsis	23% relative reduction in days of antibiotic exposure. Mean 11.6 vs. 14.3 days of antibiotic treatment ($P < 0.0001$)	No difference in mortality (21.2 vs. 20.4%)
Stolz *et al.* (ProVAP) [36]	2009	51	50	VAP	27% reduction in the overall antibiotic treatment ($P = 0.038$)	No difference in 28-day mortality
de Jong *et al.* (SAPS) [38▪▪]	2016	761	785	Proven or suspected infection	Median antibiotic consumption of 7.5 vs. 9.3 daily defined doses ($P < 0.0001$) and median treatment duration of 5 vs. 7 days, in favor of PCT group ($P < 0.0001$)	28-day mortality difference: 20 vs. 25% ($P = 0.0122$). 1-year mortality: 36 vs. 43% ($P = 0.0188$)
Shehabi *et al.* (ProGUARD) [39]	2014	196	198	Suspected sepsis	Median antibiotic therapy days: 9 vs. 11 in favor of PCT group, but nonsignificant trend ($P = 0.58$)	No difference in hospital and 90-day mortality between groups
Bloos *et al.* (SISPCT) [40]	2016	552	553	Severe sepsis/ septic shock	4.5% reduction in antibiotic of antimicrobial exposure in the PCT-guided group (823 vs. 862 days, $P = 0.02$)	No difference in 28-day mortality ($P = 0.34$)

Sager et al. BMC Medicine (2017) 15:15
DOI 10.1186/s12916-017-0795-7

BMC Medicine

MINIREVIEW Open Access

Procalcitonin-guided diagnosis and antibiotic stewardship revisited

Ramon Sager[1,2], Alexander Kutz[1,2], Beat Mueller[1,2] and Philipp Schuetz[1,2*]

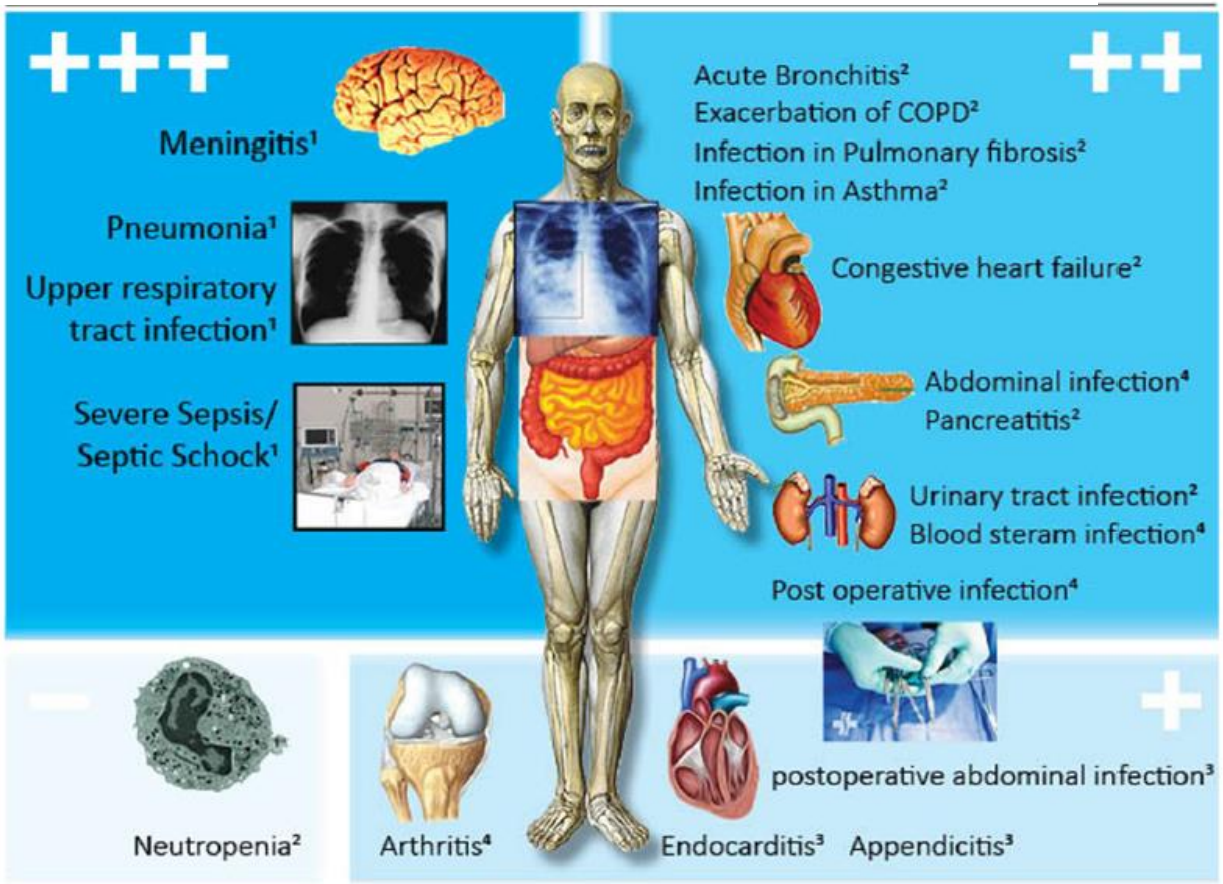


Fig. 1 Summary of evidence regarding procalcitonin (PCT) for diagnosis and antibiotic stewardship in organ-related infections. While for some infections, intervention studies have investigated benefit and harm of using PCT for diagnosis and antibiotic stewardship (*left side*), for other infections only results from diagnostic (observation) studies are available (*right side*). +: moderate evidence in favor of PCT; ++: good evidence in favor of PCT; +++: strong evidence in favor of PCT; – no evidence in favor of PCT

Sager et al. BMC Medicine (2017) 15:15
DOI 10.1186/s12916-017-0795-7

BMC Medicine

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Procalcitonin-guided diagnosis and antibiotic stewardship revisited

Ramon Sager[1,2], Alexander Kutz[1,2], Beat Mueller[1,2] and Philipp Schuetz[1,2*]

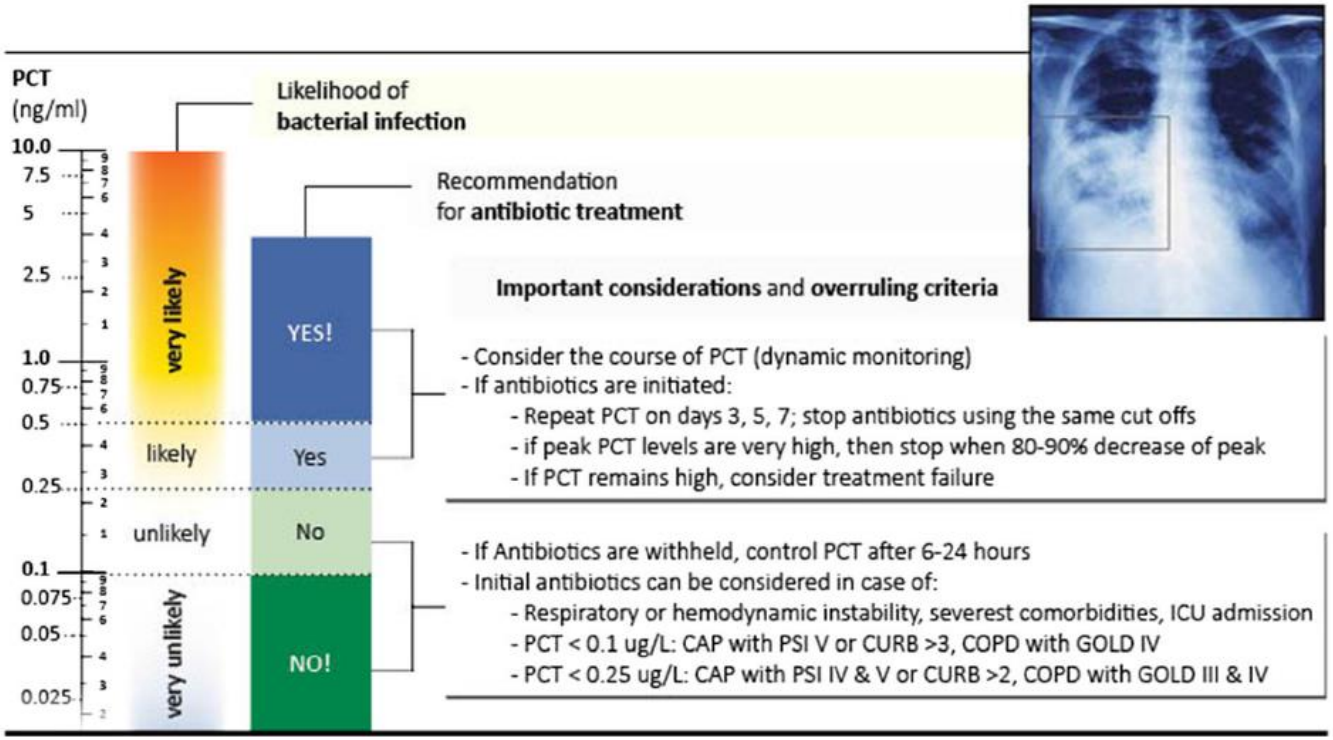

Fig. 2 Procalcitonin (PCT) algorithm in patients with respiratory tract infections in the emergency department. The clinical algorithm for antibiotic stewardship in patients with respiratory tract infections in the emergency department encourages (>0.5 ng/ml or >0.25 ng/ml) or discourages (<0.1 ng/ml or <0.25 ng/ml) initiation or continuation of antibiotic therapy more or less based on specific PCT cut-off ranges. Abbreviations: *AB* antibiotic, *LRTI* lower respiratory tract infection, *ICU* intensive care unit, *PSI* pneumonia severity score

Open questions

- May PCT guided algorithms also have an impact on the decision to initiate antibiotics, especially if applied in combination with promising molecular diagnosis tests ?
- Are different cutoffs (infection- and/or microorganism-specific) more likely to improve the efficacy of the PCT strategy without compromising its safety?

Open questions

- Is an absolute value of PCT or a percentage decrease the end point of choice before making the decision to discontinue antibiotics?
- How do the PCT algorithms perform in comparison with protocols?

Open questions

- What is the role of PCT monitoring in the management of patients who are either immunosuppressed or harboring multidrug-resistant bacteria or staying in the ICU for prolonged periods?
- What is the cost of the strategy?

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

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

Rationale. This suggestion is predicated on the preponderance of the published literature relating to the use of procalcitonin as a tool to discontinue unnecessary antimicrobials (58, 83). However, clinical experience with this strategy is limited and the potential for harm remains a concern (83). No evidence demonstrates that this practice reduces the prevalence of antimicrobial resistance or the risk of antibiotic-related diarrhea from *C. difficile*. One recent study failed to show any benefit of daily procalcitonin measurement in early antibiotic therapy or survival (84).

Antimicrobial Therapy

Antibiotic Stewardship

- We recommend that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted.
  - (BPS)
- We suggest that an antimicrobial treatment duration of 7-10 days is adequate for most serious infections associated with sepsis and septic shock.
  - (Weak recommendation; low quality of evidence)
- We recommend daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock.
  - (BPS)
- We suggest that measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients.
  - (Weak recommendation; low quality of evidence)

Table 1. Proposed biomarkers for follow-up and antibiotic shortening in HAP/VAP

Procalcitonin (PCT)
As a prognostic marker: serum PCT measured at days 1, 3 and 7 has shown to be an independent predictor of unfavorable outcome in VAP in one study. Several studies found a strong correlation between PCT levels and survival (as differential levels between days 0 and 4; measured at day 3; or in combination with clinical composite scores).
As a marker for discontinuation of antibiotic therapy: several RCTs demonstrated the usefulness of PCT for guiding antibiotic discontinuation. Two of them, showed a difference in mortality.
C-reactive protein (CRP)
One study found a strong correlation between CRP levels and outcomes; and another showed it was a good surrogate of antibiotic adequacy and bacterial burden. On the other hand, two studies analyzing several biomarkers, found that CRP levels were not associated with survival.
Copeptin
In one study, copeptin showed to be an accurate predictor of survival at VAP onset, but it did not show a good correlation with this outcome during follow-up.
Midregional pro-atrial natriuretic peptide (MR-proANP)
Proved to be a good predictor of mortality when measured at VAP onset in one study, and when used in combination with clinical scores in another one.
Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1)
Only studied as a marker for diagnosis of HAP/VAP. No proven association with follow-up.

	Follow-up	Antibiotic duration
ERS 2017	Do not recommend routine biomarker determinations in addition to bedside clinical assessment (strong recommendation).	Do not recommend the routine measurement of biomarkers to reduce antibiotic duration when the anticipated duration is 7–8 days (strong recommendation). Measurement of serial PCT levels together with clinical assessment represents good practice in specific circumstances where short duration therapy may not be possible or should be individualized.
IDSA/ATS 2016	Do not refer to follow-up. (Recommend using clinical criteria alone, rather than biomarkers, to decide whether or not to initiate antibiotic therapy.)	Suggest using PCT levels plus clinical criteria to guide the discontinuation of antibiotic therapy, rather than clinical criteria alone (weak recommendation).
SSC 2016	Do not refer to biomarkers for follow-up.	Suggest that measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients (weak recommendation).
ALAT 2005	Do not consider the use of biomarkers. Refers only to clinical assessment.	

ALAT, Asociación Latinoamericana del Tórax; ESCMID; European Society for Clinical Microbiology and Infectious Diseases; ESICM European Society of Intensive Care Medicine; ERS, European Respiratory Society; PCT, procalcitonin.

Conclusion

- PCT-guided early cessation of antibiotic therapy is associated with a significant decrease in antibiotic days, without any change in overall mortality.
- PCT may be considered part of the antimicrobial stewardship programs aimed at limiting antibiotic therapy duration, while decelerating the development of antibiotic resistance.