Usefulness of Procalcitonin in the management of Infections in ICU

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Procalcitonin

- Peptide 116 AA
- Produced by parenchymal cells during « sepsis »:

  IL1, TNF, IL6 : stimulators

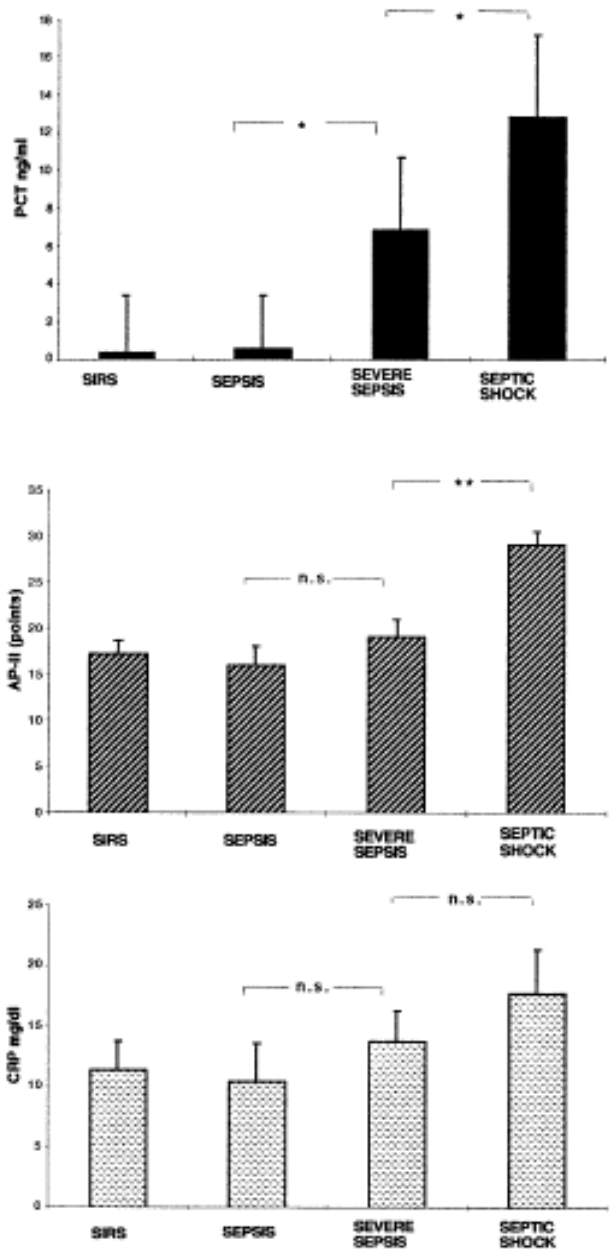
  Inf gamma: inhibitor
- Can differentiate bacterial meningitis from viral meningitis (Gendrel CID 1997)

Procalcitonin

- marker of the severity of infection?
- tool for tailoring the antibiotherapy?
- prognostical factor for the outcome?

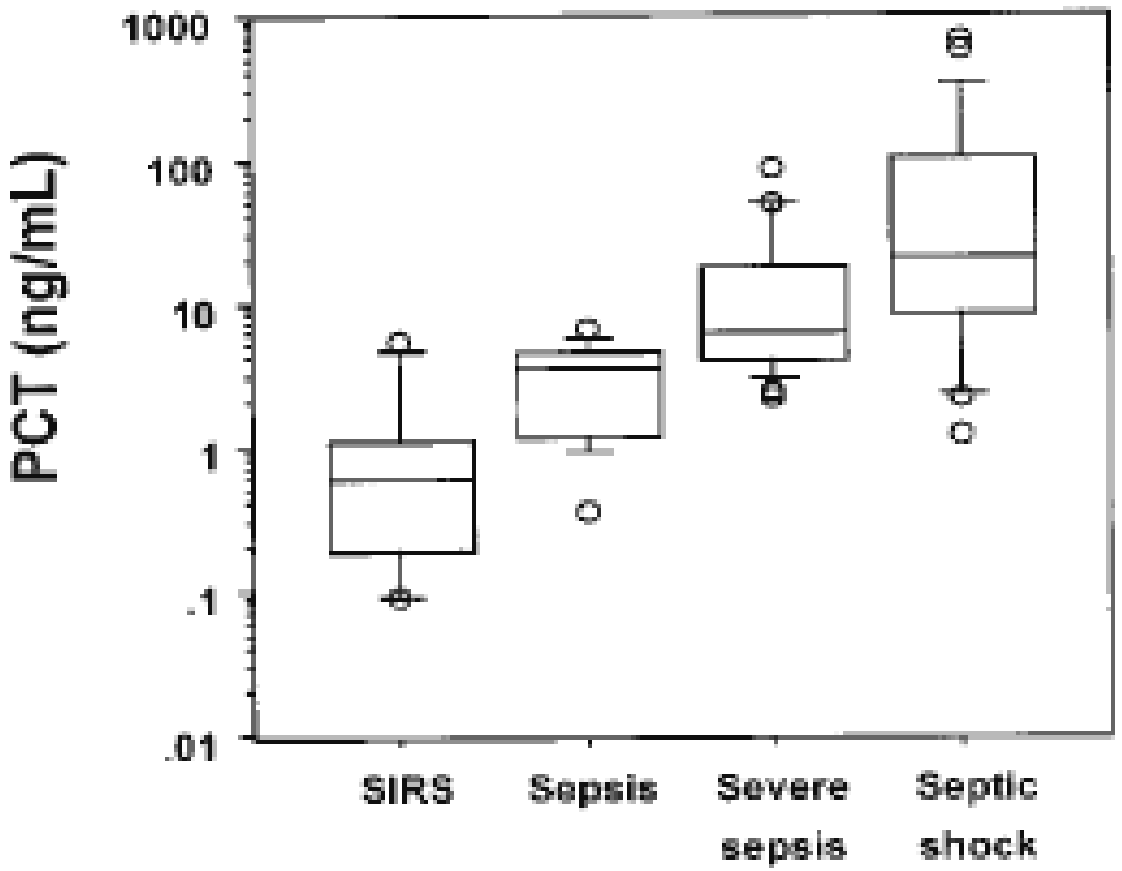
PCT as a marker of sepsis

- Brunkhorst et al ICM 2000 26: S148-152
  185 consecutive patients with suspicion of sepsis


PCT ng/ml
*
*
SIRS
SEPSIS
SEVERE SEPSIS
SEPTIC SHOCK
AP-II (points)
**
n.s.
SIRS
SEPSIS
SEVERE SEPSIS
SEPTIC SHOCK
CRP mg/dl
n.s.
n.s.
SIRS
SEPSIS
SEVERE SEPSIS
SEPTIC SHOCK

Harbarth et al AJRCCM 2001;164: 396-402

- 78 consecutive patients with suspicion of sepsis
- SIRS 18, Sepsis 14, Severe sepsis 21, Septic shock 25
- ability to differentiate between SIRS and septic patients: cut-off value of 1.1 ng/ml
- AUC = 0.92


PCT (ng/mL)
1000
100
10
1
.1
.01
SIRS
Sepsis
Severe sepsis
Septic shock

Meta-analysis (Tang et al) The Lancet 2007

- Distinction between « Sepsis » et « SIRS »
- 18 studies out of 672 abstracts
- « Procalcitonin cannot reliably differentiate sepsis from other non-infectious causes of SIRS » (se and sp = 71%)

PCT and non infectious states

- Trauma
- Surgery
- Cardiac arrest
- Hypothermia
- Acute coronary syndrome

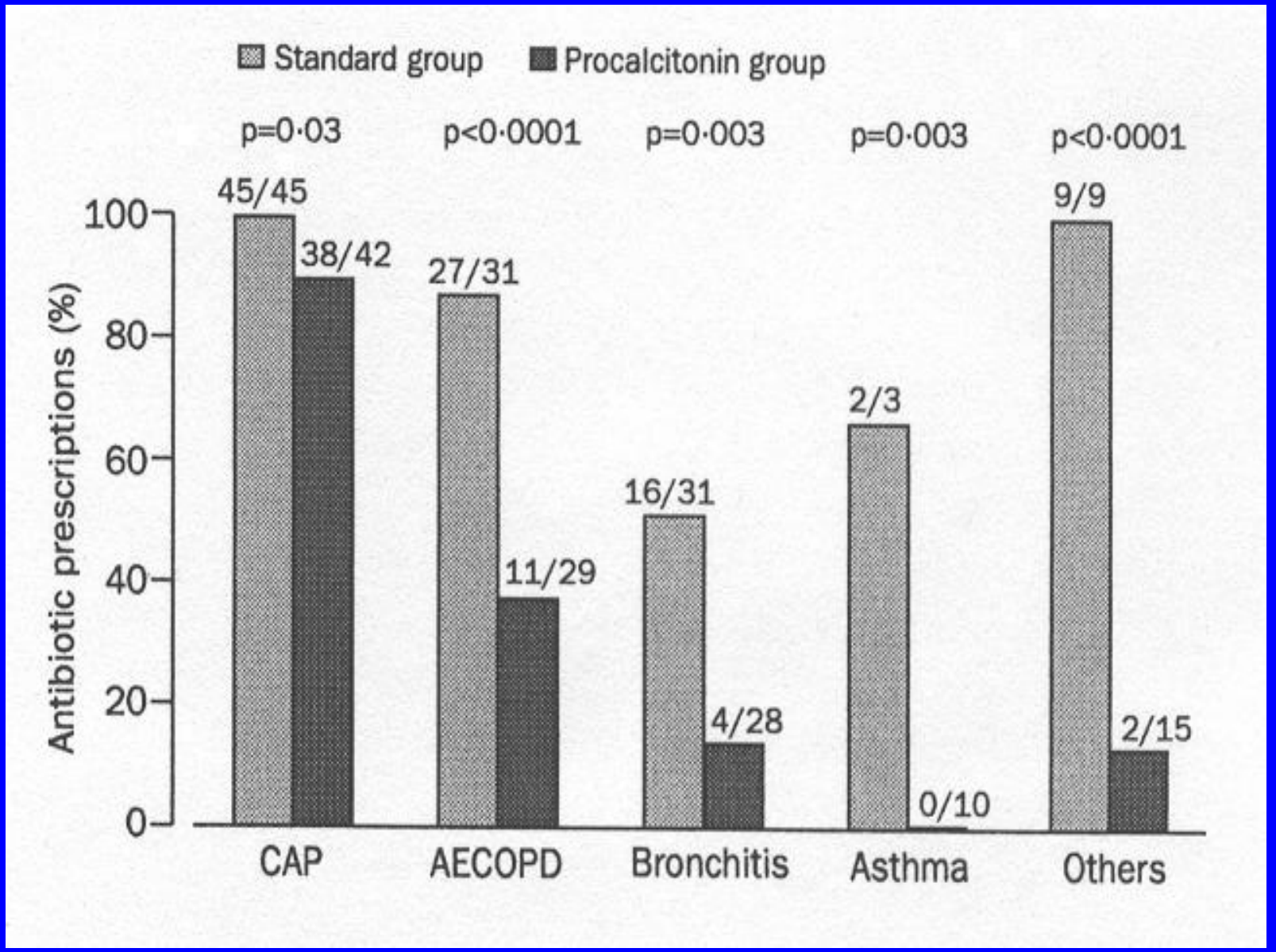
Decrease in antibiotic consumption

- Respiratory infections (out-of-hospital setting) Christ-Crain Lancet 2004
- Length of treatment in CAP
  Christ-Crain AJRCCM 2007
- COPD exacerbation
  Stolz Chest 2007

Christ-Crain et al, Lancet 2004

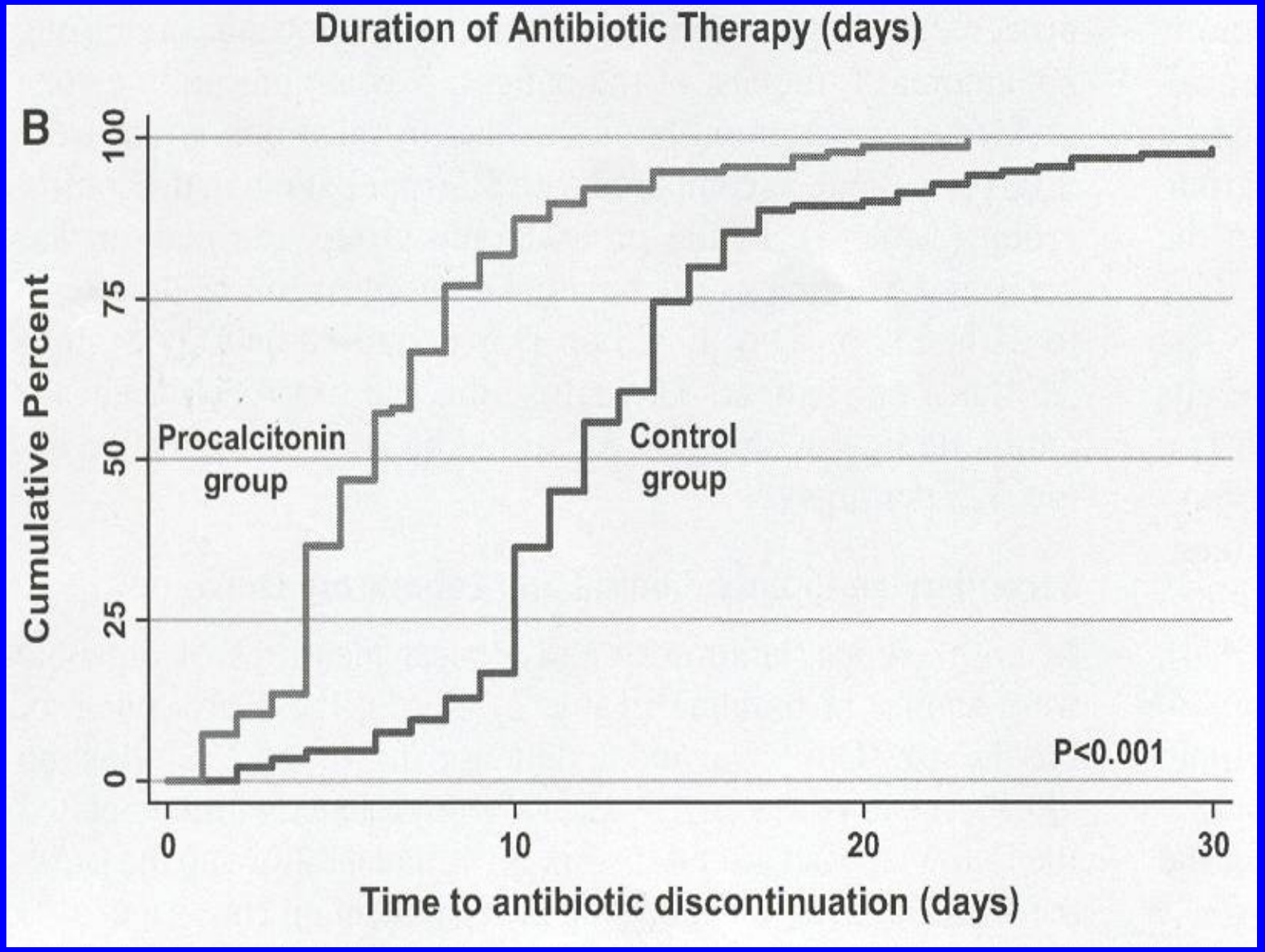
Procalcitonin

< 0.1ng/ml:	No antibiotic
< 0.25 ng/ml:	treatment discouraged
between 0.25 et 0.5ng/ml:	treatment recommended
> 0.5 ng/ml:	treatment mandatory


Standard group
Procalcitonin group
p=0·03
p<0·0001
p=0·003
p=0·003
p<0·0001
45/45
38/42
27/31
11/29
16/31
4/28
2/3
0/10
9/9
2/15
Antibiotic prescriptions (%)
100
80
60
40
20
0
CAP
AECOPD
Bronchitis
Asthma
Others

Length of treatment ?
Christ-Crain AJRRCM 2006

- Decision to stop treatment according to the same cut-off levels as for the beginning: on day 4, 6 and 8.


Duration of Antibiotic Therapy (days)
B
Cumulative Percent
100
75
50
25
0
Procalcitonin group
Control group
P<0.001
0
10
20
30
Time to antibiotic discontinuation (days)

How about ICU ?

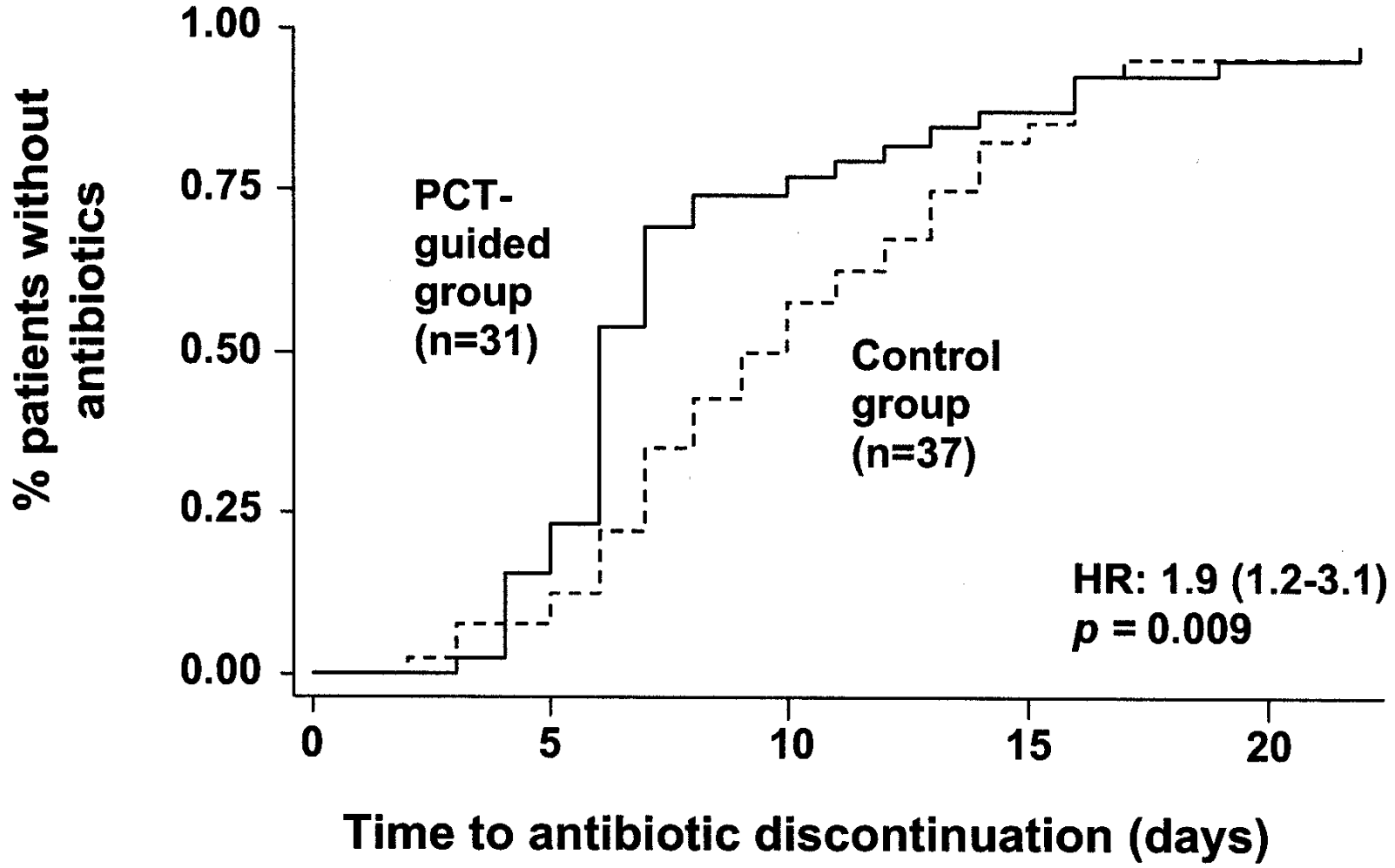
- Nobre AJRCCM 2008, 177: 498-505
  - 282 patients in severe sepsis
  - 203 excluded
  - 79 randomized
  - 68 analyzed: 31 PCT
    37 Ctrl

Exclusion criteria

- Infections caused by *P aeruginosa, A baumannii, Legionella, Pneumocystis*, BK
- Severe parasitic or viral infections
- Infections requiring prolonged treatment: endocarditis, deep abscesses
- Chronic infections
- Immunocompromised patients

Nobre et al 2008

- Daily measurement of PCT from D0 till D10
- At D5:consider stopping AB if
  PCT dropped more than 90%,
  PCT < 0,25 µg/l , baseline > 1
  PCT < 0,1 µg/l , baseline < 1 µg/l
- If blood culture was positive: at least 5 days of treatment


% patients without antibiotics
1.00
0.75
0.50
0.25
0.00
PCT-guided group (n=31)
Control group (n=37)
HR: 1.9 (1.2-3.1)
p = 0.009
0
5
10
15
20
Time to antibiotic discontinuation (days)

PCT and USI Prorata Study
Bouadma et al Lancet 2010

- All patients suspected to be infected on admission or during ICU stay (621 patients from 7 ICUs from 5 hospitals)
- PCT used to start the treatment
- PCT used to stop the treatment:
  when < 20% of the baseline or < 0.5 ng/ml

Procalcitonin levels

- If <0.25 µg/l: no antibiotics
- If 0.25 < X < 0.5 µg/l : treatment discouraged
- If 0.5 < X < 1µg/l: treatment suggested
- If > 1 µg/l: treatment highly encouraged

Types of patients

	PCT (307)	Control (314)
• Age	61	62.1
• Medical	90%	89%
• Emergency admission	47%	54%
• Cancer	3%	2%
• Immunodef	15%	16%
• SAPS II	47.1	46.9
• SOFA	8	7.7
• Septic shock	17%	18%

Types of Infection

	PCT (307)	Contrôles (314)
• Pulmonary	71%	74%
• Urinary tract	9%	6%
• Skin and soft tissue	2%	2%
• Intraabdominal	5%	7%
• CNS	3%	2%
• Catheter related	2%	1%
• Primary bacteremia	3%	4%
• Other	4%	3%

	PCT	CTRL
• Death 28 days	21.2%	20.4%
• Death 60 days	30%	26.1%
• Recurrence	6.5%	5.1%
• Superinf	34.5%	30.9%
• LOS	15.9j	14.4 j
• MDR bact	17.9%	16.6%

Antibiotic consumption

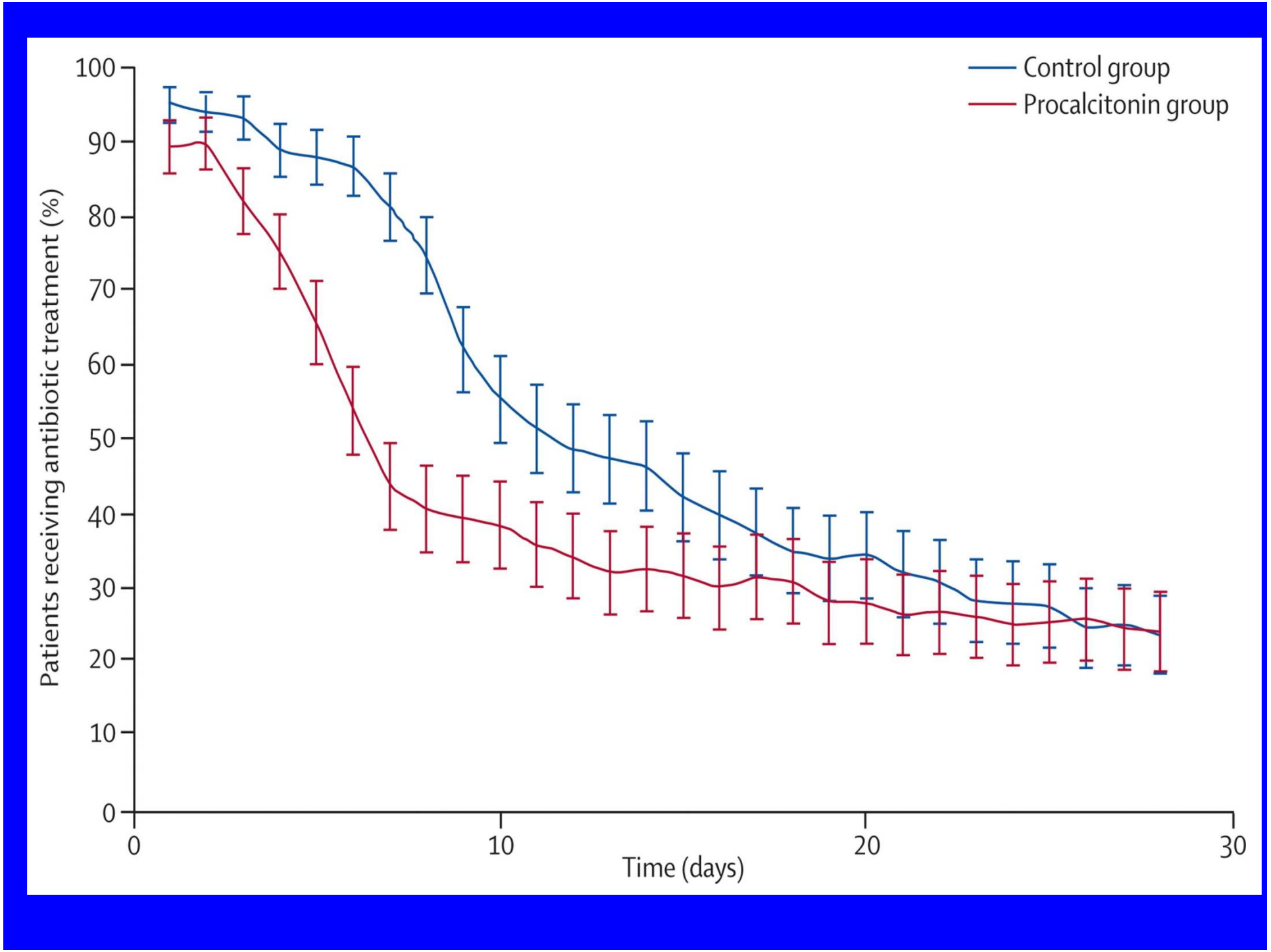
- Antibiotic free days

  14,3d vs 11,6d p<0,0001

- Days of treatment:

  65,3 vs 81,2 days/ 100 hospitalisation days

  p<0,0001


Control group
Procalcitonin group
Patients receiving antibiotic treatment (%)
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
Time (days)

Comments:

- No a posteriori confirmation of the diagnosis
- No data on the number of infections /patient
- No data on the reason for prolonged treatment
- Was the rule the same for all kinds of infections?
- Duration of VAP treatment is now 7-8 days

Diagnosis of infection

- Study in Liège in 505 patients
- Prospective, randomized study
- From April 2008 till December 2008
- 5 ICUs in the same hospital
- Inclusion criteria:
  - patients with LOS > 2 days
  - informed consent
  - > 18 years old

Design of the study

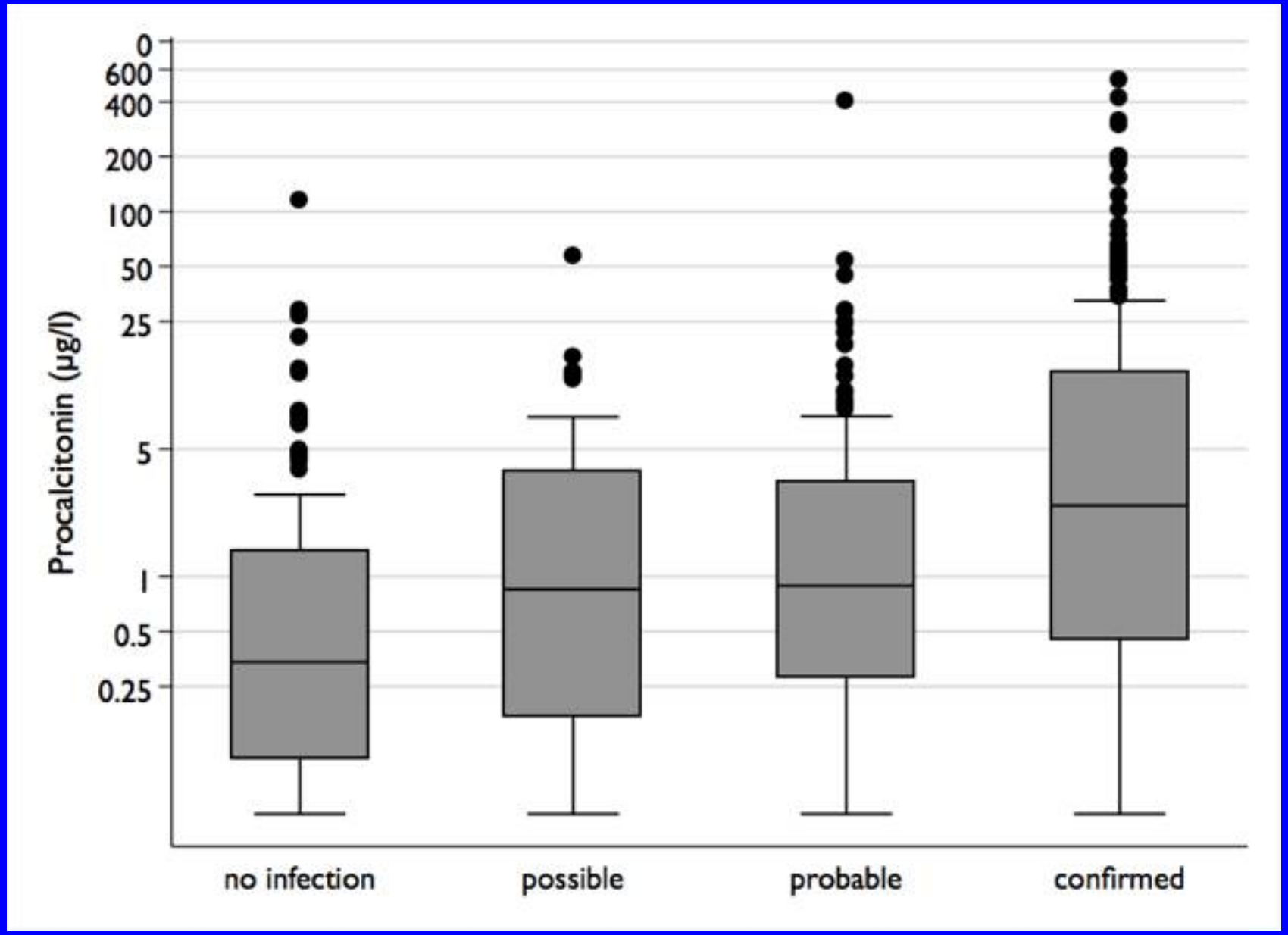
- Measurement of procalcitonin level for each clinically suspected infection.
- PCT results were blinded for 50% patients
- Clinicians were asked to take into account the Procalcitonin level in the intention to treat
- Charts were reviewed by ID specialist at the end of ICU stay

Aim of the study

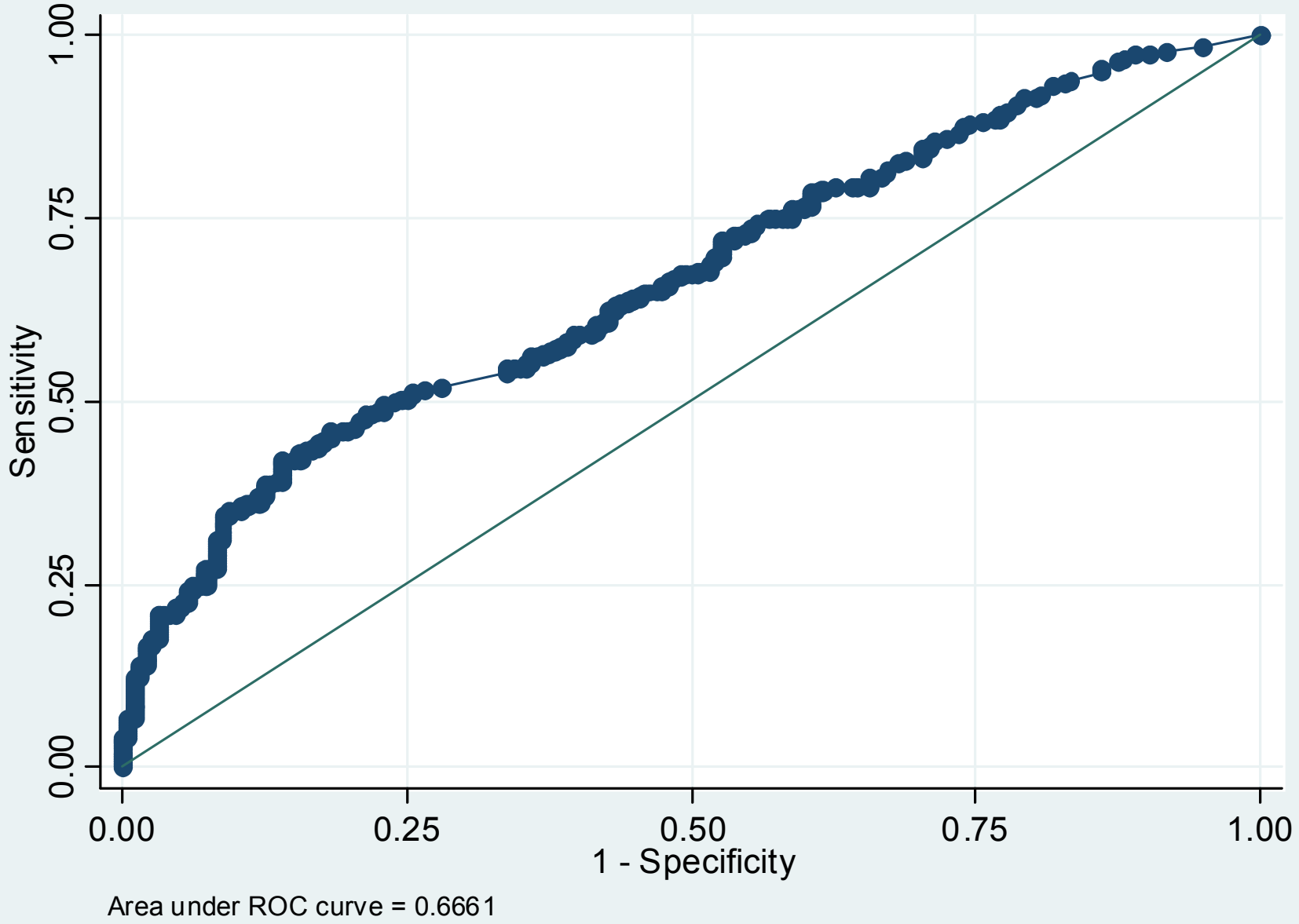
- Reduction of number of wrong diagnosis?
- Reduction in antibiotic consumption?

Types of suspected Infections

	PCT group	Ctrl group
Respiratory	229	225
Intraabdominal	33	28
Urinary	10	7
Soft tissue	14	15
Catheter related	7	4
Others	60	71
Total	**353**	**314**


Procalcitonin (µg/l)
0
600
400
200
100
50
25
5
1
0.5
0.25
no infection
possible
probable
confirmed

ROC curve


Sensitivity
0.00
0.25
0.50
0.75
1.00
0.00
0.25
0.50
0.75
1.00
1 - Specificity
Area under ROC curve = 0.6661

Consumption of antibiotics

	PCT	Ctrl
• DDD/100 ICU days	151%	158%
• days of treatment	62 %	62 %

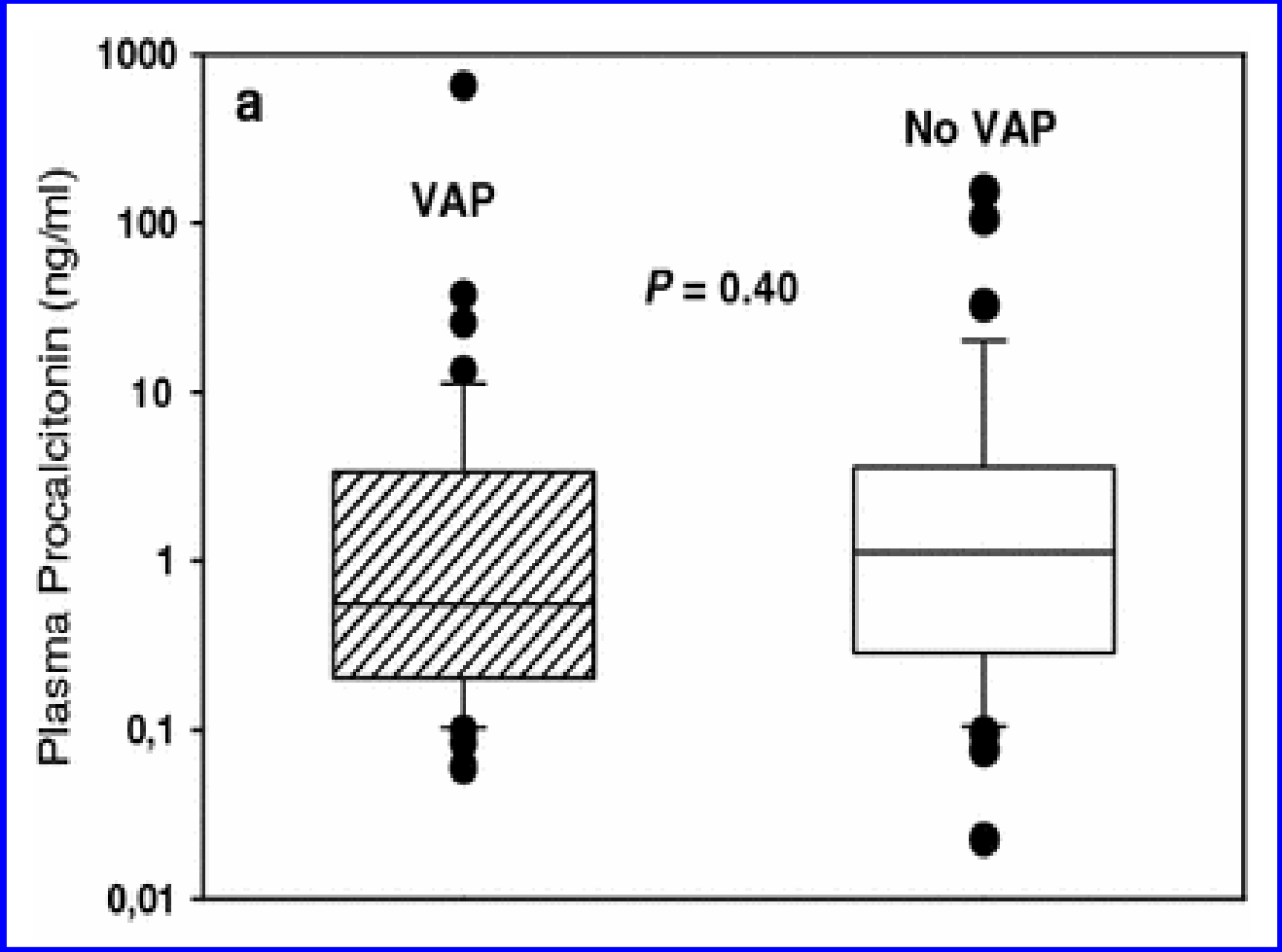
Diagnosis of VAP
Jung et al ICM 2010

- Proven by quantitative cultures on BAL (cult>10000 CFU/ml)
- Comparison between
  - CPIS
  - CPIS + previous endotracheal culture
  - CPIS + BAL exam
  - PCT
- 86 BAL in 57 patients, 56% with pos cult

Diagnostic of VAP
Jung et al ICM 2010

- Bacteriological data
  - From previous endotracheal samples
  - From direct exam of BAL

were more useful than the PCT level


a
1000
100
10
1
0,1
0,01
Plasma Procalcitonin (ng/ml)
VAP
No VAP
P = 0.40

PCT as a prognostic marker

- F Bloos et al Crit Care 2011
  multicentre study on respiratory tract infections (CAP, HAP, VAP) requiring mechanical ventilation
- PCT measured daily for 14 days in 175 patients
- Initial PCT, max PCT correlated with maxSOFA and with mortality but in the same proportion as APACHE II did

PCT in severe sepsis

- Karlsson et al Crit Care 2010
- 4-month study in 24 ICUs in Finland
- 242 adult patients with severe sepsis
- 15% had low levels of PCT !
- PCT levels did not differ between hospital survivors and non survivors, but mortality was lower in patients in whom PCT decreased >50% over 72 h.

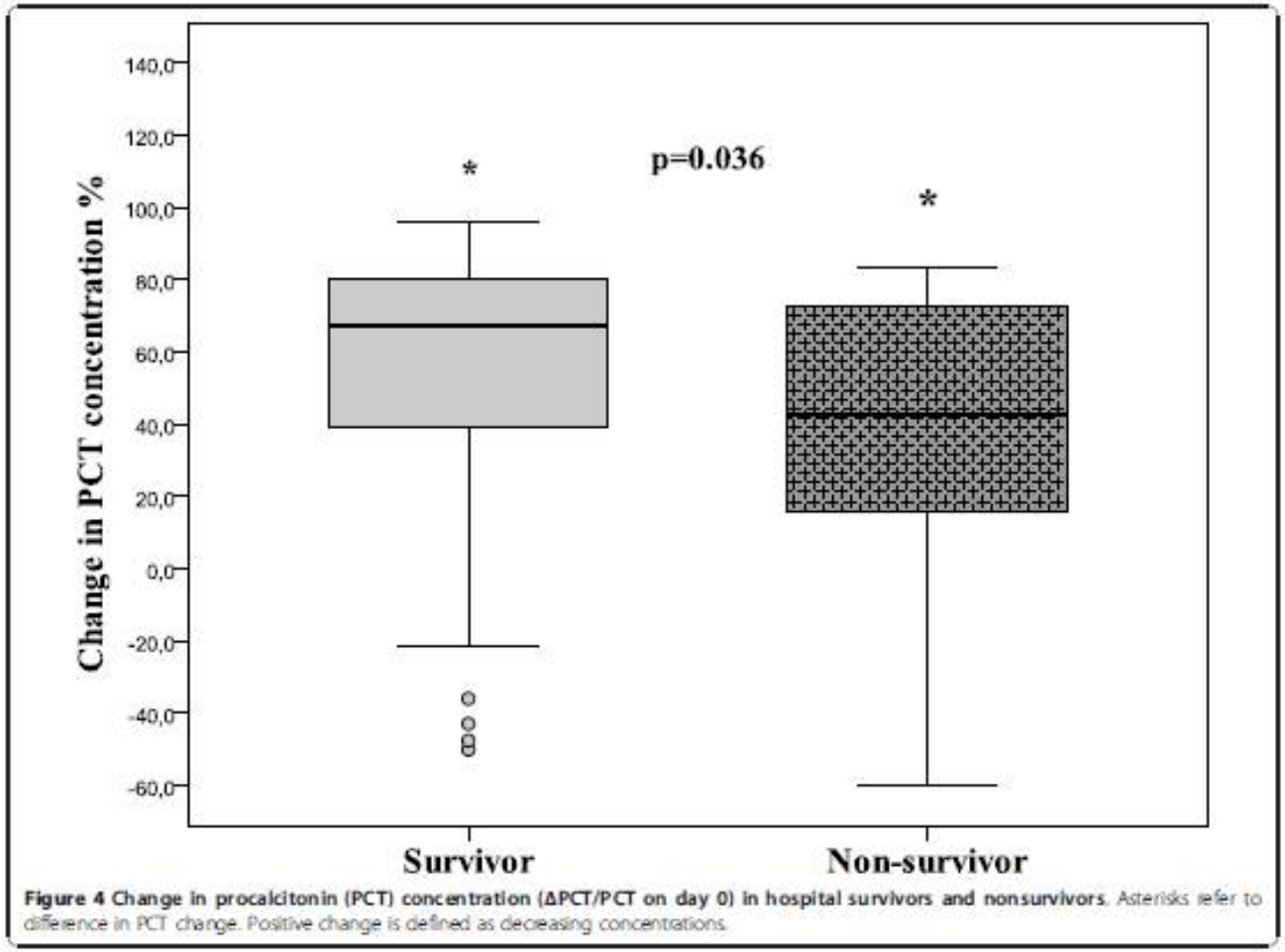


Figure 4 Change in procalcitonin (PCT) concentration (ΔPCT/PCT on day 0) in hospital survivors and nonsurvivors. Asterisks refer to difference in PCT change. Positive change is defined as decreasing concentrations.

Conclusions

- PCT measurements cannot replace the infectious diagnostic strategy, nor the evaluation of severity
- PCT has a place in the emergency room; in the ICU, the data are still limited
- The available studies allow us to treat patients for a shorter time
- To become part of the routine blood analysis, cost of measurement should be much cheaper.