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B·R·A·H·M·S PCT safely reduces antibiotic exposure

5-minute abstracts of PCT key studies

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Introduction

Procalcitonin (PCT), specific to bacterial infection, is the only biomarker which can support decisions on the antibiotic therapy.

The current scientific evidence with PCT extends to more than 5,000 publications, including a range of randomized controlled trials.

This booklet is intended to provide a quick overview of the existing evidence on PCT-guided antibiotic therapy, providing summarized information on major studies in an easy to read format.

For those interested in full publication, the reference is provided.

CONTENT

PCT IN CRITICALLY ILL PATIENTS

PCT IN LRTI

CONTENT

PCT IN NEONATES/PEDIATRICS

HEALTH ECONOMIC AND OUTCOME STUDIES

CONTENT

Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: A randomised, controlled, open-label trial

de Jong E, van Oers JA, Beishuizen A et al.*
The Lancet Infectious Diseases 2016; 16 (7): 819-827

Objective

This trial assessed the efficacy and safety of PCT-guided antibiotic treatment in patients in intensive care units (ICUs) in a health-care system with a comparatively low use of antibiotics.

Design

It was a prospective, multicentre, randomised, controlled, open-label intervention trial in 15 hospitals in the Netherlands. 1575 patients were randomised into a PCT-guided (n=776) or standard-of-care antibiotic (n=799) group.

In the PCT-guided group, a non-binding advice to discontinue antibiotics was provided if PCT concentration had decreased by 80% or more of its peak value or to 0.5 µg/L or lower. In the standard-of-care group, patients were treated according to local antibiotic protocols.

Primary endpoints

- Consumptions of antibiotics
- Duration of antibiotic treatment
- Safety outcome: Mortality at 28 days and 1 year

* VU University Medical Center, Amsterdam, Netherlands

Results

Median consumption of antibiotics was 7.5 daily doses in the PCT-guided group versus 9.3 daily doses in the standard-of-care group ($p<0.0001$).

Mortality at 28 days was 19.6% for PCT-guided group vs. 25% for standard-of-care group ($p=0.0122$) and **mortality at 1 year** was 34.8% for the PCT group vs. 40.9% for the standard-of-care group ($p=0.0158$).

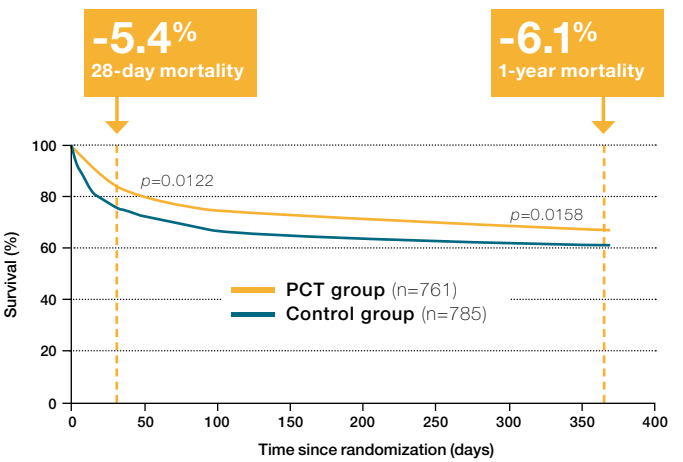

Figure Probability of survival from random assignment to day 365, in the modified intention-to-treat population

KEY FACTS

- This trial demonstrated that PCT-guided antibiotic therapy can reduce treatment duration (<2 days) and consumption (<19%).
- PCT-guided therapy among critically ill patients was associated with significant reduction in mortality at 28 days and 1 year as compared to standard-of-care.

Effect of procalcitonin-guided antibiotic treatment on clinical outcomes in intensive care unit patients with infection and sepsis patients: A patient-level meta-analysis of randomized trials

Wirz Y, Meier MA, Bouadma L et al.*
Critical Care 2018, 22: 191

Objective

This patient-level meta-analysis investigated the impact of PCT-guided antibiotic therapy on mortality, antibiotic duration and length of stay in intensive care unit (ICU) patients with infection, both overall and stratified according to sepsis definition, severity, and type of infection.

Design

4482 individual patients from 11 randomized trials in 7 countries (CH, D, F, NL, BR, BE, AUS) were included. 9 trials were on patients from medical or mixed ICU, 2 trials on surgical ICU patients.

Results

About 50% of patients had sepsis due to infection of the lung, followed by abdominal infection (18%) and urinary tract infection (5%). The mean SOFA score was 7.4 points and more than two-thirds of patients were on vasopressors and/or ventilation support. 3235 of patients met criteria of sepsis 3 definition. The PCT algorithms used in the different trials were similar and mainly focused on early discontinuation of antibiotics if PCT dropped below 0.5 µg/L or by 80% from the peak level. Adherence to the PCT protocols ranged from 44% to 97%.

* Medical University Department, Kantonsspital Aarau, Aarau, Switzerland

Reduced mortality

Mortality in the 2252 PCT-guided patients was significantly lower as compared with the 2230 control group patients (21.1% vs 23.7%; adjusted odds ratio 0.89, 95% confidence interval (CI) 0.8 to 0.99; p=0.03). These effects on mortality persisted in a subgroup of patients meeting the sepsis 3 definition as well as for the type of infection (respiratory, urinary tract, abdominal, skin, or central nervous system).

Reduced antibiotic treatment duration

PCT guidance also facilitated earlier discontinuation of antibiotics, with a reduction in treatment duration (9.3 vs 10.4 days; p<0.001).

	Control group	PCT group	Adjusted OR or difference (95% CI)	*p* value
All Patients (n)	**2230**	**2252**		
30-day mortality	529 (23.7%)	475 (21.1%)	0.89 (0.8 to 0.99)	p=0.03
Antibiotic therapy (days)	10.4±9.7	9.3±9.2	-1.19 (-1.73 to -0.66)	p<0.001
Patients meeting sepsis 3 definition (n)	**1630**	**1605**		
30-day mortality	397 (24.4%)	338 (21.1%)	0.86 (0.76 to 0.98)	p=0.022
Antibiotic therapy (days)	10.5±9.2	9.3±8.9	-1.22 (-1.82 to -0.62)	p<0.001

Table Impact of PCT-guided antibiotic stewardship on antibiotic therapy duration and 30 days mortality in sepsis patients treated in the ICU

KEY FACTS

- PCT-guided antibiotic treatment is shown to consistently reduce antibiotic exposure and lead to improvement in survival rates across various studies. These findings apply to all ICU patients and for subgroups, like those patients meeting sepsis 3 definition, or having different type of infection.

Procalcitonin-based therapeutic strategy to reduce antibiotic use in patients after cardiac surgery: A randomized controlled trial

Maravić-Stojković V, Laušević-Vuk L, Jović M et al.*
Srp Arh Celok Lek 2011; 139 (11-12): 736-742

Objective

Operated patients often manifest a systemic inflammatory response (SIRS) independently of whether a bacterial infection is present. The study investigated whether PCT guidance could be applied to post cardiac surgery patients to reduce antibiotic usage safely.

Design

This prospective, randomized controlled, single center trial was performed at a tertiary care hospital and included patients who underwent open heart surgery.

Patients included: Coronary artery bypass grafting (CABG) surgery (n=112), valve reconstruction or repair (n=52), and combined CABG and valve procedure (n=41). Patients were randomly assigned to PCT-guided group (n=102) or the standard care group (n=103).

Antimicrobial prophylaxis was performed in all patients with intravenous cefazolin 1.0 g after induction and 1.0 g at the end of the cardio pulmonary bypass during valve surgery. Post-surgery, in the standard group, antibiotic usage was applied based on laboratory and clinical signs. In the PCT group, antibiotic was initiated when the PCT level was >0.5 µg/L. However, the final decision to initiate antimicrobial treatment was left to the doctor in charge.

* Immunology Lab, Dedinje Cardiovascular Institute, Belgrade, Serbia

Results

- Relative risk of antibiotic exposure in the standard group compared with the PCT group was 3.81 ($p<0.0001$)
- Non-infectious complications occurred in 40/102 (PCT group) vs. 41/103 ($p=0.592$) while infections appeared in 5/102 (PCT group) vs. 22/103 ($p=0.001$) cases
- Urinary infections between PCT group and standard group; 1/102 vs. 9/103 ($p=0.016$)
- Mortality rates were equal in both groups of patients ($p=0.537$)

Variable	Groups of patients		*p*	RR
	PCT (n=102)	Standard (n=103)		
Intensive Care Unit stay (days)	5.74±11.49	6.97±11.61	0.4509	1.01
Length of hospital stay after operation (days)	12.08±11.28	12.93±10.73	0.5787	1.01
Antibiotics treatment (Yes/No)	19/83*	48/55	0.0000	3.81
Antibiotics + PCT costs per patient in Euro	193.3±636.6	372.1±841.1	0.0976	1.00
Antibiotics + PCT costs per hospital-day in Euro	8.0±18.4*	17.8±36.3	0.0204	1.00

* $p<0.05$

Table Clinical outcomes and antibiotics costs

KEY FACTS

- PCT can help to reduce post operative antibiotic exposure safely as well as reduce the cost of post operative care.

Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): A multi-centre randomised controlled trial

Bouadma L, Luyt CE, Tubach F et al. and Michel Wolff for the PRORATA trial group*
Lancet 2010; 375: 463-474

Objective

The objective of this trial was to evaluate if using a PCT-guided antibiotic therapy in patients with sepsis is non-inferior to standard of care for mortality.

Design

It was a multicentre, prospective, parallel-group, open-label trial, and patients were randomized into PCT (n=311) and control (n=319) group. Investigators were blinded to assignment before, but not after, randomization. In the PCT group, antibiotics were started or stopped based on predefined cut-off ranges of PCT concentrations; the control group received antibiotics according to current guidelines.

Endpoints

Primary endpoints

- Mortality at days 28 and 60 (non-inferiority analysis)
- Number of days without antibiotics by day 28 (superiority analysis)

Secondary endpoints

- Percentage of patients with relapse or superinfection (days 1–28)
- Number of days without mechanical ventilation
- SOFA score (days 1, 7, 14, 21, and 28)

* Service de Réanimation Médicale, Université Paris 7–Denis-Diderot, Hôpital Bichat–Claude-Bernard, Assistance Publique-Hôpitaux de Paris, Paris, France

- Length of stay in the intensive care unit and hospital
- Days of exposure to each antibiotic per 1000 inpatient days
- Duration of antibiotic treatment according to infection site
- Percentage of emerging multidrug-resistant bacteria isolated

Results

- PCT-guided approach was non-inferior to the standard of care approach in mortality at day 28 and 60
- Average antibiotic reduction in the PCT-guided group: 2.7 days ($p<0.0001$)
- The PCT-guided arm of the study was statistically better for days of antibiotic exposure per 1000 inpatient days (653 days vs 812 days; $p<0.0001$)

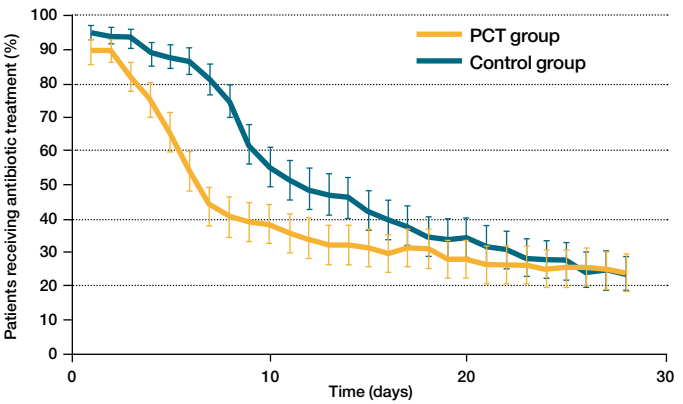

Figure Patients receiving antibiotics for days 1–28

KEY FACTS

- Procalcitonin-guided antibiotic therapy can reduce antibiotic exposure in the intensive care unit patients.
- There is no apparent adverse outcome of this strategy.

Procalcitonin-guided therapy may reduce length of antibiotic treatment in intensive care unit patients with secondary peritonitis: A multicenter retrospective study

Maseda E, Suarez-de-la-Rica A, Anillo V et al.*
Journal of Critical Care, 2015; 30 (3): 537-542

Objective

Duration of antibiotic treatment of complicated intra-abdominal infections is controversial, without wide consensus due to the absence of controlled studies supporting adequate scientific evidence. The trial investigated if PCT could act as a marker for antimicrobial discontinuation in patients with secondary peritonitis in the surgical ICU.

Design

This was a multicenter retrospective observational study across 4 surgical ICUs. All consecutive patients with secondary peritonitis, controlled infection source, requiring surgery, and at least 48-hour SICU admission were included. A total of 121 patients were included into PCT-guided group (52 patients) and non PCT-guided group (69 patients). In the PCT-guided group, antibiotics were stopped when PCT value reached less than 0.5 µg/L or had decreased at least 80% from the peak concentration.

* Anesthesiology and Surgical Critical Care Department, Hospital Universitario La Paz, Paseo de la Castellana 261, 28046 Madrid, Spain

Results

Antibiotic treatment was shorter in PCT-guided group vs. non PCT-guided group (5.1 vs 10.2 days, $p<0.001$). This was a 50% reduction in antibiotic duration. Length of SICU stay, in-hospital stay, mortality in SICU, hospital or 28-day mortality were not significantly different.

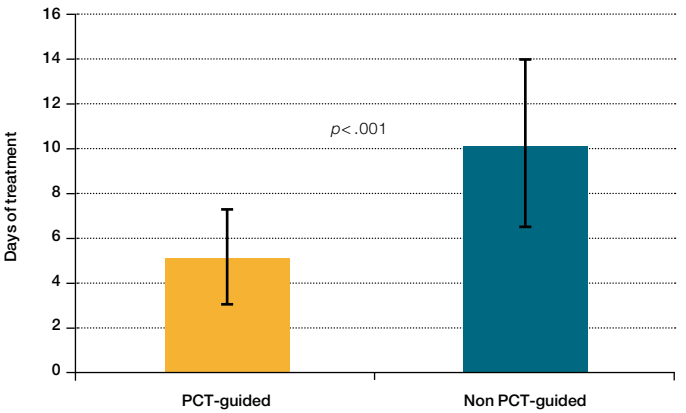

Figure Length of antimicrobial treatment in PCT-guided vs non PCT-guided groups

KEY FACTS

- Duration of antibiotic treatment of complicated intra-abdominal infections is controversial, without wide consensus due to the absence of controlled studies supporting adequate scientific evidence, which often leads to unnecessary prolonged duration of antibiotics.
- PCT-guided treatment can reduce antibiotic duration up to 50% in these patients, without affecting outcome and length of stay.

Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: A patient level meta-analysis

Schuetz P, Wirz Y, Sager R et al.*
Lancet Infect Dis 2018; 18 (1): 95-107

Objective

This meta-analysis of individual patient data from 26 randomised controlled trials was designed to assess safety of PCT-guided treatment in patients with acute respiratory infections from different clinical settings.

Design

Based on a pre-specified Cochrane protocol, individual patient data was collected on 6708 patients from 26 eligible trials in 12 countries.

- Primary endpoints: All-cause mortality within 30 days of randomization and treatment failure within 30 days of randomization (definitions of treatment failure varied by clinical setting).
- Secondary endpoints: Antibiotic use (initiation of antibiotics, duration of antibiotics in days and total exposure to antibiotics), length of stay, and antibiotic side-effects.

Results

30-day mortality was significantly lower among PCT-guided patients than control group, 9% (286) vs 10% (336) [p=0.037].

Treatment failure in PCT-guided patients was numerically lower than control patients, but not significantly different (23% vs 24.9%;) [p=0.068].

* Medical University Department, Kantonsspital Aarau, Aarau, Switzerland

Antibiotic use was significantly lower in PCT-guided group [*p*<0.0001]

- Lower initiation of antibiotics, 70% vs 86%
- Shorter duration of antibiotics, in patients in whom antibiotics were initiated, 8 days vs 9.4 days
- Reduced total exposure of antibiotics (total days of antibiotic therapy in all randomly assigned patients), 5.7 days vs 8.1 days
- Significant reduction in antibiotic related side-effects in PCT-guided patients, 16% vs 22% [*p*<0.0001]

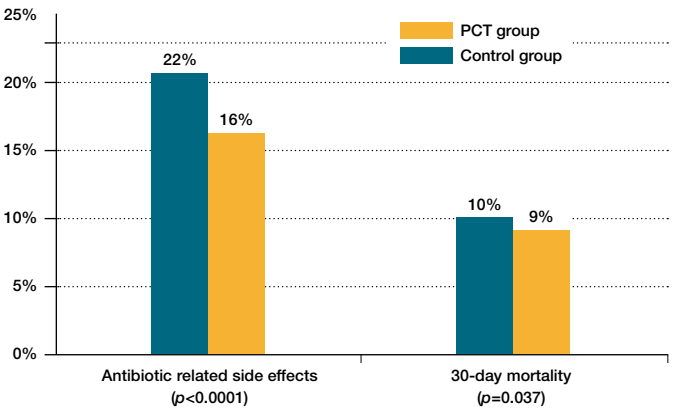

Figure Antibiotic related side-effects and 30-day mortality

KEY FACTS

- PCT guidance has been shown to significantly reduce antibiotic exposure in patients with respiratory tract infections through reduced antibiotic prescription in low-risk settings and low-risk patients, and through shorter duration and earlier discontinuation of antibiotics in high-risk patients.
- PCT-guided antibiotic treatment resulted in significantly lower antibiotic side-effects and significantly lower mortality.

Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections (ProHOSP)

Schuetz P, Christ-Crain M, Thomann R et al.*
JAMA 2009; 302 (10): 1059-1066

Objective

The objective of this trial was to examine whether a PCT algorithm can reduce antibiotic exposure without increasing the risk for serious adverse outcomes.

Design

A multicenter, non-inferiority, randomized controlled trial in emergency departments of 6 tertiary care hospitals in Switzerland with an open intervention of 1359 patients with mostly severe LRTIs.

Patients were randomized to administration of antibiotics based on a PCT algorithm with predefined cut-off ranges for initiating or stopping antibiotics (PCT group) or according to standard guidelines (control group).

Endpoints

Primary outcome was adverse outcome within 30 days of ED admission, including death, ICU admission, disease-specific complications or recurrent LRTI requiring antibiotic treatment. The secondary endpoints were antibiotic prescription rates, duration of antibiotic therapy and adverse effects.

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* Division of General and Emergency Medicine, University Department of Medicine, Kantonsspital Aarau, Aarau, Switzerland; and Medical Faculty, University of Basel, Switzerland.

Results

Overall adverse outcome rate was similar in the PCT and control groups (15.4% vs 18.9%), however the mean duration of antibiotic exposure was significantly lower in the PCT group in all patients (5.7 vs 8.7 days =-34.8%), and in patient sub-groups.

Compared to the standard care group, PCT guidance resulted in significant reductions in antibiotic exposure: lower antibiotic prescription rates, shorter mean duration of antibiotic treatment and reduced antibiotic associated adverse events.

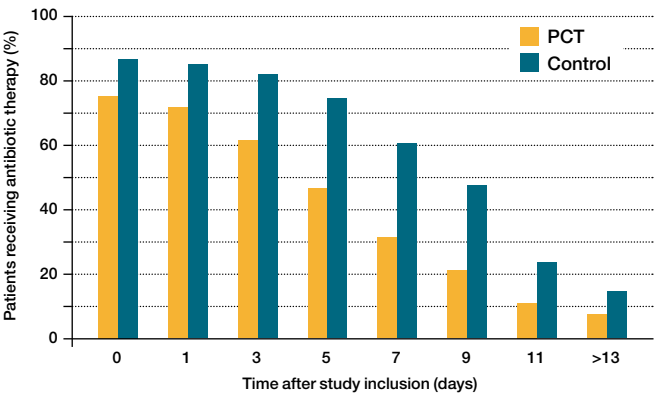


Figure Antibiotic exposure in patients receiving antibiotic therapy (n=1359)

KEY FACTS

- This study demonstrates that within all LRTI sub-groups, a PCT-guided treatment algorithm reduced antibiotic usage with no increased adverse patient outcomes.

Effectiveness and safety of procalcitonin guided antibiotic therapy in lower respiratory tract Infections in “real life”: An international multicenter post study survey

Albrich WC, Dusemund F, Bucher B et al. and Mueller B*
Arch Intern Med 2012 May 14; 172 (9): 715-722

Objective

This study investigated the effects of PCT guidance on inpatients and outpatients in hospitals and general physician offices in 3 countries with diverse antibiotic-prescribing patterns.

Most evidence regarding PCT-guided antibiotic stewardship comes from randomized controlled trials (RCTs), with minimal data outside of controlled study conditions. The objective of this international multicenter surveillance trial was to study the real life effects of PCT-guided antibiotic stewardship in daily practice in patients with lower respiratory tract infections (LRTI).

Design

The study was conducted at 14 centers in Switzerland, France, and the United States. 1850 adults with LRTI presenting to emergency departments or outpatient offices were enrolled. The PCT algorithm used pre-defined cut-off ranges for initiating or stopping antibiotics and pre-specified criteria for overruling.

Endpoints

The primary endpoint was duration of antibiotic therapy within 30 days and secondary endpoints were duration of antibiotic therapy at the index presentation, adherence to the PCT algorithm, and adverse medical outcome in the index hospitalization.

* Medical University Department, Kantonsspital Aarau, Aarau, Switzerland

Results

Results of the study demonstrated that antibiotic duration was significantly shorter (-1.52 days) if the PCT algorithm was followed compared with when it was overruled (5.9 vs 7.4 days; $p<0.001$). When the PCT algorithm was followed for non-initiation of antibiotics on hospital admission and early cessation of antibiotics, no increase in the risk of adverse outcome within 30 days of follow-up was observed.

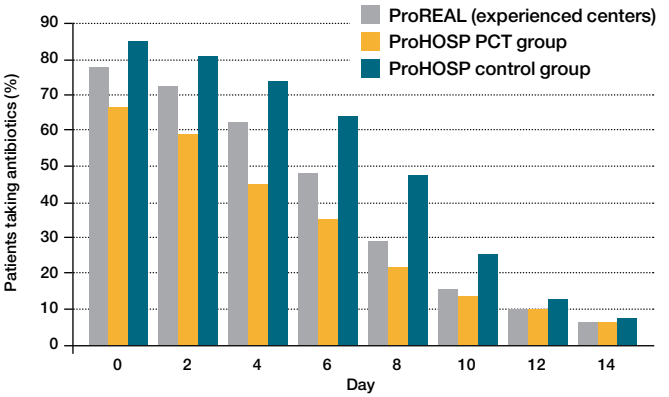


Figure Antibiotic exposure compared between real-life experience (ProREAL) and a randomized controlled trial (ProHOSP PCT group and control group) (for centers participating in both)

KEY FACTS

- This study shows that in "real life" conditions, a PCT-guided algorithm can significantly reduce antibiotic use without increasing risk of complications.
- Good compliance with a PCT algorithm has to be re-enforced to achieve optimal benefits.

Procalcitonin guidance for reduction of antibiotic use in patients hospitalized with severe acute exacerbations of asthma: A randomized controlled study with 12-month follow-up

Long W, Li LJ, Huang GZ, Zhang XM et al.*
Critical Care 2014; 18(5): 471

Objective

Patients with severe acute exacerbations of asthma often receive inappropriate antibiotic treatment. Because most exacerbations of asthma are associated with viral respiratory tract infection (RTI) and bacterial infection seems to play only a minor role, global asthma management guidelines do not recommend routine use of antibiotics. The objective of the study was to determine whether serum PCT levels can effectively and safely reduce antibiotic exposure in patients experiencing exacerbations of asthma.

Design

This was a randomized controlled trial. Asthma was defined according to the guidelines of the Global Initiative for Asthma. A severe asthma exacerbation was defined as at least one of the following: (1) need for systemic corticosteroids, or an increase from a stable maintenance dose, for at least 3 days and/or (2) hospitalization or ED visit because of asthma requiring systemic corticosteroids. 180 eligible patients were randomized into the PCT group (n=90) or the control group (n=90). PCT group patients received antibiotics based on the PCT algorithm; antibiotic treatment was strongly discouraged when PCT less than 0.1 µg/L, antibiotic treatment was discouraged when serum PCT level was less than 0.25 µg/L; and antibiotic treatment was encouraged when serum PCT level was higher than 0.25 µg/L.

* Department of Internal and Geriatric Medicine, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai

When antibiotics were withheld, a second PCT measurement was mandatory within 6 to 24 hrs. The control group received antibiotics according to the discretion of the treating physician.

Endpoints

The primary endpoint was antibiotic use, expressed as rate of antibiotic prescriptions in percentage and relative risk of antibiotic exposure.

Secondary endpoints included measures of treatment success:

- Length of hospital stay
- Clinical, laboratory and spirometry outcomes at discharge
- Results of spirometry at the 12-month follow-up examination, as well as the results of the Asthma Control Test (ACT), the results of the Asthma Quality of Life Questionnaire (AQLQ) at the 12-month follow-up visit and the clinical events during the 12-month follow-up period

Results

- Reduced antibiotic prescription in the PCT group (48.9% versus 87.8%, respectively; $p<0.001$) vs. the standard therapy
- Reduced antibiotic exposure in PCT group (relative risk, 0.56; 95% confidence interval, 0.44 to 0.70; $p<0.001$) compared to standard therapy
- No significant differences in clinical recovery, length of hospital stay or clinical, laboratory and spirometry outcomes in both groups
- Number of asthma exacerbations, emergency room visits, hospitalizations and need for corticosteroid use due to asthma were similar during the 12-month follow-up period

KEY FACTS

- PCT guided treatment is shown to result in significant reduction of inappropriate antibiotic use in patients hospitalized for severe acute exacerbations of asthma.
- Withholding antibiotic treatment on the basis of PCT guidance did not cause apparent harm for up to 12 months.

Antibiotic treatment of exacerbations of COPD: A randomized, controlled trial comparing procalcitonin-guidance with standard therapy

Stolz D, Christ-Crain M, Bingisser R et al.*
Chest 2007; 131 (1): 9-19

Objective

Therapy with antibiotics improves recovery only in selected cases of COPD Exacerbations. The objective of this study was to evaluate the efficacy and safety of PCT guidance compared to standard care with antibiotic therapy in patients experiencing exacerbations of COPD.

Design

This was a single-center, randomized controlled study on 208 consecutive patients admitted to the ED for index exacerbation of COPD. Patients were randomized into PCT-guided (n=102) and standard therapy group (n=106). A PCT level of <0.1 µg/L was considered to indicate the absence of bacterial infection, and the use of antibiotics was discouraged. A level of 0.1 to 0.25 µg/L indicated possible bacterial infection, and the use of antibiotics was discouraged or encouraged, respectively, based on the clinical stability of the patient. A PCT level of >0.25 was considered to suggest the presence of bacterial infection, and antibiotic treatment was encouraged.

Endpoints

Primary endpoints

- Antibiotic exposure at the index exacerbation
- Subsequent antibiotic requirement for COPD exacerbation within 6 months

* Clinics of Respiratory Medicine and Pulmonary Cell Research, University Hospital Basel, Basel, Switzerland

Secondary endpoints

- Clinical recovery, symptom scores, length of hospitalization, ICU stay, death, lung function, exacerbation rate, and time to next exacerbation

Results

At the index exacerbation, significant reduction in antibiotic prescriptions (40% vs 72%, respectively; $p<0.0001$) and antibiotic exposure (Relative Risk, RR 0.56; $p<0.0001$), in PCT group compared to standard therapy.

- The reduction in RR of antibiotic exposure for patients in the PCT group was 44% ($p<0.0001$), and the absolute risk reduction was 31.5% ($p<0.0001$).
- PCT-guided antibiotic therapy at the index exacerbation allowed a significant sustained reduction in total antibiotic exposure for up to 6 months (RR, 0.76; $p<0.004$).
- No difference between groups in clinical outcome and improvement in FEV1 at 14 days and 6 months
- No difference in the meantime to the next exacerbation treated with antibiotics in the PCT and standard therapy groups (76.7 vs 76.1 days, respectively; $p<0.819$)

KEY FACTS

- PCT level <0.1 µg/L indicates the absence of infection and can reduce unnecessary antibiotic exposure in patients presenting with exacerbation of COPD.
- This offers sustained reduction in antibiotic use for up to 6 months.
- The meantime to next exacerbation remains unchanged.

Procalcitonin-guided decision making for duration of antibiotic therapy in neonates with suspected early-onset sepsis: a multicentre, randomised controlled trial (NeoPInS)

Stocker M, van Herk W, el Helou S et al. and the NeoPInS Study Group*
Lancet 2017; 390: 871-881

Objective

The NeoPInS study investigated whether PCT-guided decision making could safely shorten the duration of antibiotic therapy in newborns with suspected early onset sepsis.

Design

This multicenter randomized controlled intervention trial was carried out in a large cohort of 1710 neonates from high income countries with a low incidence of proven early onset sepsis: 18 hospitals in the Netherlands (n=11), Switzerland (n=4), Canada (n=2) and the Czech Republic (n=1). 1710 neonates (gestational age >34 weeks) with suspected early onset sepsis were included, excluding those who underwent surgery in 1st week of life or had major congenital malformation (see next page for details).

Endpoints

Primary endpoints were superiority for duration of antibiotic (AB) therapy and non-inferiority for recurrence of infection requiring additional courses of AB therapy (within 72 hours after ending AB therapy) and/or death within the first month of life (non-inferiority margin of 2%).

Secondary endpoint was duration of hospitalization.

* Department of Paediatrics, Neonatal and Paediatric Intensive Care Unit, Children's Hospital Lucerne, Lucerne, Switzerland

Results

The neonates were classified into 4 risk categories based on risk factors (maternal risks, gestational age), clinical symptoms, and lab parameters (CRP, WBC). PCT-guided decision making was shown to be superior to standard care in significantly reducing the median duration of antibiotic therapy (intention to treat: 55.1 vs. 65.0 hours, $p<0.0001$; per protocol; 51.8 vs. 64.0 hours; $p<0.0001$). 9 (<1%) of 1710 neonates had possible re-infection (without culture confirmation), thereof did 5 occur in the PCT arm and 4 in the standard arm. Due to the low occurrence of re-infections and absence of study-related death, non-inferiority for re-infection or death could not be shown. Additionally, there was significant reduction in median length of stay (LOS) in hospital in PCT-guided group (-3.5 hours in intention to treat analysis; -5.2 hours in the per protocol analysis).

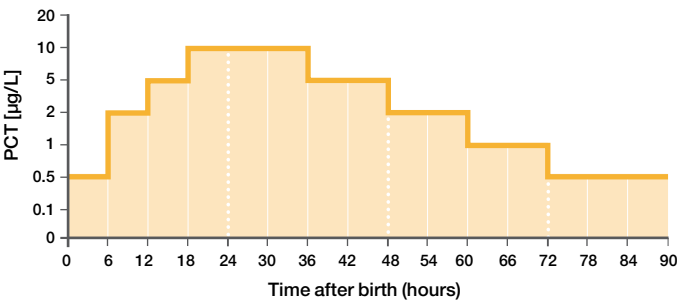


Figure Normal hourly values of post-birth PCT to rule out maternal-fetal bacterial infection

KEY FACTS

Standardized risk assessment with PCT is superior:

- Reducing the duration of antibiotic therapy and hospital stay
- With a low rate of re-infections and without study-related mortality

Check box if positive

A Risk factors

- ☐ Mother Group B streptococcus positive
- ☐ Maternal chorioamnionitis (fever >38.5 fetal tachycardia)
- ☐ Premature rupture membranes >18 hours
- ☐ Gestational age <37 weeks

0 boxes checked? Score = 0
≥1 box checked? Score = 1 → **A = 0/1**

B Clinical symptoms

- ☐ Respiratory distress or apnoea
- ☐ Tachycardia or bradycardia
- ☐ Arterial hypotension and/or poor perfusion
- ☐ Hypothermia or hyperthermia
- ☐ Seizure, floppy infant, irritability, or lethargy
- ☐ Vomiting or feeding intolerance or ileus

0 boxes checked? Score = 0
≥1 box checked? Score = 1 → **B = 0/1**

C Laboratory findings

- ☐ White blood cells <5x10 E9 cells per L
- ☐ C-reactive protein >10 mg/L

0 boxes checked? Score = 0
≥1 box checked? Score = 1 → **C = 0/1**

A+B+C = Total risk score

Category 1: Infection proven

Neonates with positive blood culture, and total score **≥1**

Category 2: Infection probable

Neonates with negative blood culture and total score **3**

Category 3: Infection possible

Neonates with negative blood culture, and total score **2**

Category 4: Infection unlikely

Neonates with negative blood culture, and total score **0 or 1**

PCT guidance to STOP antibiotic therapy for Category 3 and 4

Consider stop of antibiotics

- In neonates at low risk for early onset sepsis (low to medium infection risk categories 3+4)
- When 2 consecutive PCT values are within normal range according to the age-specific PCT reference values for neonates

Figure Risk assessment of neonates suspected of early onset sepsis and PCT guidance for duration of antibiotic therapy

A clinical prediction rule to identify febrile infants 60 days and younger at low risk for serious bacterial infections (SBIs)

Kuppermann N, Dayan PS, Levine DA et al. and the Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network (PECARN)*
JAMA Pediatr 2019; 173 (4): 342-351

Objective

The objective of this study was to derive and validate a prediction rule to identify febrile infants 60 days or younger at low risk of SBIs to balance the consequences of missed SBIs with risks of hospital-related complications, costs, and potential increases in antimicrobial resistance owing to empirical antibiotic treatment.

Design

This was a prospective, observational study at 26 Emergency Departments (general ED or pediatric ED). 1821 previously healthy febrile infants <60 days of age, with analyzable PCT results and complete SBI assessment were included. All patients had blood and urine cultures and 1383 (76%) had CSF testing (lumbar punctures). Serious bacterial infection was defined by bacterial meningitis, bacteremia, or UTI. 908 infants were randomly allocated to the derivation cohort and 913 infants to the validation cohort.

Results

Out of the total 1821 infants (derivation + validation cohort), serious bacterial infections were diagnosed in 170 infants (9.3%), including 151 with UTIs (8.3%), 26 (1.4%) with bacteremia, and 10 (0.5%) with bacterial meningitis; 16 (0.9%) had concurrent

* Departments of Emergency Medicine and Pediatrics, University of California, Davis School of Medicine, Sacramento, CA

bacterial infections. Of the 16 with multiple infections, 1 had UTI, bacteremia, and meningitis; 5 had bacteremia and meningitis; and 10 had UTI and bacteremia.

Prediction rule to identify infants with low risk of SBI: Negative urinalysis result + Absolute neutrophil count (ANC) <4090/µL + serum PCT <1.71 µg/L

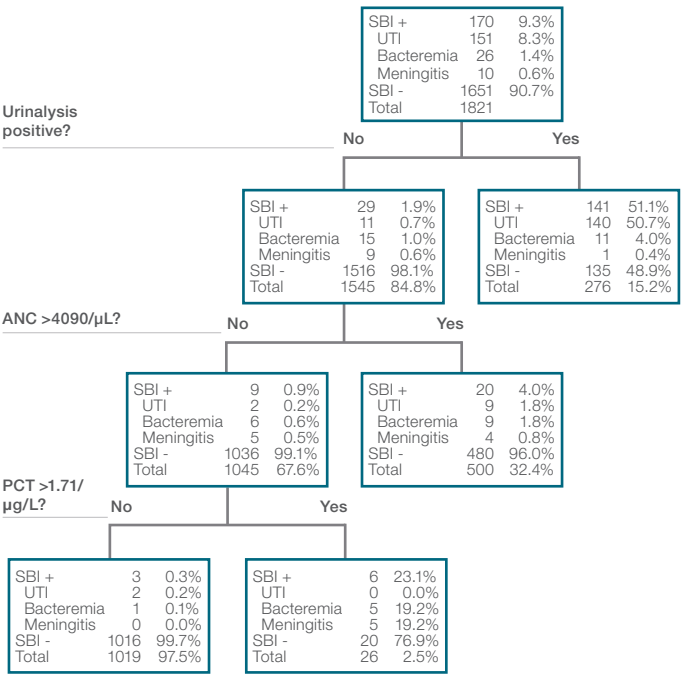
522 of 908 infants in the derivation cohort (57.5%) and 497 of 913 infants in the validation cohort (54.4%) were identified as low risk for SBIs as per the rule.

	Derivation, No.			Validation, No.		
	SBI	No SBI	Total	SBI	No SBI	Total
SBI per rule	81	305	386	86	330	416
No SBI per rule	1	521	522	2	495	497
Total	82	826	908	88	825	913

In the validation cohort, the rule sensitivity was 97.7%, specificity was 60.0%, negative predictive value was 99.6% and negative likelihood ratio was 0.04.

Of 1266 infants aged 29 to 60 days, 776 (61.3%) were at low risk according to the prediction rule, and 523 of these 776 (67.4%) had lumbar punctures performed. This number represents potential lumbar punctures spared in this age group for low risk patients.

See next page for details.



* Patients could have multiple SBIs contributing to a classification of SBI positive.
Abbreviations: SBI, Serious bacterial infection; UTI, Urinary tract infection; ANC, Absolute neutrophil count; PCT, Procalcitonin

Figure Distribution of SBIs by risk category – full patient cohort

KEY FACTS

- Clinical prediction rule using urinalysis, ANC (absolute neutrophil count), and PCT levels is accurate to identify febrile infants 60 days and younger at low risk for Serious Bacterial Infections with negative predictive value 99.6%.
- Clinical application of the rule has the potential to decrease unnecessary lumbar punctures, antibiotic administration, and hospitalizations.

Procalcitonin measurements for guiding antibiotic treatment in pediatric pneumonia

*Esposito S, Tagliabue C, Picciolli I et al.**
Respiratory Medicine 2011; 105, 1939-1945

Objective

The aim of this study was to evaluate the use of an algorithm based on a PCT cut-off value as a means of guiding the management of antibiotic therapy in hospitalized children with uncomplicated Community Acquired Pneumonia (CAP).

Design

This prospective, single-centre randomised study consecutively enrolled 310 children with CAP who were hospitalised in the Department of Maternal and Pediatric Sciences. The enrolled children were randomised to receive antibiotics on the basis of a PCT algorithm (PCT group, n=155) or in accordance with evidence based guidelines (control group, n=155). The blood samples for measuring serum PCT were taken as early as possible, typically upon admission or at most within 6 h of admission, and the results were available 60 min later. Antibiotics were not administered to the children with admission PCT levels of <0.25 µg/L, but were immediately given in the case of higher values. The untreated children were given antibiotics only if their PCT levels increased to 0.25 µg/L, and continued the therapy until the levels had returned to this value. The children who received antibiotics from the time of admission were treated until their PCT levels were >0.25 µg/L, and resumed antibiotics only if their PCT levels subsequently increased to more than this value.

* Department of Maternal and Pediatric Sciences, Università degli Studi di Milano, Fondazione IRCCS Cá Granda Ospedale Maggiore Policlinico, Milan, Italy, Via Commenda 9, 20122 Milano, Italy

Results

In comparison to the control group, the PCT group received significantly fewer antibiotic prescriptions (85.8% vs 100%), were exposed to antibiotics for a shorter time (5.37 vs 10.96 days), and experienced fewer antibiotic-related adverse events (3.9% vs 25.2%), regardless of CAP severity.

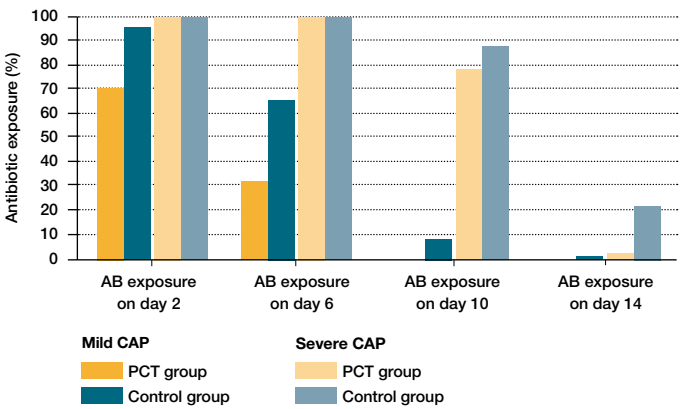


Figure Antibiotic exposure by treatment group and CAP severity

KEY FACTS

- PCT cut-off value of 0.25 µg/L can be useful in separating the cases of pediatric CAP that, regardless of etiology, do not need antibiotic treatment or, even if due to bacteria, can be treated for a shorter time than that usually recommended by the guidelines.
- The use of the algorithm allowed 15% of the children to avoid antibiotics altogether, and significantly reduced the duration of administration in most of the cases treated upon admission, without any increased risk of a negative evolution even in severe cases.

Procalcitonin guidance to reduce antibiotic treatment of lower respiratory tract infection in children and adolescents (ProPAED): A randomized controlled trial

Baer G, Baumann P, Buettcher M et al.*
PLoS One 2013; 8 (8): e68419

Objective

This trial investigated whether PCT-guided antibiotic treatment could reduce antibiotic prescribing rates and therapy duration in children and adolescents with LRTI presenting to the ED using cut-off ranges established in trials of adults with LRTI.

Design

337 children between the ages of 1 month and 18 years, presenting to the ED with signs of LRTI to two pediatric hospitals in Switzerland, were included and randomized.

In the PCT group, initiation, continuation or termination of antibiotic treatment was strictly guided by PCT algorithm which provided PCT based decision categories for the likelihood of requiring antibiotic treatment for bacterial LRTI: “definitely” (>0.5 µg/L), “probably” (0.26–0.5 µg/L), “probably not” (0.1–0.25 µg/L), and “definitely not” (<0.1 µg/L).

For all patients, discontinuation of antibiotics was encouraged upon clinical stabilization and when PCT values fell below 0.25; for patients with initial PCT values >10 µg/L when levels decreased below 90% of the initial value. Continuation of treatment on day 5 was determined according to the following algorithm: >1 µg/L: 7 days, 0.51–1 µg/L: 5 days, 0.26–0.5 µg/L: 3 days, and ≤0.25 µg/L: no antibiotic. In the control group, antibiotic treatment was initiated based on physician assessment and clinical

* Department of Pediatrics, University Basel, Basel, Switzerland

guidelines for a duration of 7–10 days for uncomplicated CAP and 14 or more days for complicated CAP.

Endpoints

Primary endpoint

- Antibiotic prescription rate within 14 days of randomization

Secondary Endpoints

- Duration of antibiotic treatment
- Rate and duration of side effects of antibiotic treatment
- Rate and duration of hospitalization
- Occurrence of serious adverse events, complications of LRTI or disease specific failure
- Impairment of daily activity attributable to LRTI during the 14 days following randomization

Results

Antibiotic prescribing rates were not significantly different in PCT-guided patients compared to controls (OR 1.26; 95% CI 0.81, 1.95). Mean duration of antibiotic exposure was reduced from 6.3 to 4.5 days under PCT guidance (21.8 days; 95% CI 23.1, 20.5; p=0.039) for all LRTI and from 9.1 to 5.7 days for pneumonia (23.4 days 95% CI 24.9, 21.7; p,0.001).

There was no apparent difference in impairment of daily activities between PCT-guided and control patients. Rates of antibiotic side effects and hospitalizations were similar in both groups.

KEY FACTS

- First major trial to impact PCT-guided therapy in pediatric patients.
- Although antibiotic prescribing rates were not significantly different in the PCT-guided group as compared to the control group, PCT-guided therapy led to reduced antibiotic exposure in children with LRTI reducing the duration of antibiotic treatment.

Procalcitonin (PCT)-guided antibiotic stewardship: An international experts consensus on optimized clinical use

Schuetz P, Beishuizen A, Broyles M et al.*
Clin Chem Lab Med 2019. https://doi.org/10.1515/cclm-2018-1181

Objective

PCT-guided antibiotic stewardship (ABS) has been shown to reduce antibiotics (ABx), with lower side-effects and an improvement in clinical outcomes. The aim of this experts workshop was to derive a PCT-guided ABS algorithm for easier implementation into clinical routine across different clinical settings.

Design

Clinical evidence and practical experience with PCT-guided ABS was analyzed and discussed, with a focus on optimal PCT use in the clinical context and increased adherence to PCT protocols. The group consisted of experts from different hospital departments who are usually the stakeholders of an antibiotic stewardship program in a hospital, eg. Intensivists, ID physicians, Microbiologist, Clinical Pharmacists, Internal Medicine experts etc. Using a Delphi process, the experts group reached consensus on different PCT algorithms based on clinical severity of the patient and probability of bacterial infection.

Results

The group agreed that there is strong evidence that PCT-guided ABS supports individual decisions on initiation and duration of ABx treatment in patients with acute respiratory infections and sepsis from any source, thereby reducing overall ABx exposure and associated side effects, and improving clinical outcomes. To simplify practical application, the expert group refined the

* Department of Internal Medicine, Kantonsspital Aarau, Aarau, Switzerland; and University of Basel, Basel, Switzerland

established PCT algorithms by incorporating severity of illness and probability of bacterial infection and reducing the fixed cut-offs to only one for mild to moderate and one for severe disease (0.25 µg/L and 0.5 µg/L, respectively). An 80% decrease of PCT vs peak level was included for decision on AB discontinuation for all three scenarios. Further, guidance on interpretation of PCT results to initiate, withhold or discontinue ABx treatment was included (see next page for details).

Conclusions

A combination of clinical patient assessment with PCT levels in well-defined ABS algorithms, in context with continuous education and regular feedback to all ABS stakeholders, has the potential to improve the diagnostic and therapeutic management of patients suspected of bacterial infection, thereby improving ABS effectiveness.

KEY FACTS

- The experts group recommended an approach to first classify the patients based on their clinical severity, followed by clinical assessment of likelihood of bacterial infection and integration of PCT value to arrive at the decision on antibiotic treatment.
- Clinician education on use of PCT and adherence to the PCT algorithm were considered the two important factors for successful routine integration of PCT for antibiotic stewardship.

PCT-guided ABS algorithms based on clinical patient assessment

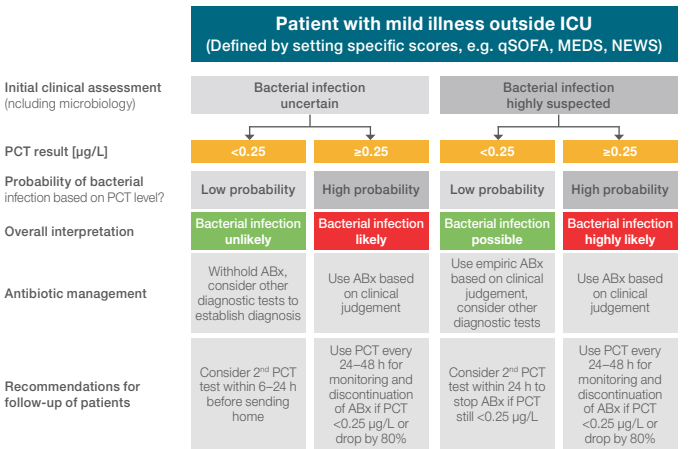


Figure 1 PCT use in patients with mild illness outside the ICU

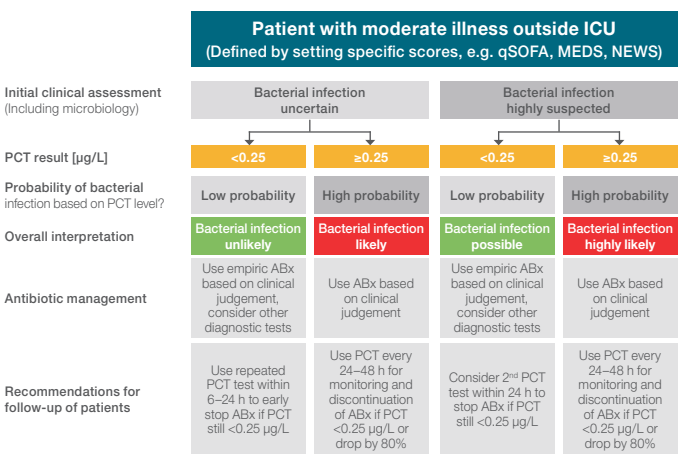


Figure 2 PCT use in patients with moderate illness outside the ICU

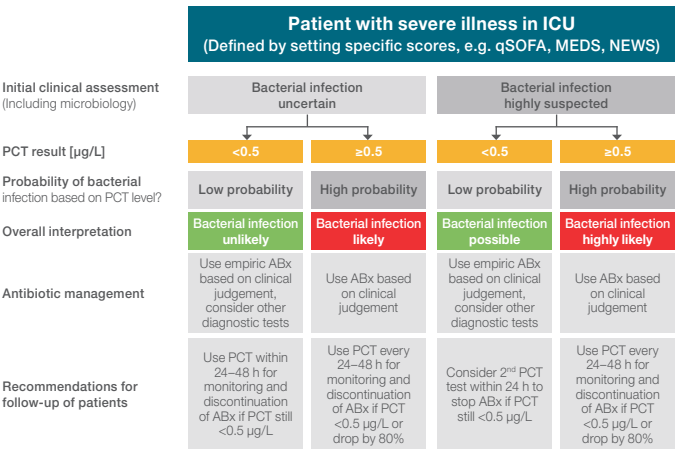


Figure 3 PCT use in patients with severe illness in the ICU

* Caution in patients with immuno-suppression (including HIV), CF, pancreatitis, trauma, pregnancy, high volume transfusion, malaria; PCT-guided stewardship should not be applied to patients with chronic infections (e.g. abscess, osteomyelitis, endocarditis).

Impact of procalcitonin (PCT)-guided antibiotic management on antibiotic exposure and outcomes: Real world evidence

*Broyles MR**
Open Forum Infect Diseases 2017; 4(4): ofx213

Objective

The objective of this study was to evaluate the impact of a PCT algorithm (PCT-A) to guide antibiotic management in a real world setting of patients with suspected infection.

Design

It was a single-center, pre-post, retrospective cohort study conducted in a community hospital to evaluate the impact of adding PCT-A to stewardship practices.

Data from four years prior to and after PCT-A implementation was compared in critical and acute care patients of all ages receiving parenteral antibiotics for a DRG coded for infection. 985 patients (pre PCT-A group) were compared to 1167 patients (post PCT-A group). Outcomes of interest were antibiotic exposure, hospital mortality, 30-day readmission, *C.difficile* infection (CDI) and adverse drug events (ADE) during hospitalization.

A baseline PCT was obtained on admission in patients with suspected bacterial infection. Antibiotics were not recommended in clinically stable patients with low PCT values (<0.25 µg/L) and low likelihood of bacterial infection. If antibiotics were withheld, PCT was repeated within 24 hours. Serial PCT measurements were repeated daily for the first 72 hours to evaluate effectiveness of therapy. Therapy modifications were made after the first 24 hours, if required, based on clinical presentation and changes in PCT. Cessation of antibiotics was suggested when clinical

* Department of Clinical Pharmacy and Laboratory Services, Five Rivers Medical Center, Pocahontas, AR, United States of America

disposition had improved and PCT had decreased by more than 80-90% or had reached a value of 0.25-0.5 µg/L.

Results

All studied outcomes were significantly improved in the post PCT-A group. Antimicrobial stewardship alone (pre PCT-A) resulted in a median Days of Therapy (DOT) of 17 (IQR 8.5-22.5) vs. 9.0 (IQR 6.5-12) in the post PCT-A group (p<0.0001). Secondary outcomes were also significantly reduced in the post PCT-A group.

	Pre-PCT n=985	Post-PCT n=1167	Be-tween-Group Differ-ence	% Reduc-tion	P value
Primary Outcome					
Days of Therapy (DOT), median IQR	17.0 (8.5-22.5)	9.0 (6.5-12.0)	-8.0	47	<0.001
Secondary Outcome					
Hospital All-Cause Mortality, n (%)	75 (7.6)	35 (2.9)	4.7%	62	<0.001
Hospital Mortality from Infection, n (%)	68 (6.9)	33 (2.8)	4.1%	59	<0.001
30-day All-Cause Readmission, n (%)	204 (22.4)	119 (11.1)	11.3%	50	<0.001
30-day Readmission for Infection, n (%)	177 (19.5)	111 (9.8)	9.5%	49	<0.001
Hospital *C.difficile* Infection, n (%)	25 (2.5)	10 (0.9)	1.6%	64	0.002
ADEs from Anti-microbials, n (%)	160 (16.2)	94 (8.1)	8.1%	50	<0.001

KEY FACTS

- Significant reduction in antibiotic exposure, improvement in hospital mortality, 30-day readmission, CDI during hospitalization, and antimicrobial ADEs during hospitalization was achieved in an institution with an established stewardship program.

The cost impact of PCT-guided antibiotic stewardship versus usual care for hospitalized patients with suspected sepsis or lower respiratory tract infections in the US: A health economic model analysis

Mewes JC, Pulia MS, Mansour MK et al.*
PLoS ONE 2019; 14 (4): e0214222. https://doi.org/10.1371/journal.pone.0214222

Objective

The aim of this analysis was to compare effectiveness and cost of a PCT algorithm vs. standard of care to guide antibiotic prescription for patients hospitalized with diagnosis of suspected sepsis or LRTI in the US.

Design

A previously published decision-tree model was used to compare costs and effects considering the hospital and societal perspective. The final publication selection contains 13 US-based articles, 2 RCTs, 8 retrospective studies, and 3 economic analyses. In case of US data gaps, selected EU data have been used.

Endpoints

Main outcomes were total cost per patient, incl. treatment costs and productivity losses, the number of patients with antibiotic resistance or *C.difficile* infections, and costs per antibiotic day avoided.

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* Panaxea B.V., Amsterdam, the Netherlands

Results for sepsis

- Antibiotic treatment was reduced by 5.83 days, ward stay by 0.7 days, and ICU stay by 3.6 days. Including all costs, the difference in cost per patient in the PCT group was -$11,311.
- The number of patients with antibiotic resistant infections was estimated to be lowered by 13,222 cases due to shorter antibiotic treatment durations in the PCT group, which equals a cost effect of -$131.16 per sepsis patient, and the number of *C.difficile* infections was lower by 16,103 cases, with a cost difference of -$191.32 per sepsis patient, respectively.

	Outcome	Standard care	PCT-guided ABS	Difference
SEPSIS	**Effectiveness measures**			
	Antibiotic days	13.37	7.54	-5.83
	Patients with antibiotic resistant infection	206,441.76	193,218.28	-13,222.48
	C.difficile infections	29,374.58	13,271.51	-16,103.07
	Cost outcomes			
	Hospital stay	$30,087.16	$22,382.42	-$7,704.75
	Antibiotics	$763.60	$430.52	-$333.18
	Mechanical ventilation	$5,775.00	$3,675.00	-$2,100.00
	Lab tests (including PCT tests in the PCT-group)	$1,711.27	$1,625.63	-$85.64
		//	//	//
	Average total costs per sepsis patient	**$43,430.34**	**$32,119.76**	**-$11,310.57**

Table Results for patients with sepsis (reduced to cost drivers and important clinical parameters)

Results for LRTI

- Antibiotic treatment was reduced by 4.91 days, ward stay by 0.7 days, and ICU stay by 3.6 days (10% of LRTI patients are expected to be submitted to the ICU). Including all costs the difference in cost per patient in the PCT group was -$2,867.
- The number of patients with antibiotic resistant infections was estimated to be lowered by 64,466 cases lower due to shorter antibiotic treatment durations in the PCT group, which equals a cost effect of -$380.40 per LRTI patient, and the number of *C.difficile* infections was lower by 31,487 cases, with a cost difference of -$187.18 per LRTI patient, respectively.

	Outcome	Standard care	PCT-guided ABS	Difference
LRTI	**Effectiveness measures**			
	Antibiotic days	11.90	6.99	-4.91
	Patients with antibiotic resistant infection	369,639.33	305,173.70	-64,465.64
	C.difficile infections	51,485.59	19,998.90	-31,486.69
	Cost outcomes			
	Hospital stay	$9,754.73	$8,149.72	-$1,605.02
	Antibiotics	$585.87	$295.90	-$289.97
	Mechanical ventilation	$606.38	$385.88	-$220.50
	Lab tests (including PCT tests in the PCT-group)	$1,292.32	$1,361.80	$69.48
		//	//	//
	Average total costs per LRTI patient	**$16,217.65**	**$13,350.73**	**-$2,866.92**

Table Results for patients with LRTI (reduced to cost drivers and important clinical parameters)

Sensitivity & scenario analysis

- All parameters were varied by +/-25% to test the robustness of the results and to identify key cost drivers of the model. The highest impact on the cost difference was found for the duration for ICU and ward stay.
- In order to pressure test the cost effectiveness of PCT the evaluation of the base case was followed by scenario analyses, in particular, a worst case scenario analysis for which "no difference" in length of stay, and lower antibiotic treatment duration difference between PCT group and standard of care was modelled. The total incremental cost stayed in the cost-saving range, with -$3,416 and -$554, for sepsis and LRTI, respectively.

KEY FACTS

- Using a PCT algorithm to aid antibiotic use in sepsis and hospitalized patients with LRTI reduced the total costs, including treatment costs and productivity losses, in the US by $11,311 (-26%) and $2,867 (-17.7%), respectively.
- Future investigations should focus on impact of PCT-aided ABS on the number of patients with antibiotic resistance infection and *C.difficile* infection, as this has been shown to decrease and could have further impact on cost savings.

Serial procalcitonin predicts mortality in severe sepsis patients: Results from the multicenter procalcitonin MOnitoring SEpsis (MOSES) Study

Schuetz P, Birkhahn R, Sherwin R et al.*
Critical Care Medicine 2017; 45 (5): 781-789

Objective

The objective of this trial was to prospectively validate if the inability to decrease PCT levels by more than 80% between baseline and day 4 is associated with increased 28-day all-cause mortality in a large sepsis patient population recruited across the United States. It was a blinded, prospective multicenter observational clinical trial following a Food and Drug Administration-approved protocol.

Design

Thirteen U.S.-based emergency departments and ICUs enrolled 858 patients. 646 patients were alive and in the hospital on day 4 and included in the main intention-to-diagnose analysis. PCT was measured daily over the first 5 days.

Results

The 28-day all-cause mortality was two-fold higher when PCT did not show a decrease of more than 80% from baseline to day 4 (20% vs 10%; p=0.001).

The study demonstrated that PCT is a significant independent predictor of mortality even after adjusting for other clinical outcome predictors such as demographics, sepsis severity, patient location (ICU or ward).

* Division of General and Emergency Medicine, University Department of Medicine, Kantonsspital Aarau, Aarau, Switzerland; and Medical Faculty, University of Basel, Switzerland

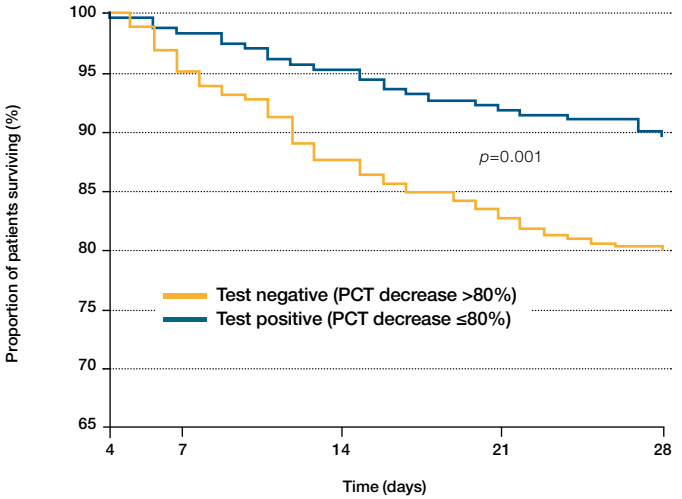

Figure Survival curves comparing the survival of patients (n=646) with PCT decrease of at least 80% (● high-risk group) and patients with PCT decrease >80% (● low-risk group) in the overall population, in patients in the ICU at day 4

KEY FACTS

- Large, prospective multicenter U.S. study indicates that inability to decrease PCT by more than 80% is a significant independent predictor of mortality and may aid in sepsis care.

Procalcitonin as a rapid diagnostic biomarker to differentiate between culture-negative bacterial sepsis and systemic inflammatory response syndrome: A prospective, obser-vational, cohort study

Anand D, Das S, Bhargava S, Srivastava LM et al.*
Journal of Critical Care 2015; 30 (1): 218.e7-12

Objective

More than 30% of all infections are culture-negative and the differentiation to a non-infectious systemic inflammatory response syndrome (SIRS) remains a challenge for clinicians because of the similar clinical presentation. The aim of this study was to evaluate the potential diagnostic role of biomarkers, PCT and interleukin 6 (IL-6), in culture-negative sepsis patients.

Design

The prospective study enrolled 208 patients admitted to the ICU and with diagnosis of non-infectious SIRS, sepsis, severe sepsis, or septic shock. PCT and IL-6 estimations were performed on day 1 of ICU admission. Enrolled patients were classified into SIRS and suspected sepsis at the time of enrollment based on clinical presentation. Culture-negative and culture-positive groups were defined, once the microbiological results were available.

Endpoints

To evaluate the discriminative ability of PCT and IL-6 between culture-negative and culture-positive sepsis.

* Department of Biochemistry, Sir Ganga Ram Hospital, New Delhi, 110060, India

Results

Patients were classified into 3 groups:

Group I – non-infectious SIRS patients (n=46)

Group II – Patients with suspected sepsis and negative culture results (n=90)

Group III – Septic patients with microbiologically documented source of infection (n=72)

PCT was a better predictor of sepsis in both culture-negative (AUC 0.892 vs 0.636) and culture-positive (AUC 0.959 vs 0.784) groups as compared with IL-6. In culture-negative group, the best cutoff point for PCT was at 1.43 µg/L (92% sensitivity; 83% negative predictive value), best cutoff point for IL-6 was at 219.85 pg/mL (47% sensitivity and 42% negative predictive value).

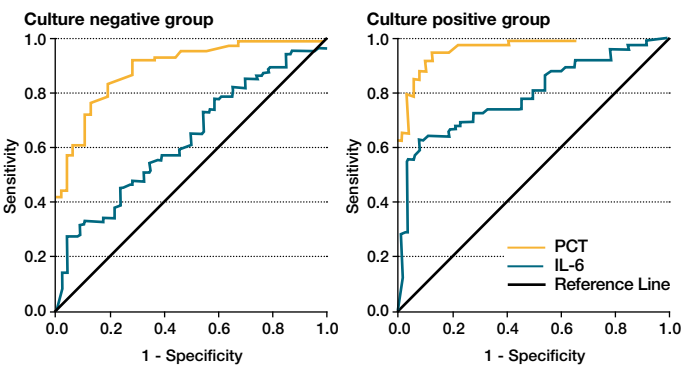

Figure PCT vs. IL-6 as a predictor of sepsis in culture-negative (AUC 0.892 vs 0.636) and culture-positive (AUC 0.959 vs 0.784) groups.

KEY FACTS

- A single value of PCT can differentiate between culture-negative sepsis and non-infectious systemic inflammatory response syndrome (SIRS), thus aiding in appropriate therapeutic continuum.
- IL-6 does not offer similar differentiation.

Diagnostic accuracy of procalcitonin for predicting blood culture results in patients with suspected bloodstream infection: An observational study of 35,343 consecutive patients

Oussalah A, Ferrand J, Filhine-Tresarrieu P et al.*
Medicine Volume 94, Number 44, November 2015

Objective

The objective of this study was to evaluate if PCT is a reliable marker for predicting bacteremia.

Design

This cross-sectional study included 35,343 consecutive patients who underwent concomitant PCT assays and blood cultures for suspected bloodstream infections.

Endpoints

The primary endpoint of this study was to investigate the diagnostic accuracy of PCT for predicting or excluding clinically relevant pathogen categories in patients with suspected bloodstream infections. The secondary endpoint was to look for organisms significantly associated with internationally validated PCT intervals.

Results

Depending on blood culture results, patients were classified into 1 of the 5 following groups: negative blood culture, Gram-positive bacteremia, Gram-negative bacteremia, fungi, and potential contaminants found in blood cultures (PCBCs).

* Department of Molecular Medicine and Personalized Therapeutics, Department of Biochemistry, Molecular Biology, Nutrition, and Metabolism, University Hospital of Nancy

- The highest PCT concentration was observed in patients with blood cultures growing Gram-negative bacteria (median 2.2 µg/L), and the lowest PCT concentration was observed in patients with negative blood cultures (median 0.3 µg/L).
- With optimal thresholds ranging from ≤0.4 to ≤0.75 µg/L, PCT had a high diagnostic accuracy for excluding all pathogen categories with the following negative predictive values: Gram-negative bacteria (98.9%) (including enterobacteria [99.2%], nonfermenting Gram-negative bacilli (NFGNB) [99.7%], and anaerobic bacteria [99.9%]), Gram-positive bacteria (98.4%), and fungi (99.6%).
- A PCT concentration ≥10 µg/L was associated with a high risk of Gram-negative (odds ratio 5.98) or Gram-positive (odds ratio 3.64) bacteremia but dramatically reduced the risk of PCBCs or fungemia.

KEY FACTS

- Use of PCT can guide the initiation of antibiotic therapy in patients with suspected bloodstream infection and prevent antibiotic exposure in low-risk patients who may not benefit from empirical antibiotic therapy pending blood culture results.
- NFGNB-PCT concentrations ≤0.6 µg/L excluded NFGNB bacteremia with an NPV of 99.7%. A significantly increased risk of NFGNB bacteremia was observed only in patients with PCT concentrations of 2 µg/L or above, thus helping to target patients at high risk for NFGNB bacteremia among those with suspected bloodstream infection pending blood culture results.
- A PCT concentration of 10 µg/L or above was associated with a high risk of Gram-positive or Gram-negative bacteremia but dramatically reduced the risk of PCBCs or fungemia, thus identifying patients who will not benefit from empirical antifungal therapy pending blood culture results.

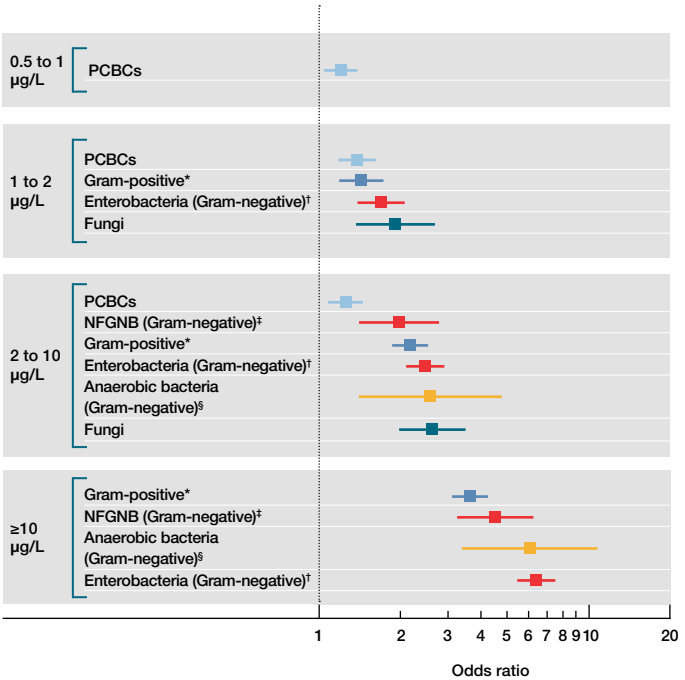

Figure Forest plot showing the odds ratios and confidence intervals of the association between PCT concentration strata and pathogen categories in a stepwise multivariate logistic regression analysis.
PCBC = potential contaminants found in blood culture
NFGNB = nonfermenting Gram-negative bacilli

* *Staphylococcus aureus, Streptococcus* (other than viridans-group streptococci), and *Enterococcus.*
† Enterobacteria: Escherichia, *Enterobacter, Klebsiella,* and *Citrobacter.*
‡ Nonfermenting Gram-negative bacilli: *Pseudomonas* and *Acinetobacter.*
§ Anaerobic bacteria: *Bacteroides.*

NOTES

thermoscientific

Clinical Diagnostics

Thermo Fisher Scientific
B·R·A·H·M·S GmbH
Neuendorfstr. 25
16761 Hennigsdorf
Germany

+49 (0)3302 883 0
+49 (0)3302 883 100 fax
info.pct@thermofisher.com
www.thermoscientific.com/brahms

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