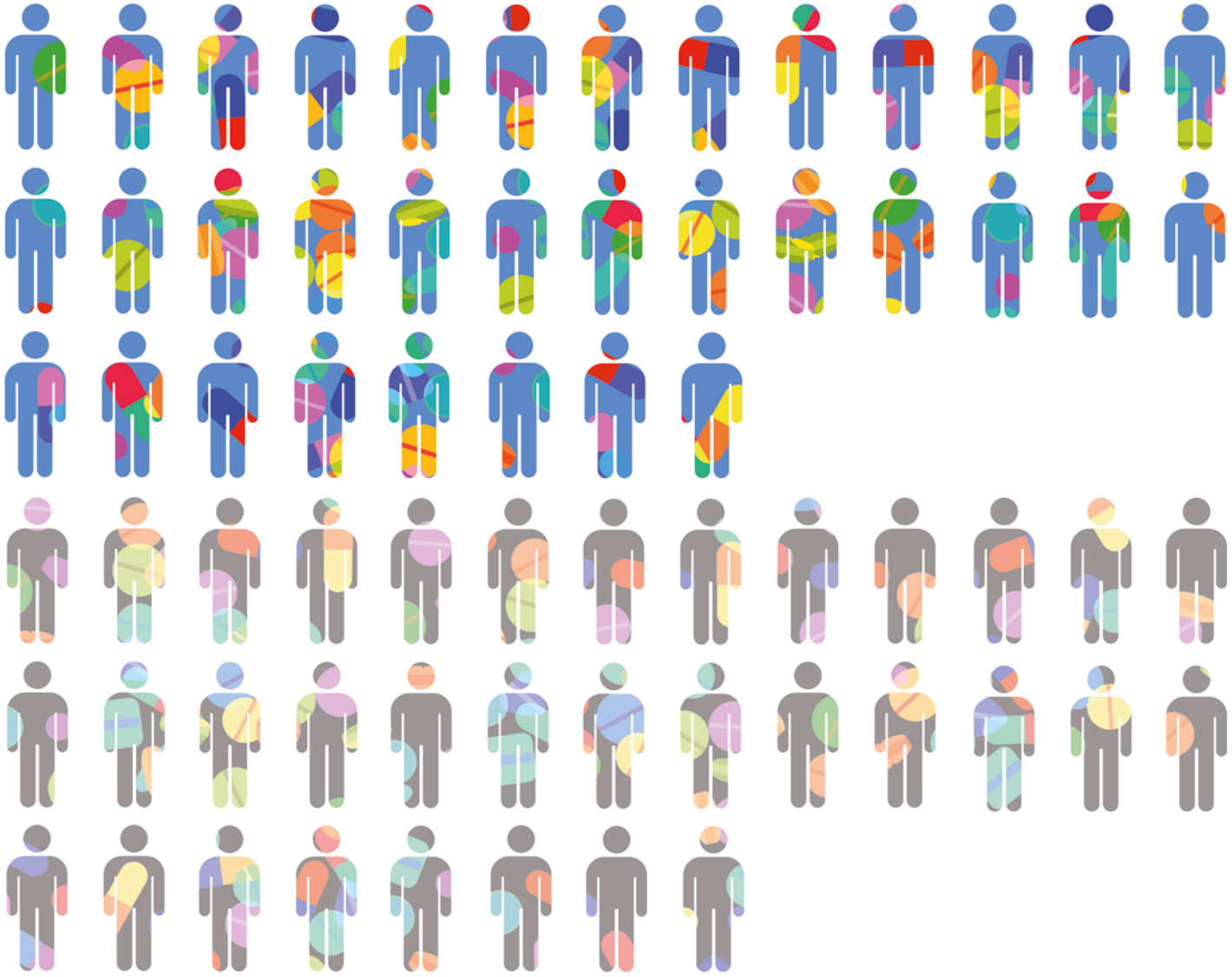
BIOMÉRIEUX

PROCALCITONIN-GUIDED ANTIBIOTIC THERAPY

Selection of publications

2018 EDITION



PIONEERING DIAGNOSTICS

“ 50% of antibiotics prescribed for acute respiratory conditions are unnecessary”[1]

“ ... antibiotic therapy is of great importance in critically ill patients, but overly long antimicrobial treatment is undesirable because of increasing antibiotic resistance”[2]

“Use of sensitive procalcitonin measurements in clinical algorithms can reduce antimicrobial overuse, decreasing the risk of side effects and controlling emerging bacterial multiresistance”[3]

PREFACE

Inappropriate and unnecessary use of antibiotics represents a significant healthcare burden, in terms of costs of treatment and the increased risk of resistant micro-organisms. Rising rates of antimicrobial resistance and the serious issue of *Clostridium difficile* infections call for **more effective antibiotic stewardship efforts** to reduce the unnecessary and prolonged use of antibiotics in self-limiting non-bacterial and resolving bacterial infections.

Procalcitonin (PCT) is a useful diagnostic biomarker, which is more specific for bacterial infections compared to other inflammatory markers (i.e. C-reactive protein) and helps to distinguish bacterial infections from other inflammatory reactions or viral infections.

PCT levels increase substantially within 4-6 hours upon stimulation and decrease daily by around 50% if the bacterial infection is controlled by the immune system supported by effective antibiotic therapy.[4] **These kinetics set PCT apart from other markers**, and have proven to be of **diagnostic and prognostic value** since they correlate with the extent and severity of infection as well as the resolution of illness.[4, 5]

Based on PCT regulation and kinetics, many studies have documented the **clinical utility of PCT in different settings** (outpatients, Emergency Departments and Intensive Care Units) to help **guide decisions to start, continue or stop antibiotic therapy** using both initial PCT levels and serial measurements.[6, 7]

In the case of **lower respiratory tract infections (LRTI)**, measurement of the initial PCT level on hospital admission has been found to **significantly reduce the initiation of antibiotic treatment**, whereas in **septic patients**, monitoring of PCT kinetics has led to **shorter durations of antibiotic exposure through early cessation of therapy.**[5]

Today, a growing body of evidence-based literature supports **the use of PCT to improve the clinical management of patients with suspicion of sepsis or LRTI and to contribute to antibiotic stewardship initiatives**[5]. Importantly, PCT-guided antibiotic therapy strategies have been demonstrated to be safe and effective for patients, without increasing the risk for mortality, adverse effects, complications, length of stay or treatment failure.[8-10]

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CRITICAL CARE AND LABORATORY MEDICINE 2015;53(4):583-92.

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Schneider J., Stojanovic I., Vargas C., *et al.*
VALUE IN HEALTH 2016;19(3):a306

➔ ADDITIONAL RECOMMENDED READING

Procalcitonin-guided Diagnosis and Antibiotic Stewardship Revisited.
Sager R, Kutz A., Mueller B., Schuetz P., *et al.*
BMC MEDICINE 2017;15:15

Effects of Procalcitonin Testing on Antibiotic Use and Clinical Outcomes in Patients with Upper Respiratory Tract Infections. An Individual Patient Data Meta-analysis.
Odermatt, J., Friedli N., Kutz A., *et al.*
CLINICAL CHEMISTRY AND LABORATORY MEDICINE 2017; 56(1):170-177.

Procalcitonin as an Early Marker of the Need for Invasive Respiratory or Vasopressor Support in Adults With Community-Acquired Pneumonia.
Self W.H., Grijalva C.G., Williams D.J., *et al.*
CHEST 2016; 150(4):819-828

Clinical Outcomes Associated With Procalcitonin Algorithms to Guide Antibiotic Therapy in Respiratory Tract Infections
Schuetz P., Briel M., Mueller B., *et al.*
JOURNAL OF AMERICAN MEDICAL ASSOCIATION 2013;309(7):717-718

Role of Procalcitonin in Managing Adult Patients With Respiratory Tract Infections.
Schuetz P., Amin D., Greenwald J.
CHEST 2012;141;1063-1073

Procalcitonin for Reduced Antibiotic Exposure in the Critical Care Setting: A Systematic Review and an Economic Evaluation.
Heyland D.K., Johnson A.P., Reynolds S. C., Muscedere J
CRITICAL CARE MEDICINE 2011;39(7):1792-1799

Procalcitonin Guidance of Antibiotic Therapy in Community-acquired Pneumonia: A Randomized Trial.
Christ-Crain M., Stolz D., Bingisser R., et al.
AMERICAN JOURNAL OF RESPIRATORY CRITICAL CARE MEDICINE 2006;174:84-93

PCT FOR DIAGNOSIS, MONITORING AND ANTIBIOTIC THERAPY GUIDANCE IN SEPSIS

CRITICAL CARE MEDICINE
2017;45(5):781–789

CLICK TO ACCESS ARTICLE

Serial Procalcitonin Predicts Mortality in Severe Sepsis Patients: Results From the Multicenter Procalcitonin MOnitoring SEpsis (MOSES) Study.

Schuetz P[1], Birkhahn R, Sherwin R, Jones AE, Singer A, Kline JA, Runyon MS, Self WH, Courtney DM, Nowak RM, Gaieski DF, Ebmeyer S, Johannes S, Wiemer JC, Schwabe A, Shapiro NI.

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

This article's objective was to investigate the relationship between a PCT decrease of >80% from baseline to day 4 and 28-day mortality in patients with severe sepsis or septic shock. This was a blinded, prospective, multicenter, observational trial involving 13 US-based emergency departments and ICUs.

858 patients who met criteria for severe sepsis or septic shock, were admitted to the ICU and had PCT measured over the first five days, were enrolled in this study. 646 of those patients were alive and in the hospital on day 4 and were included in the intent-to-diagnose analysis. A 28-day follow-up was additionally conducted to verify vital status.

The primary analyses for this study were PCT changes from baseline to day 4 and survival at 28 days. The secondary analyses were PCT change from baseline to day 1 for mortality prediction, baseline PCT for mortality prediction, and combined initial PCT, PCT change and ICU status. The primary endpoint was 28-day all-cause mortality.

28-day mortality was nearly double in patients whose PCT decreased ≤80% from baseline to day 4 compared with those whose PCT decreased >80% (20% vs. 10.4%; $P = 0.001$). Patients with a PCT increase from baseline to day 1 had an almost three-fold higher mortality than those with a short-term decrease (29% vs. 12%; $P<0.001$). This study demonstrates that PCT is a significant independent predictor of mortality even after adjusting for other clinical outcome predictors such as demographics, sepsis severity, and patient location (ICU or ward). PCT values for non-survivors were higher at baseline and stayed higher on all days compared to survivors.

In conclusion, monitoring of PCT changes over time aids in risk assessment and kinetics of PCT over the first 4 days were predictive of survival of patients diagnosed with sepsis or septic shock. Initial PCT changes (baseline to day 1) also provide important information for mortality prediction and may prove useful during early critical care management. Furthermore, the first draw in the emergency room is crucial for later risk assessment.

"Results of this large, prospective multicenter U.S. study indicate the inability to decrease procalcitonin by more than 80% is a significant independent predictor of mortality and may aid in sepsis care."

KEY POINTS

- ➔ Hospitalized patients whose PCT levels did not decrease >80% from baseline at day 4 had two times greater likelihood of dying from any cause at day 28.
- ➔ Changes in PCT levels over 5 days:
  - are strongly correlated with risk of death,
  - provide important information for prognosis,
  - can aid in the decision to discharge patients from the ICU.

THE LANCET INFECTIOUS DISEASES
2016;16(7):819–827

CLICK TO ACCESS ARTICLE

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[1], van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, Loef BG, Dormans T, van Melsen GC, Kluiters YC, Kemperman H, van den Elsen MJ, Schouten JA, Streefkerk JO, Krabbe HG, Kieft H, Kluge GH, van Dam VC, van Pelt J, Bormans L, Otten MB, Reidinga AC6, Endeman H, Twisk JW, van de Garde EM, de Smet AM, Kesecioglu J, Girbes AR, Nijsten MW, de Lange DW.

[1] VU University Medical Center, Amsterdam, Netherlands.

This trial evaluated the safety and efficacy of procalcitonin guidance in reducing duration of antibiotic use in critically ill ICU patients with a presumed bacterial infection. This was a prospective, multicenter, randomized, controlled, open-label intervention trial in 15 hospitals in the Netherlands, where 1575 patients were randomized (1:1 ratio) to a PCT-guided (n=776) or standard-of-care antibiotic (n=799) group.

The primary outcome for this study was consumption of antibiotics and duration of antibiotic treatment. The primary safety outcome was mortality at 28 days and 1 year. Secondary outcomes were the percentage of patients with recurrent infections, hospital and ICU length of stay (LOS), cost of antibiotics, and cost of PCT. The analyses for this study were intent-to-treat.

71% of the patients in the PCT-guided therapy group discontinued antibiotics in the ICU, with a median consumption of antibiotics of 7.5 daily doses vs. 9.3 daily doses for the standard of care group ($P<0.0001$). Mortality at 28 days was less at 19.6% for the PCT-guided group vs. 25% for the standard of care group ($P=0.0122$) and mortality at 1 year was 34.8% for the PCT group vs. 40.9% for standard of care ($P=0.0158$). A median reduction of antibiotic costs in the PCT-guided group was 34 Euros per patient ($P=0.0006$).

"Procalcitonin guidance stimulates reduction of duration of treatment and daily defined doses in critically ill patients with a presumed bacterial infection. This reduction was associated with a significant decrease in mortality."

KEY POINTS

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

THE LANCET
2010;375(9713):463-74

Use of Procalcitonin to Reduce Patients' Exposure to Antibiotics in Intensive Care Units (PRORATA trial): A Multicentre Randomised Controlled Trial.

Bouadma L[1], Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, Schortgen F, Lasocki S, Veber B, Dehoux M, Bernard M, Pasquet B, Régnier B, Brun-Buisson C, Chastre J, Wolff M; PRORATA trial group.

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

The purpose of this study was to evaluate whether using PCT-guided therapy in patients with sepsis is non-inferior to standard of care for mortality; this was an intent-to-treat analysis.

This study was a randomized (1:1 ratio), multicenter, prospective, parallel-group, open-label trial, of 630 patients in the PCT (n=311 patients) or control (n=319) groups. Since this was an open-label design, the investigators were blinded to the assignment before, but not after, randomization.

The primary endpoints were all-cause mortality in 28 and 60 days (non-inferiority) and the number of days without antibiotics at 28 days after inclusion (superiority), with a 10% non-inferiority margin for mortality. The secondary endpoints were relapse of superinfection, number of days without mechanical ventilation, length of stay in the hospital and ICU, days of exposure to antibiotics per 1000 inpatient days, duration of antibiotic treatment, and percentage of emerging multi-drug resistant bacteria isolated.

The outcomes of this trial demonstrated that the use of a PCT-based approach was non-inferior to standard of care in mortality at day 28 and 60. The number of days without antibiotics at 28 days was statistically significant for the PCT-guided therapy group, with an average reduction of 2.7 days of treatment (P<0.0001) (Figure 1). For the secondary endpoints, the PCT-guided arm of the study was favored statistically for days of antibiotic exposure per 1000 inpatient days (14.3 days vs 11.6 days; P<0·0001) and overall duration of antibiotic therapy (6.1 vs 9.9; P<0.0001).

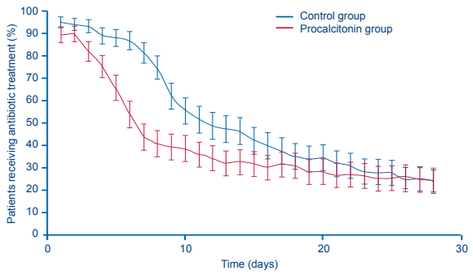


Figure 1. Patients receiving antibiotics for days 1-28. Adapted from Figure 4 - Bouadma, et al. The Lancet, 2010; 375(9713): 463 – 474.

"A procalcitonin-guided strategy to treat suspected bacterial infections in non-surgical patients in intensive care units could reduce antibiotic exposure and selective pressure with no apparent adverse outcomes."

KEY POINTS

- ➔ PCT-guided therapy to treat sepsis leads to fewer days of antibiotic use (23% relative reduction in antibiotic exposure).
- ➔ Mortality in the PCT-guided therapy group is non-inferior when compared to standard of care.

JOURNAL OF INFECTION
2016;72(2):143-51

Procalcitonin (PCT) Levels for Ruling-out Bacterial Coinfection in ICU Patients with Influenza: A CHAID Decision-tree Analysis.

Rodríguez AH[1], Avilés-Jurado FX, Díaz E, Schuetz P, Trefler SI, Solé-Violán J, Cordero L, Vidaur L, Estella Á, Pozo Laderas JC, Socias L, Vergara JC, Zaragoza R, Bonastre J, Guerrero JE, Suberviola B, Cilloniz C, Restrepo MI, Martín-Loeches I; SEMICYUC/GETGAG Working Group.

[1] Critical Care Department, Hospital Universitari de Tarragona Joan XXIII, IISPV/URV/CIBERes, Tarragona, Spain.

In this secondary analysis of a prospective, multicenter, observational study of 148 ICUs in Spain, the authors' main objective was to determine which specific biomarkers and variables are associated with co-infection in patients admitted to the ICU, using the CHAID (Chi-square Analysis Interaction Detection) analysis.

During three determined time periods, 972 patients were admitted to the ICU for influenza symptoms (also PTC-tested), who were found positive for Influenza A(H1N1) pdm09, and subsequently confirmed with or without CARC (community acquired respiratory co-infection). A CHAID decision tree model was utilized in order to analyze independent variables in each subgroup of cases.

Findings showed that PCT levels were higher in co-infected patients, making it the most important variable for identifying coinfection (84% sensitivity, 94% NPV, AUC 0.716 (95% CI 0.67-0.75)), (Figure 1), especially in the absence of shock. PCT was found to be more accurate than CRP.

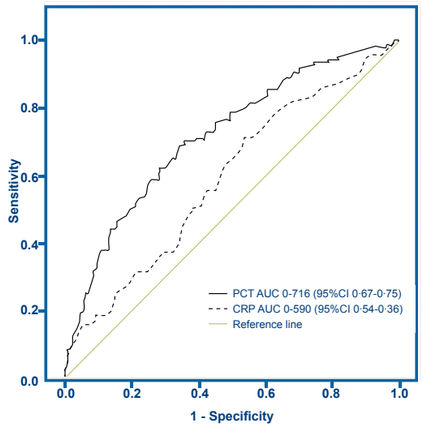


Figure 1. Area under the receiver operating characteristic (AUC) curves of procalcitonin (PCT) and C-reactive protein (CRP) for differentiation of patients with community acquired respiratory coinfection (CARC) from primary viral infection. Adapted from Figure 1 - Rodriguez, et al. Journal of Infection 2016;72(2):143-51.

"Our study showed that the most decisive variable at the time of classification was the level of PCT, with a greater discriminative value greater than other clinical variables such as the presence of shock, or the other level of CRP."

KEY POINTS

- ➔ The CHAID model is a tool that aids in helping determine stepwise pathways to detect CARC.
- ➔ In this study, PCT was shown to be a more accurate biomarker than CRP to define CARC.

➔ PCT FOR DIAGNOSIS, MONITORING AND ANTIBIOTIC THERAPY GUIDANCE IN SEPSIS

CLICK TO ACCESS ARTICLE

CRITICAL CARE
2013;17(6):R291

Procalcitonin-guided Therapy in Intensive Care Unit Patients with Severe Sepsis and Septic Shock – a Systematic Review and Meta-analysis.

Prkno A[1], Wacker C, Brunkhorst F.M., Schlattmann P.

[1] Department of Medical Statistics, Computer Sciences and Documentation, Jena University Hospital, Bachstrasse 18, D-07743 Jena, Germany.

This meta-analysis of seven randomized controlled trials involved 1075 patients with severe sepsis and septic shock, treated in surgical and medical ICUs. As this was a meta-analysis of multiple studies, the risk for bias was assessed and found to be low-to-moderate. The primary outcome was 28-day hospital mortality in severe sepsis, whereas duration of antimicrobial and length of hospital stay were the secondary outcomes. PCT assays, PCT-guided treatment algorithms, and standard of care were analyzed in each study; each group varied in their cut-off values of PCT to determine escalation or de-escalation of antibiotic treatment.

With regards to the primary outcome, no significant difference was found between the PCT-guided therapy group and standard of care. Outcomes for length of stay in the hospital and ICU were not significant either, however, this meta-analysis did find a significant reduction in the length of antibiotic treatment in the PCT-guided therapy group of approximately two days. The authors agree that utilizing PCT-guided therapy can reduce the length of antibiotic use and can decrease the risk of antimicrobial resistance in patients.

"Procalcitonin-guided therapy is a helpful approach to guide antibiotic therapy and surgical interventions […]. The major benefit of PCT-guided therapy consists of a shorter duration of antibiotic treatment compared to standard care."

KEY POINTS

- ➔ First meta-analysis to review the effect of PCT-guided therapy in ICU patients with severe sepsis or septic shock.
- ➔ This review showed that PCT-guided treatment reduces the duration of antimicrobial therapy in severe sepsis patients, without increasing 28-day and in-hospital mortality rates.

PCT-GUIDED ANTIBIOTIC THERAPY IN LOWER RESPIRATORY TRACT INFECTIONS (LRTI)

ARCHIVES OF INTERNAL MEDECINE
2012;172(9):715-722

CLICK TO ACCESS ARTICLE

Effectiveness and Safety of Procalcitonin-Guided Antibiotic Therapy in Lower Respiratory Tract Infections in "Real Life": An International, Multicenter Poststudy Survey (ProREAL).

Albrich WC[1], Dusemund F, Bucher B, Meyer S, Thomann R, Kuhn F, Bassetti S, Sprenger M, Bachli E, Sigrist T, Schwietert M, Amin D, Hausfater P, Carre E, Gaillat J, Schuetz P, Regez K, Bossart R, Schild U, Mueller B, for the ProREAL Study Team

[1] Medical University Department, Kantonsspital Aarau, Aarau, Switzerland.

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 control 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).

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 outcomes in the index hospitalization.

The study was conducted in 14 centers in Switzerland [(10)], France [(3)], and the United States [(1)]. 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. There were pre-specified criteria for overruling, but in some cases, the algorithm advice was overruled based only on clinical judgment (see Figure 1 opposite).

Results of this study demonstrated that antibiotic duration was significantly shorter (-1.51 days) if the PCT algorithm was followed compared with when it was overruled (5.9 vs 7.4 days; $P<.001$).

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.

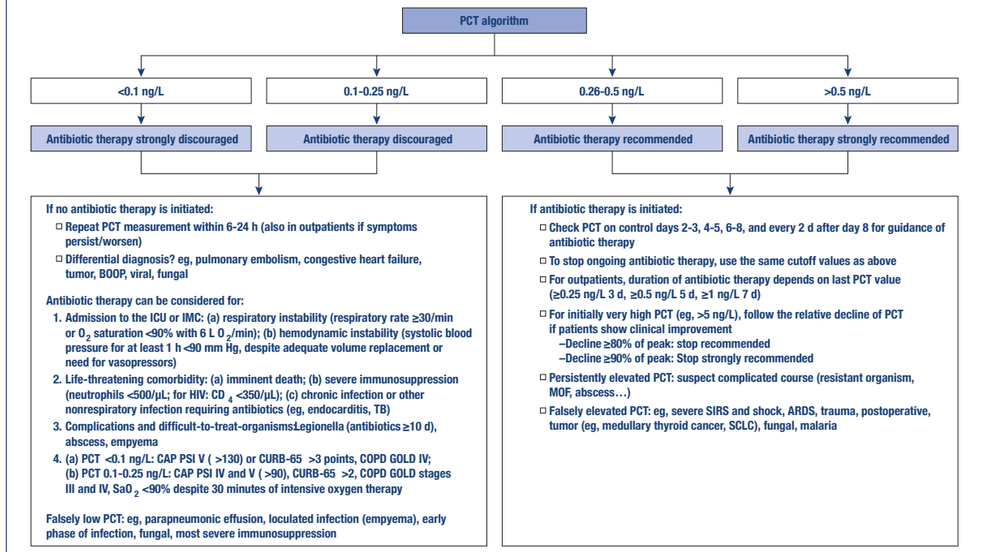
"We demonstrate that good compliance with the PCT algorithm is possible in real-life conditions but has to be reinforced to achieve optimal benefit."

KEY POINTS

- ➔ 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 depends on antibiotic-prescribing cultures, and has to be reinforced to achieve optimal benefits.
- ➔ Both VIDAS® and KRYPTOR (Thermo Fisher) demonstrated similar PCT results. VIDAS® showed ease-of-use in different settings (ED, primary care).

Figure 1: PCT Algorithm for Antibiotic Stewardship in patients with LRTI - ProREAL

Adapted from the ProREAL study: Albrich WC et al. Effectiveness and Safety of Procalcitonin-Guided Antibiotic Therapy in Lower Respiratory Tract Infections in "Real Life": An International, Multicenter Poststudy Survey (ProREAL). Arch Intern Med. 2012;172(9):715-722.



ARDS indicates acute respiratory distress syndrome; BOOP, bronchiolitis obliterans with organizing pneumonia; CAP, community-acquired pneumonia; COPD GOLD, chronic obstructive pulmonary disease Global Initiative for Chronic Obstructive Lung Disease; CURB-65, confusion, serum urea nitrogen, respiratory rate, blood pressure, and age 65 years or older; HIV, human immunodeficiency virus; ICU, intensive care unit; IMC, intermediate care unit; MOF, multiple organ failure; PSI, Pneumonia Severity Index; SCLC, small-cell lung cancer; SIRS, sepsis inflammatory response syndrome; and TB, tuberculosis.

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION
2009;302(10):1059-1066

CLICK TO ACCESS ARTICLE

Effect of Procalcitonin-Based Guidelines vs Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections: The ProHOSP Randomized Controlled Trial.

Schuetz P[1], Christ-Crain M, Thomann R Falconnier C, Wolbers M, Widmer I, Neidert S, Fricker T, Blum C, Schild U, Regez K, Schoenenberger R, Henzen C, Bregenzer T, Hoess C, Krause M, Bucher HC, Zimmerli W, Mueller B; ProHOSP Study Group

[1] Department of Internal Medicine, Kantonsspital Aarau, Tellstrasse, CH-5001 Aarau, Switzerland

This multi-center, non-inferiority, randomized controlled trial investigated the effects of PCT guidance on patients admitted to the ED departments of 6 Swiss tertiary care hospitals with symptoms of severe lower respiratory tract infections (LRTI).

The objective of the study was to examine whether a PCT algorithm can reduce antibiotic exposure without increasing the risk for serious adverse outcomes in the Emergency Department setting.

1359 patients admitted to the ED with symptoms of severe LRTI were randomized into 2 groups:

- PCT guided group: pre-defined cut-off ranges were used to initiate or stop antibiotics (see Figure 1 opposite)
- Control group: patients received antibiotic therapy according to standard guidelines.

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

Results showed that the 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 side-effects from antibiotics.

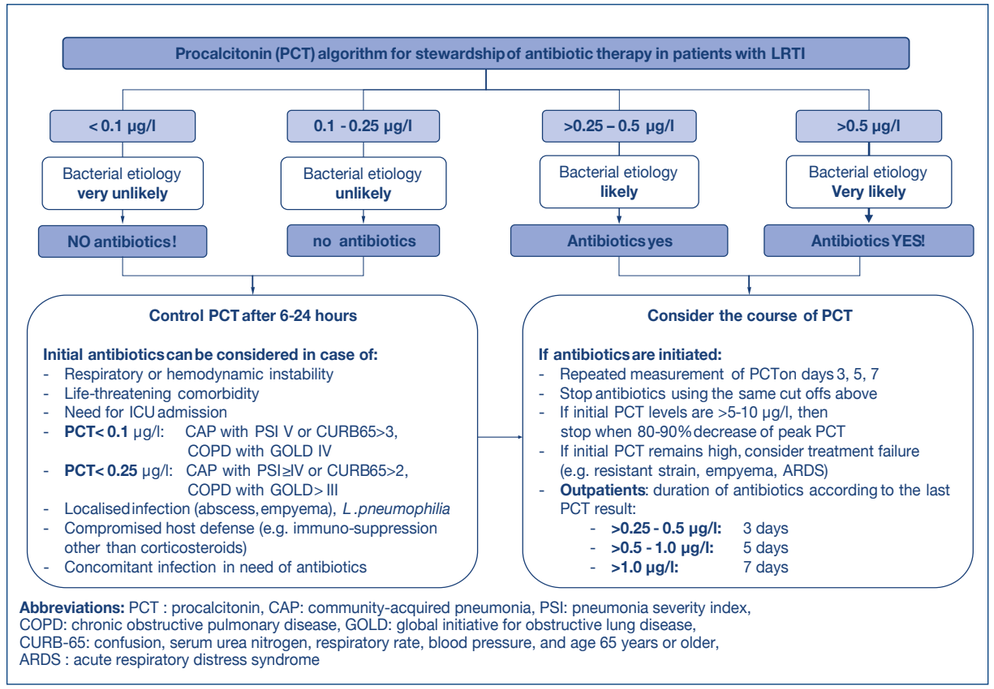
"PCT guidance will have substantial clinical and public health implications to reduce antibiotic exposure and associated risks of adverse effects and antibiotic resistance."

KEY POINTS

- ➔ Multicenter study (in both non-academic and academic hospitals), as opposed to previous single-center academic studies (ProRESP).
- ➔ This study demonstrates that within all LRTI subgroups, a PCT-guided treatment algorithm reduced antibiotic usage with no increased adverse patient outcomes.
- ➔ First study to include a primary end-point composed of many adverse outcome parameters within 30 days of ED admission.

Figure 1: PCT Algorithm for Antibiotic Stewardship in patients with LRTI - ProHOSP

Adapted from the ProHOSP study: Schuetz P, et al. Effect of Procalcitonin-Based Guidelines vs Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections: The ProHOSP Randomized Controlled Trial. JAMA 2009;302(10):1059-1066



Abbreviations: PCT : procalcitonin, CAP: community-acquired pneumonia, PSI: pneumonia severity index, COPD: chronic obstructive pulmonary disease, GOLD: global initiative for obstructive lung disease, CURB-65: confusion, serum urea nitrogen, respiratory rate, blood pressure, and age 65 years or older, ARDS : acute respiratory distress syndrome

CHEST
2007;131(1):9-19

Antibiotic Treatment of Exacerbations of COPD: A Randomized, Controlled Trial Comparing Procalcitonin-guidance with Standard Therapy.

Stolz D[1], Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Müller C, Huber P, Müller B, Tamm M.
[1] Clinics of Respiratory Medicine and Pulmonary Cell Research, University Hospital Basel, Basel, Switzerland

This prospective, interventional, single-center (RCT) study evaluated the efficacy and safety of procalcitonin (PCT) guidance to reduce antibiotic use in patients experiencing acute exacerbations of COPD (AECOPD) by comparing total antibiotic use (prescriptions and exposure) and clinical outcome between routine and PCT-guided treatment strategies.

208 adult patients > 40 years with suspected Chronic Obstructive Pulmonary Disease (COPD) exacerbations within 48 h of emergency department admission were randomized to receive antibiotic therapy based on routine practice (N=106) or based on PCT measurements (N=102).

The primary outcome was the antibiotic exposure at the index exacerbation and the subsequent antibiotic requirement for COPD exacerbation within 6 months. Secondary outcomes were clinical recovery, symptom scores, length of hospitalization, ICU stay, death, lung function, exacerbation rate, and time to next exacerbation.

In the PCT arm, a procalcitonin 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 stability of the patient's clinical condition. A PCT level of >0.25 µg/L was considered to suggest the presence of bacterial infection, and antibiotic treatment was encouraged.

Results of the study showed a reduction in antibiotic prescribing in the PCT group (40% vs 72%) compared to standard therapy and a significant sustained reduction in total antibiotic exposure for up to 6 months.

Clinical outcomes and improvement in FEV1 at 14 days and 6 months did not differ between groups. Within 6 months, the exacerbation rate, the re-hospitalization rate and mean time to the next exacerbation were similar in both groups.

"Given the prevalence of COPD and the duration of illness, a reduction in antibiotic prescriptions for the treatment of exacerbations could have a tremendous impact on the overall economic burden of the disease under current budget constraints. In addition, the controlled prescription of antibiotics decreases selective pressure for the emergence of bacterial resistance."

KEY POINTS

- ➔ In the United States, COPD affects approximately16 million adults, and is one of the fastest growing causes of morbidity and mortality. AECOPD are responsible for 2.4% of all acute medical hospital admissions and constitute the most important direct health-care costs associated with COPD.
- ➔ PCT guidance for exacerbations of COPD offers a sustained reduction in antibiotic use for the treatment of COPD both at short-term (14-21 days) and long-term (up to 6 months) follow-up.
- ➔ Overall clinical success rates in PCT-guided therapy and standard therapy group were equivalent.

ARCHIVES OF INTERNAL MEDICINE
2008;168:2000-2007

Procalcitonin-guided Antibiotic Use vs a Standard Approach for Acute Respiratory Tract Infections in Primary Care.

Briel M[1], Schuetz P, Mueller B, Young J, Schild U, Nusbaumer C, Périat P, Bucher HC, Christ-Crain M.
[1] Department of Internal Medicine, Basel Institute for Clinical University Hospital Basel, Basel, Switzerland.

The objective of this prospective, interventional, multi-center study was to assess whether PCT-guided antibiotic therapy reduces antibiotic use in patients with Acute Respiratory Tract Infections (ARTI) in a primary care setting without restricting patient's activities by more than 1 day.

The primary outcome was the number of days, within the first 14 days after baseline, during which a patient's daily activities were restricted by a respiratory tract infection. Secondary outcomes were antibiotic prescription rate, duration of actual antibiotic treatment, degree of discomfort from infection, days of work missed, days with adverse effects from medication, and the proportion of patients reporting any symptoms of an ongoing or relapsing respiratory tract infection at 28 days after baseline.

458 patients (from 53 primary care physicians) with an acute respiratory tract infection (ARTI) and in need of antibiotic treatment were randomized to receive antibiotics based on current practice guidelines (N=226) or based on PCT measurement (N=232).

For patients randomized to PCT-guided therapy, the use of antibiotics was more or less strongly discouraged (PCT level, ≤0.1 or ≤0.25 µg/L, respectively) or recommended (PCT level,≥0.25 µg/L). Follow-up data were collected at 7 days by treating physicians and at 14 and 28 days by blinded interviewers.

Results of the study demonstrated that PCT-guided therapy markedly reduces antibiotic use for ARTI in primary care without compromising patient outcome. Both patients with PCT-guided therapy (n=231) and those with standard therapy (n=224) reported a mean of 8.7 days with restricted daily activities. With PCT-guided therapy, the antibiotic prescription rate was 72% lower (95% CI, 66%-78%) than with standard therapy. Both approaches led to a similar proportion of patients reporting symptoms of ongoing or relapsing infection at 28 days (adjusted odds ratio, 1.0 [95% CI, 0.7-1.5]).

"In conclusion, this trial suggests that as an adjunct to guidelines, PCT-guided therapy can markedly reduce the use of antibiotics for acute respiratory tract infections in primary care without compromising patient outcome."

KEY POINTS

- ➔ First study of PCT-guided antibiotic prescription in the primary care setting.
- ➔ PCT-guided therapy reduced antibiotic prescription rate by 72%, without affecting patient outcome including re-infection rates.
- ➔ In practice, reduced use of antibiotics could be achieved with 1 to 2 PCT measurements in patients for whom the physician intends to prescribe antibiotics.

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CLINICAL INFECTIOUS DISEASES
2017; 65(2):183-190

Procalcitonin as a Marker of Etiology in Adults Hospitalized With Community-Acquired Pneumonia.

Self WH[1], Balk RA, Grijalva CG, Williams DJ, Zhu Y, Anderson EJ, Waterer GW, Courtney DM, Bramley AM, Trabue C, Fakhran S, Blaschke AJ, Jain S, Edwards KM, Wunderink RG.

[1] Vanderbilt University Medical Center, Nashville, Tennessee, USA.

This research article describes a large cohort study with comprehensive pathogen testing to evaluate the accuracy of PCT for discriminating between viral and bacterial pneumonia. The analysis was performed on 1735 patient samples collected upon hospital admission for the CDC Etiology of Pneumonia in the Community (EPIC) study, a prospective, multicenter, active surveillance study conducted in the United States.

All enrolled patients had clinical signs of CAP and radiographic evidence of pneumonia. Each enrolled patient underwent extensive systemic pathogen testing for bacterial and viral pathogens, and patients were grouped as follows (1) typical bacteria (detection of any bacteria other than atypicals); (2) atypical bacteria (*M. pneumoniae*, *C. pneumoniae*, or *Legionella*); (3) viral (detection of a virus without co-detection of bacteria); (4) mycobacterial/fungal; and (5) unknown (no pathogen detected). PCT concentrations were measured for each patient.

Median PCT was higher in the typical bacterial group (2.5 mg/mL) than the viral (0.09 ng/mL) or atypical bacterial (2.5 ng/mL) groups. Typical bacteria were detected in 21% of patients with PCT ≥0.5 ng/mL, and only in 3% of patients with PCT <0.1 ng/mL and 4% of patients with PCT <0.25 ng/mL. The presence of typical bacterial pathogens in patients with PCT levels <0.25 ng/mL indicates that no PCT threshold perfectly predicts the presence or absence of typical bacteria. However, higher PCT concentrations strongly correlated with increased probability of detecting bacterial pathogens, particularly typical bacteria.

The authors constructed ROC curves to evaluate the accuracy of PCT for identifying bacterial CAP. The area under the curve (AUC) was 0.73 for distinguishing between any bacterial pathogens and viral pathogens, and 0.79 for distinguishing between typical bacterial CAP versus viral and atypical CAP. A PCT cut-point of ≥0.1 ng/mL discriminated between any bacterial pathogens and viral pathogens with a sensitivity of 80.9% and a specificity of 51.6%, and discriminated between typical bacterial pathogens and atypical bacterial or viral pathogens with a sensitivity of 87.6% and a specificity of 49.3%. A PCT cut-point of ≥0.1 ng/mL discriminated between bacterial CAP and all nonbacterial CAP with a sensitivity of 80.0% and a specificity of 46.2%.

Taken together, these data demonstrate that PCT has clinical utility as an indicator of pneumonia etiology, with higher PCT values strongly indicating the presence of typical bacteria.

"Serum PCT concentration, which can be available to clinicians within 60 minutes after a simple blood draw, could be a useful adjunct in the etiologic assessment of patients hospitalized with CAP"

KEY POINTS

- ➔ Higher levels of serum PCT at hospital admission strongly correlated with increased probability of a bacterial pathogen.
- ➔ PCT is a useful tool for judging the relative likelihood of a viral or bacterial infection.

PCT-GUIDED ANTIBIOTIC THERAPY IN PEDIATRICS

THE LANCET
2017;390(10097):871-881

Procalcitonin-guided Decision Making for Duration of Antibiotic Therapy in Neonates with Suspected Early-onset Sepsis: A Multicentre, Randomised Controlled Trial (NeoPIns).

Stocker M[1], van Herk W[1], el Helou S, Dutta S, Fontana M, Schuerman F, van den Tooren-de Groot R, Wieringa J, Janota J, van der Meer-Kappelle L, Moonen R, Sie S, de Vries E, Donker A, Zimmerman U, Schlapbach L, de Mol A, Hoffman-Haringsma A, Roy M, Tomaske M, Kornelisse R, van Gijsel J, Visser E, Willemsen S, van Rossum A, and the NeoPInS Study Group.

[1] Department of Paediatrics, Neonatal and Paediatric Intensive Care Unit, Children's Hospital, Lucerne, Switzerland; Department of Paediatrics, Division of Paediatric Infectious Diseases & Immunology, Erasmus MC University Medical Centre-Sophia Children's Hospital, Rotterdam, Netherlands

The Neonatal Procalcitonin Intervention Study (NeoPIns) investigated whether PCT-guided decision making could safely shorten the duration of antibiotic therapy in newborns with suspected early onset sepsis. This multi-center randomized controlled intervention trial was carried out in a large cohort of neonates from high-income countries with a low incidence of proven early-onset sepsis: 18 hospitals in Holland (n=11), Switzerland (n=4), Canada (n=2), and the Czech Republic (n=1).

The study population included 1,710 neonates aged 34 weeks or older presenting with signs of early-onset sepsis in the first 72 hours of life and who required antibiotic therapy. The babies were randomized in a 1:1 ratio to either PCT-guided therapy (n=866) or standard therapy (n=844). Analyses were intention to treat and per-protocol. 1408 neonates were included in the per-protocol analysis (745 in the PCT group and 663 in the standard group).

Primary outcomes were superiority for duration of antibiotic therapy and non-inferiority for re-infection or death in the first month of life (margin 2·0%). Secondary outcome was length of hospital stay (LOS).

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; $P<0·0001$).

Non-inferiority for re-infection or death could not be shown due to the low occurrence of re-infections in 9 (<1%) of 1710 neonates, and the absence of study-related death. LOS was significantly shorter in the PCT group. In the intention-to-treat analysis, there was a median reduction of 3·5 hours in hospital LOS between the PCT group and the standard group (123·0 hours vs 126·5 hours, respectively; $P=0·0019$). In the per-protocol analysis, neonates in the PCT had a shorter median hospital stay of 5·2 hours (115·8 hours vs 121·0 hours, respectively; $P=0·0039$).

In conclusion, standardized risk assessment for suspected early-onset sepsis and PCT-guided decision making reduced the duration of antibiotic therapy and hospital stay, with a low rate of re-infection and without study-related mortality.

"Combining serial procalcitonin measurements with initial assessment […] supports antimicrobial stewardship and helps physicians to decide to discontinue antibiotic treatment sooner in neonates classified as having low or moderate risk of infection."

KEY POINTS

- ➔ First neonatal intervention study on suspected early-onset sepsis to show superiority (reduced duration of antibiotic treatment) of PCT-guided antibiotic therapy – thereby improving antimicrobial stewardship.
- ➔ PCT-guided decision making was shown to significantly reduce the median duration of antibiotic therapy by 9.9 hours and hospital stay by 3.3 hours compared to standard care.

JOURNAL OF THE PEDIATRIC INFECTIOUS DISEASES SOCIETY
2017 Feb 3. doi: 10.1093/jpids/piw091

Procalcitonin Accurately Identifies Hospitalized Children With Low Risk of Bacterial Community-Acquired Pneumonia.

Stockmann C[1], Ampofo K, Killpack J, Williams DJ, Edwards KM, Grijalva CG, Arnold SR, McCullers JA, Anderson EJ, Wunderink RG, Self WH, Bramley A, Jain S, Pavia AT, Blaschke AJ.

[1] University of Utah School of Medicine, Salt Lake City, USA

This retrospective study assessed whether serum PCT concentrations are associated with disease severity and the presence of viral, "typical" bacterial, or "atypical" bacterial pathogens in 532 children hospitalized with radiologically confirmed CAP and enrolled in the CDC's Etiology of Pneumonia in the Community (EPIC) study. The study further evaluated whether PCT thresholds can identify children at low risk for CAP caused by typical bacterial pathogens so they may be spared unnecessary antibiotic therapy.

Each patient sample was comprehensively tested for pathogens and classified as (1) typical bacterial pathogen(s), with or without viral and/or atypical bacteria; (2) atypical bacterial pathogen(s), with or without viral detection; (3) viral pathogen(s) only; or (4) no pathogen detected. Typical pathogens included *Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae, Staphylococcus aureus*, certain streptococci, and Gram-negative bacteria. Atypical bacteria were *Chlamydophila pneumoniae* or *Mycoplasma pneumoniae*.

Median PCT concentrations were significantly higher in children with typical bacterial pathogens (6.10 ng/mL) than in those with atypical bacteria (0.10 ng/mL), viral pathogens only (0.33 ng/mL) or no pathogens (0.44 ng/mL). No typical bacterial pathogens were detected in children with PCT concentrations <0.1 ng/mL. Thus, the PCT <0.1 ng/mL threshold had a 100% negative predictive value, which is the probability that subjects with values below this threshold do not have typical bacterial CAP. In this study, children with PCT <0.1 ng/mL accounted for 23% of the population; therefore, adoption of this cutoff may substantially reduce antibiotic exposure in children with CAP.

Elevated PCT levels were also associated with higher severity of clinical disease. The median PCT concentration was significantly higher for children admitted to the ICU (0.61 ng/mL) compared with children not in the ICU (0.24 ng/mL). PCT concentrations <0.25 ng/ml were strongly associated with a lower likelihood of detection of typical bacteria and decreased disease severity, reduced odds of ICU admission, and a 2.3 day decrease in the average hospital length of stay. The Area Under the Curve (AUC) and diagnostic accuracy of this study are illustrated in Figure 1.

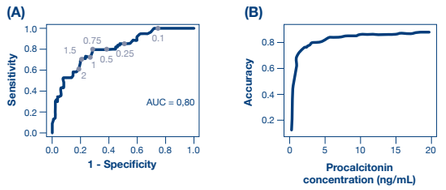

Figure 1: (A) Receiver operating curve depicting the classifier performance of procalcitonin cutoffs of <0.1, <0.25, <0.5, <0.75, <1, <1.5, and <2 ng/ml.
(B) Accuracy in identifying typical bacteria at procalcitonin concentrations ranging from 0 to 20 ng/ml. Accuracy measures how correct a diagnostic test identifies and excludes patients with a condition.
Adapted from J Pediatric Infect Dis Soc. 2017 Feb 3.

"… PCT may safely be incorporated into treatment algorithms for children with CAP to reduce antibiotic administration and duration"

KEY POINTS

- ➔ PCT concentrations <0.25 mg/mL were strongly associated with a decreased likelihood of detecting typical bacteria and decreased disease severity.
- ➔ PCT concentrations <0.1 ng/mL have a very high negative predictive value. A PCT threshold of 0.1 ng/mL accurately identifies children at extremely low risk of typical bacterial infection.
- ➔ Lower PCT concentrations were associated with less severe disease. Higher PCT concentrations were associated with an increased likelihood of ICU admission, empyema, and increased hospital length of stay.

PLOS ONE
2013; 8:e68419

Procalcitonin Guidance to Reduce Antibiotic Treatment of Lower Respiratory Tract Infection in Children and Adolescents (proPAED): A Randomized Controlled Trial.

Baer G[1], Baumann P, Buettcher M, Heininger U, Berthet G, Schäfer J, Bucher HC, Trachsel D, Schneider J, Gambon M, Reppucci D, Bonhoeffer JM, Stähelin-Massik J, Schuetz P, Mueller B, Szinnai G, Schaad UB, Bonhoeffer J.

[1] Department of Pediatrics, University Basel, Basel, Switzerland

The ProPAED trial investigated whether PCT-guided treatment could reduce antibiotic prescribing rates and therapy duration in children and adolescents with lower respiratory tract infections (LRTI) presenting to an emergency department (ED) using cut-off ranges established in trials of adults with LRTI.

The study included all children and adolescents, from 1 month to 18 years of age, presenting with LRTI to the EDs of two pediatric hospitals in Switzerland between 01/2009 and 02/2010. Eligible patients were randomized in a 1:1 ratio to either PCT-guided antibiotic treatment established for adult LRTI patients (PCT group) or to clinically guided standard care (control group).

The primary endpoint was antibiotic prescribing rate within 14 days of randomization. Secondary endpoints included duration of antibiotic treatment, antibiotic side effects, hospitalization and impairment of daily activities due to LRTI during the same period. The analyses for this study were intent-to-treat.

In total, 337 children, mean age 3.8 years (range 0.1–18), were included. In the PCT-guided group, 104 of 168 (62%) patients and in the control group, 93 of 165 (56%) patients received antibiotics. Antibiotic prescribing rates were not found to be significantly different in the PCT-guided group compared to the control group (Odds Ratio 1.26; 95% CI 0.81, 1.95). Mean duration of antibiotic exposure was reduced from 6.3 to 4.5 days in the PCT-guided group (-1.8 days; 95% CI -3.1, -0.5; $P = 0.039$) for all LRTI and from 9.1 to 5.7 days for pneumonia (-3.4 days 95% CI -4.9, -1.7; $P<0.001$). No apparent difference in impairment of daily activities between PCT-guided and control patients was observed. Rates of antibiotic side effects and hospitalizations were similar in both groups.

This trial demonstrates that PCT-guided antibiotic therapy in children and adolescents can contribute to reduced antibiotic exposure by shortening the duration of antibiotic treatment. In this study, the antibiotic prescribing rate was not affected. However, Switzerland has a low baseline prescribing rate for pediatric LRTI and the use of adult LRTI cut-off values may be too low for use in pediatric patients. Further research is recommended to define optimal PCT cut-off values for children with LRTI.

"Reducing antibiotic treatment in pediatric patients through PCT guidance could have an impact on overall antibiotic prescribing, as the burden of viral respiratory tract infections in this population is high, and there is a paucity of reliable tests to guide prudent antibiotic use."

KEY POINTS

- ➔ First major trial to investigate the impact of PCT-guided therapy in pediatric patients (children and adolescents).
- ➔ In this trial, PCT-guided therapy led to reduced antibiotic exposure in children with LRTI by reducing the duration of antibiotic treatment.
- ➔ Antibiotic prescribing rates were not significantly different in the PCT-guided group compared to the control group.

PCT-GUIDED ANTIBIOTIC THERAPY PROTOCOLS

EXPERT REVIEW OF MOLECULAR DIAGNOSTICS
2017;17(6):593-601

CLICK TO ACCESS ARTICLE

Overview of Procalcitonin Assays and Procalcitonin-guided Protocols for the Management of Patients with Infections and Sepsis.

Schuetz P[1], Bretscher C, Bernasconi L, Mueller B.
[1] Medical University Department, Kantonsspital Aarau - Endocrinology/Diabetes/Clinical Nutrition and Internal Medicine, Aarau, Switzerland

This review provides an overview of the strengths and limitations of currently available PCT assays and PCT-guided protocols when used in different clinical settings and patient populations.

Three algorithms based on setting have been suggested: low acuity, primary care settings, where admission PCT levels may provide guidance on whether antibiotics should be initiated; moderate acuity settings, such as the emergency department and medical wards, where admission and follow-up PCT levels may guide initial use of antibiotics and duration of treatment; and highest acuity settings, such as ICUs, where PCT changes over time provide guidance on discontinuation of antibiotic therapy. In patients with respiratory infections, sepsis and other infections, PCT-guided antibiotic stewardship protocols have shown utility in reducing unneeded antibiotic use (initiation and duration) and are associated with positive clinical outcomes.

A number of fully automated PCT assays are currently available and have been validated for routine clinical use. Of these, the BRAHMS PCT assays (based on BRAHMS antibodies) have been studied most extensively, including on the KRYPTOR and VIDAS® platforms. In numerous published clinical studies, the assays have shown good correlation with the reference standard (KRYPTOR) and demonstrated similar performance and reproducibility. The VIDAS® BRAHMS PCT assay has been recently cleared by the FDA for expanded use for antibiotic stewardship in patients with sepsis and lower tract respiratory infections.

Before implementing any new PCT assay in clinical practice, rigorous assessment is essential to evaluate functional assay sensitivity and clinically relevant cut-off ranges by setting and patient population. Tests, such as the Diazyme PCT and Maglumi PCT tests are not based on BRAHMS antibodies, have limited sensitivity at lower levels and require additional validation. Newly developed point of care assays include ABSOGEN™ PCT, a semi-quantitative test, which may limit its use in clinical practice. The total internal reflection-based highly sensitive fluorescence immunoassay monoclonal antibody can detect very low levels of PCT but has yet to demonstrate clinical utility in diagnosis and antibiotic decision-making.

The review concludes that, along with physician judgment, PCT levels may be used to support clinical decisions on antibiotic therapy initiation and duration. Consideration should be given to assay sensitivity, cutoffs for a specific setting and patient population and type of infection.

"Use of sensitive procalcitonin measurements in clinical algorithms can reduce antimicrobial overuse, decreasing the risk of side effects and controlling emerging bacterial multiresistance."

KEY POINTS

- ➔ Interpretation of PCT levels should consider the clinical setting, type of infection and assay characteristics.
- ➔ Newly developed PCT assays should be evaluated carefully for functional sensitivities and concordance with reference tests before routine use in clinical practice.

CURRENT OPINION IN CRITICAL CARE
2013, 19:453–460

CLICK TO ACCESS ARTICLE

Using Procalcitonin-guided Algorithms to Improve Antimicrobial Therapy in ICU Patients with Respiratory Infections and Sepsis.

Schuetz P[1], Raad I, Amin DN.
[1] University Department of Medicine, Kantonsspital Aarau, Aarau, Switzerland

This review summarized published evidence regarding the utility of PCT in the critical care setting; discussed the potential benefits and limitations of the use of PCT for clinical decision-making; and illustrated how PCT can be applied to support risk-stratification of patients at risk for sepsis to safely individualize treatment and patient management decisions.

The authors reviewed recent major meta-analyses of randomized controlled trials (RCTs) that investigated the use of PCT-guided protocols in a variety of settings, including ICU patients with respiratory tract infection and sepsis [Wacker, Lancet Inf Dis, 2013; Schuetz, Clin Inf Dis, 2012; Schuetz, Cochrane Database Syst Rev, 2012] as well as "real-life" studies [Albrich, Arch Intern Med, 2012; Schuetz, Eur J Clin Microbiol Infect Dis, 2010; Hohn, BMC Infect Dis, 2013].

This literature has largely demonstrated that the use of PCT-guided protocols to support earlier antibiotic de-escalation can significantly lower antibiotic exposure without increasing rates of mortality, relapsing infections or other adverse patient outcomes. In addition, serial PCT measurements have shown value for risk stratification of patients with sepsis in several studies. However, the use of PCT-guided protocols for escalation of antibiotics when PCT increases cannot yet be recommended in the sepsis setting [Jensen, Crit Care Med, 2011].

The review concludes that integrating PCT data in clinical algorithms improves individualized antibiotic therapy decision-making in critically ill patients with sepsis or respiratory infections. Furthermore, adding the information derived from serial PCT measurements to a thorough clinical evaluation appears to be an effective evidence-based approach for antibiotic stewardship, resulting in a more rational use of these drugs. The authors recommend that future studies should focus on further validating the use of repeat PCT measurements to risk-stratify patients, and evaluate the impact of PCT guidance in the ICU on patient outcomes.

"Inclusion of PCT data in clinical algorithms improves individualized decision-making regarding antibiotic treatment in patients in critical care for respiratory infections or sepsis."

KEY POINTS

- ➔ The findings of this review support the use of PCT-guided algorithms to improve decision-making regarding antibiotic treatment in patients with respiratory infections or sepsis in the ICU.
- ➔ The use of serial PCT measurements combined with a thorough clinical work-up is a convincing, evidence-based approach for antibiotic stewardship.

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ARCHIVES OF INTERNAL MEDICINE
2011;171:1322-31

Procalcitonin Algorithms for Antibiotic Therapy Decisions: A Systematic Review of Randomized Controlled Trials and Recommendations for Clinical Algorithms.

Schuetz P[1], Chiappa V, Briel M, Greenwald JL.
[1] Department of Emergency Medicine, Harvard School of Public Health, Boston, MA 02115, USA.

The objective of this systematic review was to summarize the design, efficacy and safety of previous European randomized controlled trials (RCTs), suggesting that PCT-guided antibiotic therapy results in reduced antibiotic use without adverse effect on clinical outcome, and to propose algorithms for use in US healthcare settings.

A systematic search was made up to 2011 in MEDLINE and EMBASE databases and in the Cochrane Central Register of Controlled Trials for RCTs using PCT levels to make antibiotic therapy decisions in adults with respiratory tract infections (RTI) and sepsis from primary care, emergency department (ED) and intensive care unit (ICU) settings.

Fourteen RCTs (n = 4467 patients) were included: 2 performed in the primary care setting (1008 patients with LRTI*), 6 in the ED (2449 patients with CAP** and AECOPD***), and 6 in the ICU (1010 patients with severe sepsis/septic shock).

Overall, no significant difference in mortality was observed between the PCT-guided and control groups (odds ratio, 0.91; 95% CI, 0.73-1.14) or in primary care (OR, 0.13; 0-6.64), ED (OR, 0.95; 0.67-1.36), and ICU (OR, 0.89; 0.66-1.20) settings individually. None of the trials reported an increase in adverse outcomes, including mortality rate.

A marked reduction in antibiotic exposure was observed in the PCT-guided groups in all settings, levels of disease acuity and patient populations, mainly due to lower prescription rates in low-acuity infections (such as bronchitis, AECOPD) in the primary care and ED settings, and shorter duration of antibiotic courses in moderate/high-acuity infections (pneumonia, sepsis) in the hospital and ICU settings.

The authors concluded that the use of PCT-guided algorithms for antibiotic therapy decisions in adult patients with RTI and sepsis can safely reduce antibiotic exposure without adversely impacting patient safety or the mortality rate. They also proposed specific PCT-guided algorithms for low-, moderate-, and high-acuity patients for use in future trials in the United States aimed at reducing antibiotic overconsumption (see Figure 1 opposite).

*LRTI – Lower Respiratory Tract Infection; **CAP – Community-Acquired Pneumonia; ***AECOPD – Acute Exacerbation of Chronic Obstructive Pulmonary Disease

"Measurement of procalcitonin levels for antibiotic decisions in patients with respiratory tract infections and sepsis appears to reduce antibiotic exposure without worsening the mortality rate."

KEY POINTS

- ➔ Major systematic review of 14 randomized controlled trials (4467 patients).
- ➔ PCT-guided protocols for antibiotic therapy decisions can safely reduce use of antibiotics without adversely impacting patient safety.
- ➔ Proposal of PCT-guided protocols based on infection acuity levels for use in US-based trials aiming to reduce overuse of antibiotics.

Figure 1: Proposed algorithms for use of procalcitonin (PCT) values to determine antibiotic treatment of infections.

Adapted from Schuetz P, et al. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. Arch Intern Med. 2011;171:1322-31.

A - Algorithm for low-acuity non-pneumonic infections (ie, low risk) in primary care and ED settings.

B - Algorithm for moderate-acuity pneumonic infections (ie, moderate risk) in hospital and ED settings.

C - Algorithm for high-acuity infections (ie, high risk; sepsis) in ICU settings.

A

Evaluation at time of admission				
PCT result	<0.10 µg/L	<0.25 µg/L	≥0.25 µg/L	>0.50 µg/L
Recommendation regarding use of Abx	Strongly discouraged	Discouraged	Encouraged	Strongly encouraged
Overruling the algorithm	Consider use of antibiotics if patients are clinically unstable, have strong evidence of pneumonia, are at high risk (ie, COPD GOLD III-IV), or need hospitalization			
Follow-up/other comments	Follow-up only needed if no symptom resolution after 1 to 2 days; if clinical situation is not improving; consider Abx if PCT level increases to≥ 0.25 µg/L		Clinical reevaluation as appropriate	

B

Evaluation at time of admission				
PCT result	<0.10 µg/L	<0.25 µg/L	≥0.25 µg/L	>0.50 µg/L
Recommendation regarding use of Abx	Strongly discouraged	Discouraged	Encouraged	Strongly encouraged
Overruling the algorithm	Consider alternative diagnosis, or Abx if patients are clinically unstable, are at high risk for adverse outcome (eg, PSI classes IV-V, immunosupression), or have strong evidence of a bacterial pathogen			
Follow-up/other comments	Reassess patients' condition and recheck PCT level after 6 to 12 hours if no clinical improvement is observed		Recheck PCT level every 2 to 3 days to consider early cessation of Abx	
Follow-up evaluation every 2 to 3 days				
PCT result	<0.10 µg/L	<0.25 µg/L	≥0.25 µg/L	>0.50 µg/L
Recommendation regarding use of Abx	Cessation of therapy strongly encouraged	Cessation of therapy encouraged	Cessation of therapy discouraged	Cessation of therapy strongly discouraged
Overruling the algorithm	Consider continuation of Abx if patients are clinically not stable			
Follow-up/other comments	Clinical reevaluation as appropriate		Consider treatment to have failed if PCT level does not decrease adequately	

C

Evaluation at time of admission				
PCT result	<0.25 µg/L	<0.50 µg/L	≥0.50 µg/L	>1.0 µg/L
Recommendation regarding use of Abx	Strongly discouraged	Discouraged	Encouraged	Strongly encouraged
Overruling the algorithm	Empirical therapy recommended in all patients with clinical suspicion of infection			
Follow-up/other comments	Consider alternative diagnosis; reassess patients condition and recheck PCT level every 2 days		Reassess patients' condition and recheck PCT level every 2 days to consider cessation of Abx	
Follow-up evaluation every 1 to 2 days				
PCT result	<0.25 µg/L or drop by> 90%	<0.50 µg/L or drop by> 80%	≥0.50 µg/L	>1.0 µg/L
Recommendation regarding use of Abx	Cessation of Abx strongly encouraged	Cessation of Abx encouraged	Cessation of Abx discouraged	Cessation of Abx strongly discouraged
Overruling the algorithm	Consider continuation of Abx if patients are clinically unstable			
Follow-up/other comments	Clinical reevaluation as appropriate		Consider treatment to have failed if PCT level does not decrease adequately	

Abx - antibiotics; COPD - chronic obstructive pulmonary disease; GOLD - Global Initiative for Chronic Obstructive Lung Disease; PSI - pneumonia severity index.

HEALTH ECONOMICS AND OUTCOMES STUDIES OF PCT

THE LANCET INFECTIOUS DISEASES
2018:18:95-107

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Effect of Procalcitonin-Guided Antibiotic Treatment on Mortality in Acute Respiratory Infections: A Patient Level Meta-Analysis.

Schuetz P[1], Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, Bouadma L, Luyt CE, Wolff M, Chastre J, Tubach F, Kristoffersen KB, Burkhardt O, Welte T, Schroeder S, Nobre V, Wei L, Bucher HC, Annane D, Reinhart K, Falsey AR, Branche A, Damas P, Nijsten M, de Lange DW, Deliberato RO, Oliveira CF, Maravić-Stojković V, Verduri A, Beghé B, Cao B, Shehabi Y, Jensen JS, Corti C, van Oers JAH, Beishuizen A, Girbes ARJ, de Jong E, Briel M, Mueller B.

[1] Medical University Department, Kantonsspital Aarau, Switzerland

This meta-analysis comprehensively assessed the safety of procalcitonin-guided treatment in patients with acute respiratory infections (ARIs) in primary care, intensive care, surgical intensive care, or emergency department settings. The analysis combined data from 6,708 patients enrolled in 26 separate randomized controlled trials in which patients with respiratory infections were randomly assigned to either a PCT-guided antibiotic treatment group or a control group. The meta-analysis relied on individual patient data rather than aggregated patient data, which allowed for harmonization of outcomes definitions.

The analysis demonstrated significant improvements in patient outcomes for the PCT-guided treatment group. Mortality at 30 days was significantly lower (8.6% vs. 10%, P = 0.037), and antibiotic related side effects were significantly reduced (16% vs. 22%, P <0.0001) in PCT guided patients compared to control patients. Mean total antibiotic exposure was also significantly lower in the PCT-guided group (5.7 days vs. 8.1 days, P <0.0001). Treatment failure, as specifically defined for each clinical setting, was less frequent in the PCT guided patients, but not significantly (23.0% vs. 24.9%, P = 0.068). No significant differences in length of hospital stay or ICU stay were observed between the two groups.

An extended version of the meta-analysis reported in this paper was published as a Cochrane Systematic Review in October 2017. Cochrane Systematic Reviews are internationally recognized as the highest standard in evidence-based health care resources and require adherence to rigorous quality standards.

"… [This meta-analysis] is the first report to describe significant and relevant improvements in clinical outcomes and specifically a decreased risk for mortality for patients with acute respiratory infections, when procalcitonin was used to guide antibiotic treatment decisions."and decreased hospital, ICU and pharmacy costs."

KEY POINTS

- ➔ This study demonstrates for the first time that PCT-guided treatment significantly improved clinical outcomes in patients with ARIs from different clinical settings
- ➔ PCT-guided treatment is associated with a decreased risk of mortality, reduced antibiotic exposure, and fewer antibiotic-related side effects compared to treatment without PCT guidance
- ➔ The meta-analysis described in this paper is the basis for a 2017 Cochrane Systematic Review which concluded that the quality of the evidence for the mortality and antibiotic exposure outcomes was high.

CRITICAL CARE MEDICINE
2017 Dec 21. doi: 10.1097/CCM.0000000000002928

CLICK TO ACCESS ARTICLE

Efficacy and Safety of Procalcitonin Guidance in Patients with Suspected or Confirmed Sepsis: A Systematic Review and Meta-Analysis

Iankova I[1], Thompson-Leduc P, Kirson NY, Rice B, Hey J, Krause A, Schonfeld SA, DeBrase CR, Bozzette S, Schuetz P.

[1] bioMérieux, Marcy-l'Étoile, France,

As part of a regulatory submission to the US FDA, a systematic review and meta-analysis of randomized controlled trials of PCT-guided therapy versus standard of care was performed. This study was conducted to summarize existing evidence on the safety and efficacy of PCT guidance in adult patients with sepsis. Ten English-language papers evaluating PCT use in this population and published between 2004 and 2016 were included in the meta-analysis.

In the PCT-guided treatment arm of these studies, physicians used both clinical judgment and PCT values when deciding to discontinue antibiotic use. Clinicians whose patients were in the PCT cohort generally adhered to the PCT algorithm (47% - 93%).

Outcomes evaluated included antibiotic duration defined as number of days on treatment; length of intensive care unit (ICU) stay, and mortality. Effectiveness of PCT was measured by the length of antibiotic treatment, and safety was measured by ICU length of stay and all-cause mortality.

A total of 3,489 patients were included in these studies. PCT-guided patients had shorter antibiotic duration compared to controls: (7.35 versus 8.85 days; P<0.001). However, ICU length of stay was not statistically significantly different between the two groups: 11.09 days in the PCT arm and 11.91 days in the control arm (P=0.329). The length of follow-up for mortality varied between studies: some studies considered in-hospital mortality and others 28-day mortality. PCT use had no adverse impact on mortality (P=0.114).

"In light of the positive effect of PCT on reducing antibiotic duration with no observed adverse impact on key safety outcomes, the use of PCT as a biomarker to guide antibiotic treatment decision-making has the potential to improve the quality of care for adults with confirmed or suspected sepsis."

KEY POINTS

- ➔ PCT-guided care is associated with reduced antibiotic duration in patients with suspected and confirmed sepsis.
- ➔ PCT-guidance had no adverse impact on mortality or length of ICU stay in this population.

THE AMERICAN JOURNAL OF MEDICINE
2017 Sep 22.doi: 10.1016/j.amjmed.2017.08.039

CLICK TO ACCESS ARTICLE

Impact of Procalcitonin Guidance with an Educational Program on Management of Adults Hospitalized with Pneumonia

Walsh TL[1], DiSilvio BE, Hammer C, Beg M, Vishwanathan S, Speredelozzi D, Moffa MA, Hu K, Abdulmassih R, Makadia JT, Sandhu R, Naddour M, Chan-Tompkins NH, Trienski TL, Watson C, Obringer TJ, Kuzyck J, Brenner DN.

[1] Allegheny General Hospital, Allegheny Health Network, Pittsburgh, PA

This paper describes a real world study of the impact of the introduction of a procalcitonin guidance algorithm on the duration of antibiotic use for adult patients with pneumonia in two teaching hospitals in Pittsburgh, Pennsylvania. This retrospective cohort study compared patient data from before and after implementation of VIDAS® B•R•A•H•M•S PCT™ testing, accompanied by education and stewardship practices to encourage adherence to the algorithm. Standard PCT cutoffs were used to discourage or recommend therapy.

The primary outcome was antibiotic treatment duration, which was significantly reduced in the post-PCT guidance group. Secondary outcomes included duration of IV antibiotics; hospital length of stay (LOS); and percentage of patients with appropriate antibiotic therapy duration (Table 1).

Table 1. Primary and secondary outcomes (Data Extracted from Paper)

Outcome	Pre-PCT Guidance (n=152)	Post-PCT Guidance (n=232)	*P* value
Mean antibiotic therapy duration (days)	9.9	6.0	$P < 0.001$
Mean IV antibiotic therapy duration (days)	5.1	3.3	$P < 0.001$
Mean hospital LOS (days)	4.9	3.5	$P = 0.006$
% patients with appropriate antibiotic therapy duration of ≤7 days	26.9%	66.4%	$P < 0.001$

Among the PCT guided group, total duration of antibiotic therapy for patients with low PCT levels (<0.25 μg/L) was compared to patients with elevated levels (≥0.25 μg/L). (Table 2). Among this population, duration of therapy was significantly shorter in the low PCT cohort.

Table 2. Outcomes in patients receiving PCT guided care by PCT level

Outcome	Peak PCT level <0.25 μg/L	Peak PCT level ≥0.25 μg/L	*P* value
Mean antibiotic therapy duration (days)	4.6	8.0	$P < 0.001$
Mean hospital LOS (days)	3.2	4.0	$P = 0.02$

"Our study demonstrates that implementation of PCT guidance, as part of a clinical decision making algorithm, in a real-world setting in the United States represents a practical method to meaningfully and safely diminish antibiotic exposure in the management of adult patients admitted with uncomplicated pneumonia."

KEY POINTS

- ➔ A real world study of PCT-guidance in patients with pneumonia replicated findings from randomized controlled trials, including significant reductions in duration of antibiotic therapy and hospital LOS compared to standard of care.
- ➔ Among patients with peak PCT values <0.25 μg/L, mean antibiotic duration was significantly shorter than in the PCT-guided groups with values of 0.25 μg/L or higher.

OPEN FORUM INFECTIOUS DISEASES
2017; Fall; 4(4):ofx213

CLICK TO ACCESS ARTICLE

Impact of Procalcitonin (PCT)-Guided Antibiotic Management on Antibiotic Exposure and Outcomes: Real World Evidence

MR Broyles[1]

[1] Five Rivers Medical Center, Pocahontas, Arkansas, USA

This study evaluated the clinical impact of introduction of PCT testing and a PCT algorithm to guide antibiotic management in a rural community healthcare facility with an established stewardship program. PCT introduction was accompanied by education on use of a PCT algorithm and stewardship practices to encourage adherence to the algorithm.

Patient data from four years before and four years after implementation of VIDAS® B•R•A•H•M•S PCT™ testing were collected. A total of 985 patients managed without PCT-guidance (the Pre-PCT cohort) and 1,167 PCT-managed patients (the Post-PCT cohort) were included in the analysis.

Median days of antibiotic therapy decreased from 17 to 9 in the post-PCT implementation group ($P<0.0001$). Significant reductions in antibiotic exposure, hospital mortality rates, 30-day readmission rates, *C. difficile* rates during hospitalization, and antimicrobial adverse drug event (ADE) rates during hospitalization were also observed (Figure 1).

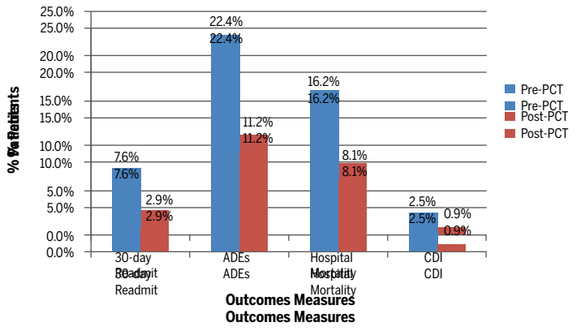

Figure 1: Comparison of outcomes measured in Pre vs. Post PCT cohorts. (Adapted from Figure 4 - Broyles. Open Forum Infect Dis., 2017; doi: 10.1093/ofid/ofx213)

"Pairing clinical assessment with trends in PCT…led to significant reductions in antibiotic exposure, hospital mortality, 30-day readmission, CDI during hospitalization, and antimicrobial ADEs during hospitalization."

KEY POINTS

- ➔ PCT guided care resulted in better patient outcomes than care guided by a mature stewardship program without PCT.
- ➔ Days of antibiotic therapy, hospital mortality rates, 30 day readmission rates, antimicrobial adverse drug events and hospital *C. difficile* infection (CDI) rates were all significantly reduced in the PCT-managed group compared to the control group.
- ➔ The observed improvements in patient outcomes were achieved by integrating PCT guidance into routine care at a small community hospital and not in the context of a highly protocolized clinical trial.

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CHEST
2017; 151(1):23-33

Effect of Procalcitonin Testing on Health-care Utilization and Costs in Critically Ill Patients in the United States.

Balk RA[1], Kadri SS, Cao Z, Robinson SB, Lipkin C, Bozzette SA.
[1] Division of Pulmonary and Critical Care Medicine, Rush Medical College and Rush University Medical Center, Chicago, IL

This retrospective database analysis used the Premier Healthcare Database to evaluate the impact of PCT guidance on day 1 of ICU admission on healthcare use and costs among patients with suspected or documented sepsis. The comparison group included patients with similar clinical and demographic characteristics without PCT guidance on their first day in the ICU. A total of 33,569 PCT managed patients were compared to 98,543 propensity-matched non-PCT patients.

Average Differences Between the Two Groups (Data Extracted from Paper)

Outcome	Mean Adjusted Value	*P* value
Total LOS (days)	-1.2	<.001
ICU LOS (days)	-0.2	0.031
Total Cost ($)	-$2,759	<.0 1
ICU Cost ($)	-$1,310	<.001
Pharmacy Cost ($)	-$331	0.002
Antibiotic Cost ($)	-$70	0.074
Lab Cost ($)	$81	0.002
Total Antibiotic Exposure (days)	-0.7	0.006

"Use of PCT testing on ICU admission was associated with a significant decrease in hospital and ICU LOS, less systemic antibiotic exposure… and decreased hospital, ICU and pharmacy costs."

KEY POINTS

- ➔ PCT-guided care is associated with reduced length of stay and lower costs.
- ➔ This study demonstrates the value and impact of PCT use in clinical practice.

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CRITICAL CARE AND LABORATORY MEDICINE
2015;53(4):583-92.

Economic Evaluation of PCT-guided Antibiotic Therapy in ARI: A US Health System Perspective.

Schuetz P[1], Balk R, Briel M, Kutz A, Christ-Crain M, Stolz D, Bouadma L, Wolff M, Kristoffersen KB, Wei L, Burkhardt O, Welte T, Schroeder S, Nobre V, Tamm M, Bhatnagar N, Bucher HC, Luyt CE, Chastre J, Tubach F, Mueller B, Lacey MJ, Ohsfeldt RL, Scheibling CM and Schneider JE.
[1] University Department of Medicine, Kantonsspital Aarau, Aarau, Switzerland.

This study is based on an individual patient-level meta-analysis of 14 clinical trials examining the impact of PCT algorithms on antibiotic initiation and/or continuation in patients with acute respiratory infection (ARI).

The clinical trials compared PCT-guided algorithms vs standard care among adult patients with ARI in 3 settings: primary care, intensive care units (ICU) and emergency departments (ED). Data on antibiotic exposure by diagnosis and setting was extracted from the meta-analysis, whereas data on lengths of stay, overall costs and practice patterns among ARI patients was adapted from US sources.

The mathematical model generated from these sources projected the likely cost impact of implementing PCT in suspected ARI versus standard care. Assumptions about use of PCT among this population were that hospital inpatients receive an initial PCT test on presentation and every other day thereafter. Among outpatients, it was assumed that a single PCT test was performed on presentation.

The annual estimated savings associated with PCT testing were over $6 million for a typical US integrated delivery network (IDN) serving 1 million members. In all 3 settings, PCT-guided care could generate cost savings for all ARI diagnoses: Overall annual outpatient cost savings were estimated at $5,329,824; inpatient cost savings were estimated at $696,777 and ICU patient cost savings at $73,326.

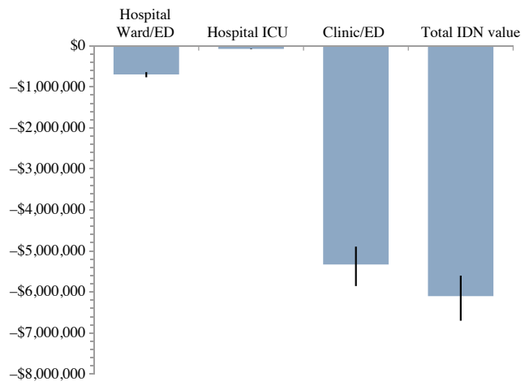

Figure 1: IDN budget impact and confidence intervals based on days of antibiotic exposure: PCT versus usual care in treatment of ARI in US hospitals, by setting, 2014. (Adapted from Schuetz P, et al. Clin Chem Lab Med. 2015; 53(4): 583–592)

"For the whole US insured population, procalcitonin-guided care would result in $1.6 billion in savings annually."

KEY POINTS

- ➔ This study demonstrates that PCT testing resulted in substantial cost savings in all 3 treatment settings.
- ➔ Savings can be achieved without any negative impact on treatment outcomes.

CLINICAL CHEMISTRY AND LABORATORY MEDICINE
2017;55(4):561-570

CLICK TO ACCESS ARTICLE

Economic Evaluation of Procalcitonin-guided Antibiotic Therapy in Acute Respiratory Infections: A Chinese Hospital System Perspective.

Stojanovic I[1], Schneider J., Wei L., Hong Z, Keane C, Schuetz P.
[1] Avalon Health Economics, 26 Washington Street, Morristown, NJ 07960, USA

As with the previous Schuetz (2015) paper on the economic evaluation of PCT-guided antibiotic therapy in the US, this study is based on an individual patient-level meta-analysis of 14 clinical trials examining the impact of PCT algorithms on antibiotic initiation and/or continuation in patients with acute respiratory infection (ARI).

The clinical trials compared PCT-guided algorithms vs standard care among adult patients with ARI in 3 settings: primary care, intensive care units (ICU) and emergency departments (ED). Data on antibiotic exposure by diagnosis and setting was extracted from the meta-analysis. Data on lengths of stay, dosages and mix of expected antibiotic therapies, costs and practice patterns were based on Chinese sources and assumed a typical urban hospital system in China.

The mathematical model generated from these sources projected the likely cost impact of implementing PCT in suspected ARI versus standard care. Assumptions about use of PCT among this population were that hospital inpatients receive an initial PCT test on presentation and every other day thereafter. Among outpatients, it was assumed that a single PCT test was performed on presentation.

Annual estimated savings of PCT-guided care were $523,963 in a typical hospital system in urban China. In all 3 settings, PCT-guided care could generate cost savings for all ARI diagnoses: approximately $369,856 in the outpatient setting; approximately $111,197 among inpatients; and approximately $38,634 for ICU patients. In China, most guidelines suggest empiric prescribing of antibiotics for ICU patients, which accounts for the relatively lower level of savings in ICUs.

"Our results show substantial savings associated with the use of PCT to guide antibiotic treatment of ARI in common Chinese treatment settings."

KEY POINTS

- ➔ PCT-guided care may reduce costs of ARI care and antibiotic exposure.
- ➔ This model shows that PCT testing more than pays for itself resulting in real savings to the Chinese healthcare system.

Poster presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Congress, 2016

Economic Evaluation Of Procalcitonin-Guided Antibiotic Therapy In Acute Respiratory Infections: A Chile Health System Perspective.

Schneider JE[1], Stojanovic I, Vargas C, Schuetz P, Giglio A.
[1] Avalon Health Economics, Morristown, NJ, USAa

ABSTRACT

Background: Mathematical models have indicated that, in the United States, the use of antibiotic stewardship protocols based on procalcitonin (PCT) levels for patients with suspected acute respiratory tract infection (ARI) results in cost savings.

Objectives: To assess the clinical and economic impact of adopting PCT testing and monitoring versus usual care among patients with suspected lower respiratory tract infection from the perspective of the Chilean public health system.

Methods: To conduct an economic evaluation of PCT testing versus usual care, we built a cost-impact model based on patient-level meta-analysis data from randomized trials. The meta-analytic data was adapted to the Chilean setting by applying Chilean data to lengths of stay, costs, and practice patterns relevant to the treatment of ARI in Chile. We estimated the annual ARI visit rate for the public system healthcare members (about 13 million people), by clinical setting (inpatient, ICU, outpatient) and ARI diagnosis.

Results: In the inpatient setting, the costs of procalcitonin-guided compared to usual care for the Chilean public health system was $1.3 billion Chilean pesos (CLP), compared to $2 billion CLP, resulting in net savings of nearly $712 million CLP to the health system for 2015. In the ICU and outpatient settings, savings were $117 million CLP and $298 million CLP, respectively. Across all three settings, the overall net savings of PCT-guided care was $1.1 billion CLP (or approximately $1.6 million USD) for the Chilean population utilizing the public health system. Results were robust for all ARI diagnoses.

Conclusions: Our results show substantial savings associated with PCT protocols for ARI across common Chile treatment settings mainly by direct reduction in unnecessary antibiotic utilization. These results are robust to changes in key parameters, and savings can be achieved without any negative impact on treatment outcomes.

Background

- Improved diagnostics and clinical biomarkers have been shown to be an important part of cost-effective medical care in acute care settings.
- Biomarkers have been shown to be very effective in aiding diagnosis and management of hospital patients with suspected systemic bacterial infections, particularly community-acquired pneumonia (CAP) and sepsis.
- The use of PCT supplies caregivers with added information, which enables them to improve the selection of patients for treatment, the timing of treatment initiation, and the overall duration of treatment.
- Procalcitonin (PCT) is a novel and effective marker of assumed bacterial infections that safely helps guide antibiotic therapy in acute respiratory tract infections and sepsis in hospitals.
- PCT has been shown to reduce antibiotic usage, with relative reductions ranging from 21% to 38% (Soni et al., 2012).
- Compared to usual care, PCT has been shown to reduce inpatient length of stay between 0 and 2.5 days, or 0-11% (ibid).
- Schuetz et al. (2012) performed a meta-analysis of patient-level data from 4,221 adults with ARI from 14 clinical trials. In addition to a marked reduction in antibiotic exposure, they found significant differences in treatment failure overall between the PCT group and the control group (19.1% and 21.9%, respectively).
- In a cost-effectiveness study, Michaelidis et al. (2013) found the likelihood of PCT use being favored (compared to usual care) was 58.4%.
- In a recent study, we developed a model depicting the economic effects of PCT-guided care versus the standard treatment approach to patients with ARI in the U.S. Our results showed that PCT-guided care if applied to the whole U.S. insured population would result in $1.6 billion in savings annually (Schuetz et al., 2015).
- The Chilean National Institute of Statistics reported in 2012 that respiratory diseases (11%) represent the third leading cause of death.
- The Ministry of Health Chile reported that patients who have respiratory conditions are responsible for 11.18% of hospital discharges.

Methods

- Patient-level data from a recently published comprehensive meta-analysis of available clinical trial data was used (Schuetz et al., 2012).
- 4,221 patients with different types of respiratory infections of varying severity, including upper respiratory infections, acute bronchitis (AB), exacerbation of chronic obstructive pulmonary disease (ECOPD), CAP and ventilator-associated pneumonia (VAP) from 14 randomized trials were included.
- The main variables from the meta-analytic database were days of antibiotic exposure and length of hospital stay by diagnosis and setting.
- To conduct the economic evaluation of PCT testing and monitoring versus usual care, we built a cost-impact model in MS Excel®.
- Patients are assumed to enter the "usual care" arm or the PCT arm.
- The perspective of the model is that of the public Chilean health system, which assumes full or partial financial risk for all care settings.
- The cost-impact model was intended to capture the current burden of managing suspected ARI and the potential impact of implementing routine PCT testing.
- The primary outcome measure was total antibiotic-related costs by setting (hospital ward/ED, hospital ICU, or clinic/ED) attributable to PCT-guided care versus usual care.
- Costs were expressed per episode ($CLP) and were converted to per-day costs using a typical average length of antibiotic therapy.
- We estimated the weighted average cost of additional antibiotics, weighted by the likelihood of receiving multiple drugs during a typical stay.

Table 1

Acute Lower Respiratory Infection Estimated Number of Cases and Mean Antibiotic Initiation Rates, Chile (2012)

		--Mean antibiotic initiation rate (b)--		
Setting/ Diagnosis	Total No. of Annual Cases (2012) (a)	PCT	Usual Care	% point difference PCT vs. Usual Care
Hospital Ward	58,136	75.7%	89.5%	-15.5
CAP	50,702	93.%	99.7%	-6.7
ECOPD	7,434	67.3% (c)	99.7% (c)	-32.5
Hospital ICU	14,262	99.7%	100.0%	-0.3
CAP	12,675	100.0%	100.0%	0.0
VAP/HAP	1,587	99.4%	100.0%	-0.6
Outpatient/ED	89,481	40.1% (c)	76.9% (c)	-47.8
AB	18,164	22.7%	65.7%	-65.5
CAP	56,553	75.4%	97.0%	-22.2
ECOPD	14,764	36.5%	67.9%	-46.2

Notes & Sources: (a) Number of annual cases and mean length of stay based on data from Chile Ministry of Health (public system); (b) Chile rates assumed to be similar to rates calculated from meta-analysis by Schuetz et al. unless otherwise noted; (c) data adjusted for Chile ARI prescribing patterns. CAP, community acquired pneumonia; ECOPD, exacerbations of chronic obstructive pulmonary disease; VAP/HAP, ventilator-associated pneumonia, also referred to as hospital-acquired pneumonia.

Table 2

Mean Antibiotic Days Among Those Initiated on Antibiotic Treatment and Mean Length of Stay/Visits Per Episode, by treatment protocol, setting and diagnosis, Chile (2014)

		---Mean Antibiotic Days (a)---		
Setting/ Diagnosis	Mean Length of Stay/Visits Per Episode	PCT	Usual Care	% Difference PCT vs. UC
Hospital Ward		7.76 (5.02)	10.73 (5.58)	-27.7%
CAP	8.5 (c)	8.10 (5.09)	11.61 (5.57)	-30.3%
ECOPD	3.3 (c)	6.81 (4.29)	8.33 (3.68)	-18.2%
Hospital ICU		10.52 (6.86)	13.73 (7.27)	-23.4%
CAP	2.3 (c)	9.39 (5.65)	14.00 (7.49) (b)	-33.0%
VAP/HAP	7.7 (c)	11.78 (7.51)	14.00 (7.07) (b)	-15.8%
Outpatient/ED		9.00 (3.18)	7.86 (3.32)	14.6%
AB	1.0 (d)	7.45 (3.02)	7.00 (2.63) (b)	6.5%
CAP	3.0 (d)	4.93 (3.34)	7.00 (3.95) (b)	-29.6%
ECOPD	4.0 (d)	4.09 (2.24)	7.00 (3.56) (b)	-41.6%

Notes & Sources: From meta-analysis by Schuetz et al., adjusted for Chile prescribing patterns; (a) standard deviations in brackets; (b) data adjusted based on Chile ARI prescribing patterns; (c) inpatient length of stay; (d) outpatient visits per episode of care. CAP, community acquired pneumonia; ECOPD, exacerbations of chronic obstructive pulmonary disease; VAP/HAP, ventilator-associated pneumonia, also referred to as hospital-acquired pneumonia.

Table 3

Cost Inputs by Setting and Diagnosis, Chile (2015 $CLP)

Diagnosis/Setting/Measure	Value (2015 CLP)
Hospital Ward Antibiotic Cost (per day)	
CAP (a)	$2,407.83
ECOPD (a)	$1,787.05
Hospital Ward Antibiotic Administration Cost (per day)	$714.93
Hospital ICU Antibiotic Cost (per day)	
CAP (b)	$5,860.36
HAP/VAP (c)	$10,074.01
Hospital ICU Antibiotic Administration Cost (per day)	$2,715.68
Outpatient Antibiotic Prescription Cost (per day)	
AB (d)	$248.19
CAP (d)	$503.95
ECOPD (d)	$630.14
Follow-up costs (per day)	
AB	$399.86
CAP	$1,002.71
ECOPD	$1,015.22
PCT Cost per Test (Chile Public System)	$7,316.05

Table 4

Health System Budget Impact of PCT versus usual care in treatment of ARI in Chile, by setting (2015 $CLP)

Protocol & Diagnosis	Total Cost of ABx ($CLP)
Hospital Ward	
PCT	
CAP	1,248,489,449
ECOPD	49,147,188
Total	1,297,636,637
Usual Care	
CAP	1,920,494,633
ECOPD	88,965,306
Total	2,009,459,939
PCT Value to Public Healthcare System	-711,823,302
Hospital ICU	
PCT	
CAP	177,861,713
VAP/HAP	150,744,135
Total	328,605,848
Usual Care	
CAP	265,277,751
VAP/HAP	180,234,650
Total	445,512,401
PCT Value to Public Healthcare System	-116,906,554
Outpatient/ED	
PCT	
AB	8,286,942
CAP	247,587,599
ECOPD	36,380,450
Total	292,254,991
Usual Care	
AB	22,549,044
CAP	452,053,011
ECOPD	115,800,180
Total	590,402,235
PCT Value to Public Healthcare System	-298,147,245
TOTAL PCT Value to Public Healthcare System	-1,126,877,100

Results

- In all three clinical settings, PCT-guided care was shown to generate cost savings across all ARI diagnoses.
- In the hospital ward, the costs of PCT-guided care for ARI patients treated in the Chilean public-sector health system was $1.3 billion CLP, compared to $2 billion CLP for the usual care group, resulting in a net savings of approximately $712 million CLP to the public health system.
- Across all three settings, PCT-guided care is associated with a total cost of $1.9 billion CLP for the 13 million public health system adult member cohort, compared to $3.0 billion CLP for the usual care group.
- Thus, overall net savings to the health system was found to be $1.1 billion CLP.

Sensitivity Analysis

- Key model parameters were increased or decreased by 20% to assess the effect of each assumption on model results, including the following model inputs: (1) percentage reduction in antibiotic days in the PCT group; (2) daily cost of antibiotics and monitoring; and (3) antibiotic resistance costs.
- Model results are most sensitive to estimates of percentage reduction in antibiotic days in the PCT group, ranging from $967 million CLP savings to $1.286 billion CLP savings.

Table 5

Sensitivity Analysis of +/- 20% Total Savings to Chile Health System (2015 $CLP)

Variable 20%	20%	Baseline	+20%
Percentage reduction in Antibiotic Days	-$967,073,661	-$1,126,877,100	-$1,286,673,222
Daily Antibiotic Costs	-$971,593,050	-$1,126,877,100	-$1,282,161,149
Cost of Antibiotic Resistance	-$1,056,766,708	-$1,126,877,100	-$1,196,987,492

Limitations

- The meta-analytic data used pertain primarily to European settings. The model was designed to account for these differences two ways–by using Chile data on lengths of stay, utilization rates, and costs, and by applying Chilean practice patterns as reflected in clinical practice guidelines.
- A key assumption was that PCT testing correlates with actual change in care management which may be different in trials compared to real life.

Conclusions:

- Across all three settings, PCT-guided care was associated with a total of $1.9 billion CLP, compared to $3 billion CLP for usual care.
- There was an overall net savings to the health system of $1.1 billion CLP ($1.6 million USD) based on all ARI patients treated in the public health system.
- These results are robust to changes in key parameters.
- Our calculations take into account the costs of the tests and the administration of the tests. The implication is that the savings are "real" savings to a health system–the tests more than pay for themselves without negatively affecting treatment outcomes.

KEY POINTS

➔ Annual estimated savings associated with PCT testing are approximately US$1.6 million for Chilean public healthcare system members (around 13 million adults).

➔ Cost savings are largely the result of reductions in unnecessary antibiotic use.

Notes

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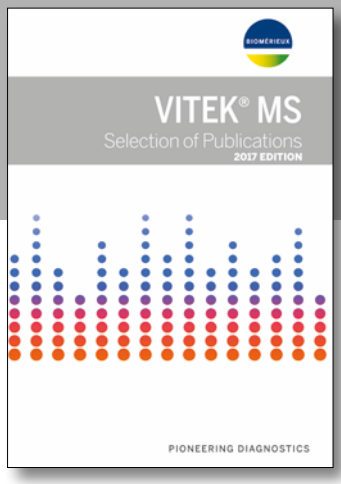

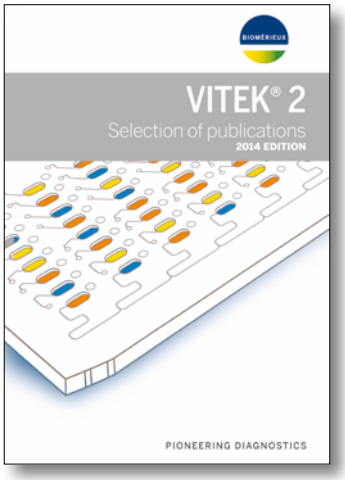

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