BIOMÉRIEUX

PROCALCITONIN-GUIDED ANTIBIOTIC THERAPY

Selection of publications

2021 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]

INTRODUCTION

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 *Clostridioides 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 upon 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]. Currently, **PCT is the only biomarker** included in Second WHO Model List of Essential *In Vitro* Diagnostics to guide antibiotic therapy or discontinuation in sepsis and lower respiratory tract infection [11].

This document provides summaries of major publications demonstrating the medical value of PCT-guided antibiotic therapy in an easy-to-read format.

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HEALTH ECONOMICS AND OUTCOMES STUDIES OF PCT

ADDITIONAL RECOMMENDED READING

Procalcitonin-guided Diagnosis and Antibiotic Stewardship Revisited.

Sager R, Kutz A, Mueller B, et al.
BMC MEDICINE 2017;15(1):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):170-77

Procalcitonin as an Early Marker of the Need for Invasive Respiratory or Vasopressor Support in Adults with Community-Acquired Pneumonia.

Self WH, Grijalva CG, Williams DJ, et al.
CHEST 2016;150(4):819-28

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):717-18

Role of Procalcitonin in Managing Adult Patients with Respiratory Tract Infections.

Schuetz P, Amin D, Greenwald J.
CHEST 2012;141(4):1063-73

Procalcitonin for Reduced Antibiotic Exposure in the Critical Care Setting: A Systematic Review and an Economic Evaluation.

Heyland DK, Johnson AP, Reynolds S C, et al.
CRITICAL CARE MEDICINE 2011;39(7):1792-99

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

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

Schuetz P, Balk R, Briel M, et al.
CRITICAL CARE AND LABORATORY MEDICINE 2015;53(4):583-92

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

Stojanovic I, Schneider J, Wei L, et al.
CLINICAL CHEMISTRY AND LABORATORY MEDICINE 2017;55(4):561-70

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

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

PCT FOR DIAGNOSIS, MONITORING AND ANTIBIOTIC THERAPY GUIDANCE IN SEPSIS

CLICK TO ACCESS ARTICLE

CRITICAL CARE MEDICINE
2017;45(5):781–89

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

Schuetz P, 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.

OBJECTIVE

The objective of this study 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.

STUDY DESIGN

Eight hundred and fifty-eight (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. Six hundred and forty-six (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.

RESULTS

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.

CONCLUSIONS

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 FINDINGS

- 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 from baseline to day 4:
  - are strongly correlated with risk of death,
  - provide important information for prognosis,
  - can aid in the decision to discharge patients from the ICU.

CLICK TO ACCESS ARTICLE

LANCET INFECTIOUS DISEASES
2016;16(7):819–27

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, 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 AC, Endeman H, Twisk JW, van de Garde EM, de Smet AM, Kesecioglu J, Girbes AR, Nijsten MW, de Lange DW.

OBJECTIVE

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.

STUDY DESIGN

This was a prospective, multicenter, randomized, controlled, open-label interventional trial in 15 hospitals in the Netherlands, where 1,575 patients were randomized (1:1 ratio) to a PCT-guided (n=776) or standard-of-care antibiotic (n=799) group.

In the PCT-guided group, physicians were advised to discontinue antibiotics if the PCT level decreased by 80% or more from peak value or to 0.5 µg/L or lower. Patients in the standard-of-care group were treated according to local antibiotic protocols.

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.

RESULTS

In the PCT-guided therapy group, 71% of the patients 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 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). The median reduction of antibiotic costs in the PCT-guided group was 34 Euros per patient (p=0.0006).

CONCLUSIONS

This large multi-center study in critically ill patients shows that PCT concentrations help physicians in deciding whether or not a presumed bacterial infection is truly of bacterial origin. Furthermore, use of a PCT-guided algorithm reduces duration of antibiotic therapy, which is one of the pillars of antibiotic stewardship. This reduction of antibiotic duration was associated with a significant decrease in mortality.

"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 FINDINGS

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

CLICK TO ACCESS ARTICLE

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, 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.

OBJECTIVE

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.

STUDY DESIGN

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 not blinded to the randomization assignment.

The primary endpoints were all-cause mortality at 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 1,000 inpatient days, duration of antibiotic treatment, and percentage of emerging multi-drug resistant bacteria isolated.

RESULTS

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 1,000 inpatient days (14.3 days *vs.* 11.6 days; p<0.0001) and overall duration of antibiotic therapy (6.1 *vs.* 9.9 days; p<0.0001).

CONCLUSIONS

This study showed that PCT-guided care in non-surgical patients in the ICU could substantially reduce antibiotic exposure and selective pressure with no apparent adverse outcomes. Reduction of selection pressure could be potentially beneficial in the current era of multi-drug resistance.

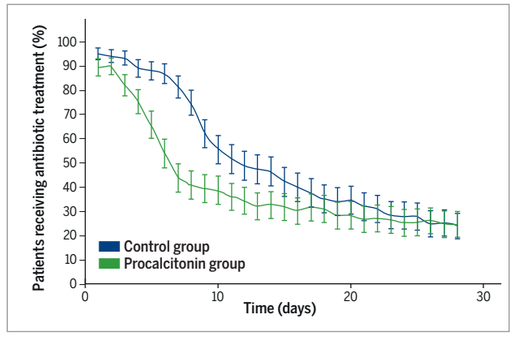


Figure 1. Patients receiving antibiotics for days 1-28.
Adapted from Bouadma L, et al. *Lancet* 2010;375(9713):463-74

"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 FINDINGS

- 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.

CLICK TO ACCESS ARTICLE

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, 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.

OBJECTIVE

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.

STUDY DESIGN

During three pre-determined time periods, 972 patients were admitted to the ICU for influenza symptoms (also PCT-tested), who were found positive for Influenza A (H1N1), 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.

RESULTS

Findings showed that PCT levels were higher in co-infected patients, making it the most important variable for identifying coinfection (84% sensitivity, 94% negative predictive value (NPV), area under the curve (AUC) 0.716 (95% CI 0.67-0.75)), especially in the absence of shock (**Figure 1**).

CONCLUSIONS

In ICU patients with confirmed influenza A (H1N1) infection without shock, PCT was found to have a high negative predictive value (94%) and seemed to be useful for excluding coinfection (for ruling out the presence of CARC). Also, in this study, PCT was more accurate than CRP.

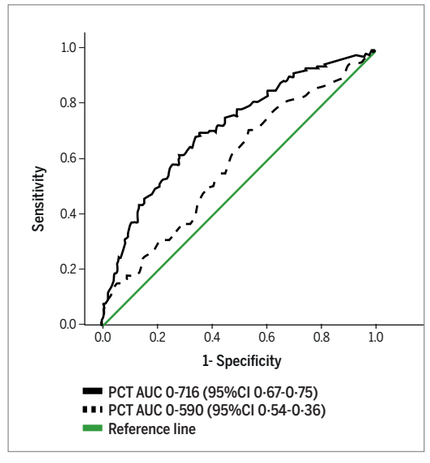


Figure 1. Area under the receiver operating characteristic (AUC) curves of procalcitonin (PCT) and C-reactive protein (CRP) for differentiation of patients with community acquired respiratory coinfection (CARC) from primary viral infection.
Adapted from Rodriguez AH, et al. *J Infect.* 2016;72(2):143-51

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

KEY FINDINGS

- PCT has a high negative predictive value (94%) and low PCT levels could be a good tool for ruling out the presence of CARC in ICU patients with confirmed influenza A (H1N1) infection and without shock.
- In this study, PCT was shown to be a more accurate biomarker than CRP to define CARC.

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

CLICK TO ACCESS ARTICLE

ARCHIVES OF INTERNAL MEDICINE
2012;172(9):715-22

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

Albrich WC, 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.

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 from real-world practice. 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).

STUDY DESIGN

The study was conducted in 14 centers in Switzerland (10), France (3), and the United States (1). One thousand eight hundred and fifty (1,850) adults with LRTI presenting to emergency departments or outpatient offices were enrolled.

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 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 (**Figure 1**).

RESULTS

Of 1,520 patients with LRTIs, the mean duration of antibiotic therapy was 6.9 days. 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; $p<0.001$).

CONCLUSIONS

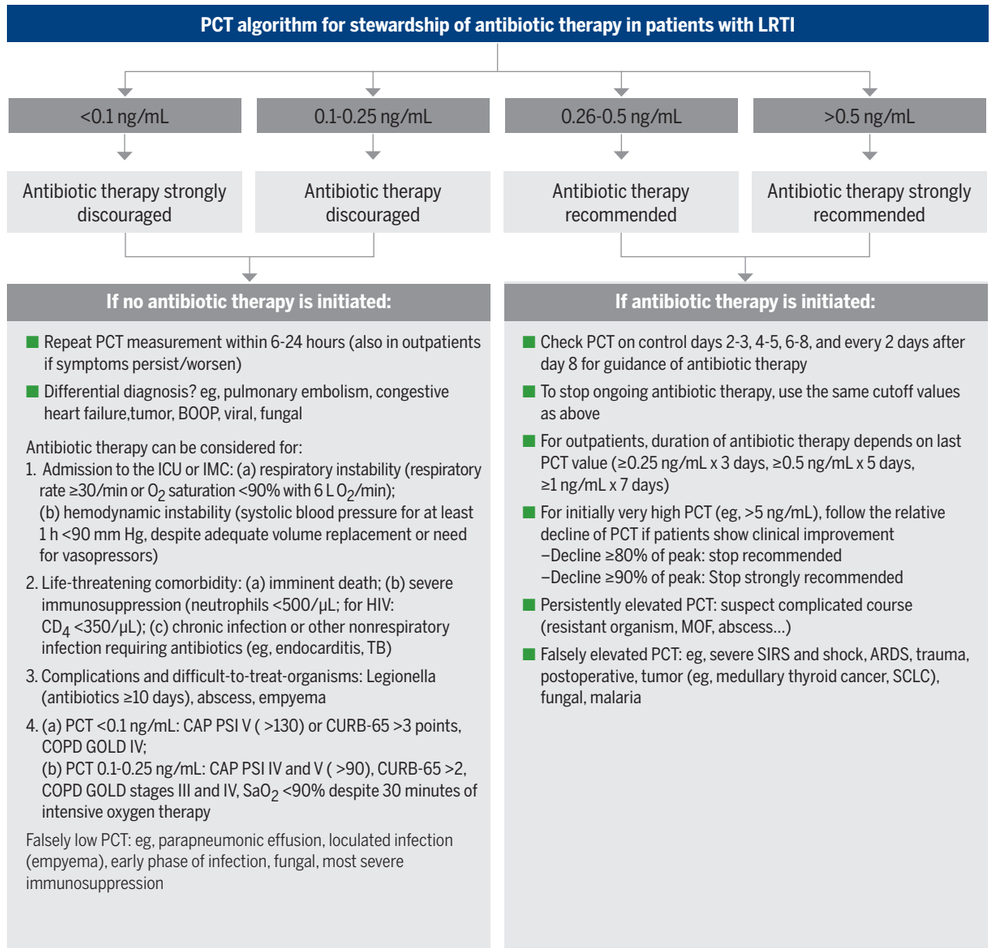
When the PCT algorithm was followed for non-initiation of antibiotics on hospital admission and early cessation of antibiotics, no increase in the risk of adverse outcomes within 30 days of follow-up was observed.

"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 FINDINGS

- 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 Albrich WC et al. *Arch Intern Med.* 2012;172(9):715-22



Abbreviations:
ARDS: 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.

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JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION
2009;302(10):1059-66

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

Schuetz P, 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.

OBJECTIVE

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

STUDY DESIGN

One thousand three hundred and fifty-nine (1,359) 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 (**Figure 1**)
- 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 antibiotic prescription rates, duration of antibiotic therapy and adverse effects.

RESULTS

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 lower in the PCT group in all patients (5.7 *vs.* 8.7 days = -34.8%), and in patient sub-groups.

CONCLUSIONS

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.

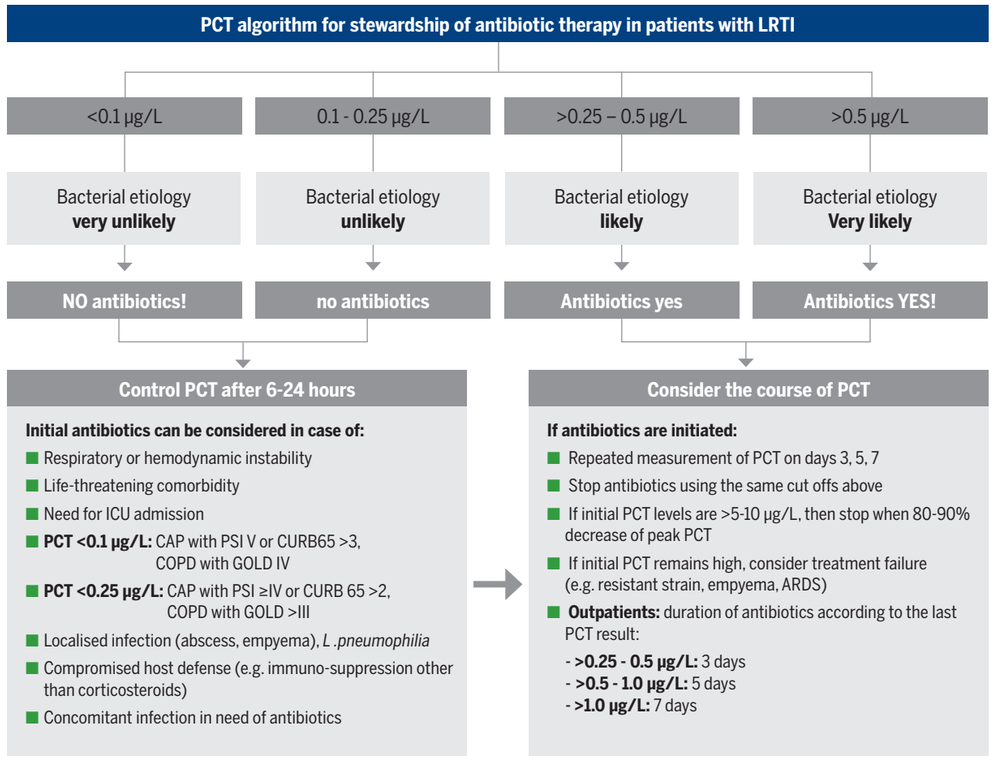
"PCT guidance will have substantial clinical and public health implications to reduce antibiotic exposure and associated risks of adverse effects and antibiotic resistance."

KEY FINDINGS

- Multicenter study performed in a mix of non-academic and academic tertiary care hospitals.
- 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.

PCT-GUIDED ANTIBIOTIC THERAPY IN LRTI

Figure 1: PCT Algorithm for Antibiotic Stewardship in patients with LRTI - ProHOSP
Adapted from Schuetz P, et al. *JAMA* 2009;302(10):1059-66



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

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CLINICAL CHEMISTRY LABORATORY MEDICINE
2018 26;56(8):1200-09

Procalcitonin Guidance in Patients with Lower Respiratory Tract Infections: A Systematic Review and Meta-Analysis.

Hey J, Thompson-Leduc P, Kirson NY, Zimmer L, Wilkins D, Rice B, Iankova I, Krause A, Schonfeld SA, DeBrase CR, Bozzette S, Schuetz P.

OBJECTIVE

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 lower respiratory tract infections (LRTI), comprising acute bronchitis, exacerbations of chronic obstructive pulmonary disease (COPD), and pneumonia.

STUDY DESIGN

Eleven English-language papers evaluating PCT use in this population and published between 2004 and 2016 were included.

In the PCT-guided treatment arm of these studies, physicians used both clinical judgment and PCT values when deciding whether to initiate and when to discontinue antibiotic use. To evaluate the effectiveness of PCT in guiding antibiotic therapy among adults with LRTI compared to standard care, the study examined the proportion of patients initiating antibiotics and length of antibiotic treatment. Safety was measured by length of hospital stay (LOS) and all-cause mortality.

RESULTS

When compared to patients treated according to standard care, patients whose treatment was guided by PCT had lower odds of initiating antibiotic treatment (odds ratio: 0.26, 95% confidence interval [CI]: 0.13; 0.52); and fewer days of antibiotic use (weighted mean difference [WMD]: -2.15 days, 95% CI: -3.30; -0.99). Patients in the PCT arm did not have a statistically different length of hospital stay (WMD: -0.15, 95% CI: -0.60; 0.30); or a statistically different risk of mortality (relative risk [RR]: 0.94, 95% CI: 0.69; 1.28).

CONCLUSIONS

The use of PCT as a biomarker for adults with LRTI reduced antibiotic use with no adverse effects on LOS or mortality.

"PCT is an effective biomarker in guiding [antibiotic] AB therapy in LRTI by reducing AB initiation and use compared to the standard of care, with no observed adverse effects on hospital LOS and all-cause mortality."

KEY FINDINGS

- PCT is a biomarker that can help guide decision-making for both the initiation and cessation of antibiotics in patients with LRTIs.
- PCT-guidance had no adverse impact on mortality or LOS in this population.
- The reduction in antibiotic use can have important implications for antimicrobial resistance and side-effects from prescribing unneeded antibiotics.

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CLINICAL INFECTIOUS DISEASES
2017; 65(2):183-90

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

Self WH, 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.

OBJECTIVE

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 1,735 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.

STUDY DESIGN

All enrolled patients had clinical signs of community-acquired pneumonia (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.

RESULTS

Median PCT was higher in the typical bacterial group (2.5 ng/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 receiver operating characteristic (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%.

CONCLUSIONS

Taken together, these data demonstrate that PCT has clinical utility as an indicator of pneumonia etiology, as higher PCT values strongly correlated with increased probability 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 FINDINGS

- 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 whether an infection is caused by a virus or bacteria.

PCT-GUIDED ANTIBIOTIC THERAPY IN PEDIATRICS

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LANCET
2017;390(10097):871-81

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, 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.

OBJECTIVE

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.

STUDY DESIGN

This multi-center randomized controlled interventional 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. 1,408 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).

RESULTS

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 1,710 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 arm had a shorter median hospital stay of 5.2 hours (115.8 hours *vs.* 121.0 hours, respectively; $p=0.0039$).

CONCLUSIONS

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 FINDINGS

- 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.

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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, 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.

OBJECTIVE

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.

STUDY DESIGN

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.

RESULTS

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.

CONCLUSIONS

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 FINDINGS

- 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.

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JOURNAL OF THE PEDIATRIC INFECTIOUS DISEASES SOCIETY
2018;7(1):46-53

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

Stockmann C, 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.

OBJECTIVE

This retrospective study assessed whether serum PCT concentrations are associated with disease severity and the presence of viral, "typical" bacterial, or "atypical" bacterial pathogens. 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.

STUDY DESIGN

The study involved 532 children hospitalized with radiologically confirmed CAP and enrolled in the CDC's Etiology of Pneumonia in the Community (EPIC) study.

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.*

RESULTS

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**.

CONCLUSIONS

In this large cohort, PCT cut-offs of <0.1 and <0.25 ng/mL accurately identified children at lower risk of typical bacterial CAP, helping to improve patient management and decreasing the use of unnecessary antibiotics. The study findings suggest that PCT may be safely incorporated into treatment algorithms for children with CAP to reduce both antibiotic use and duration.

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

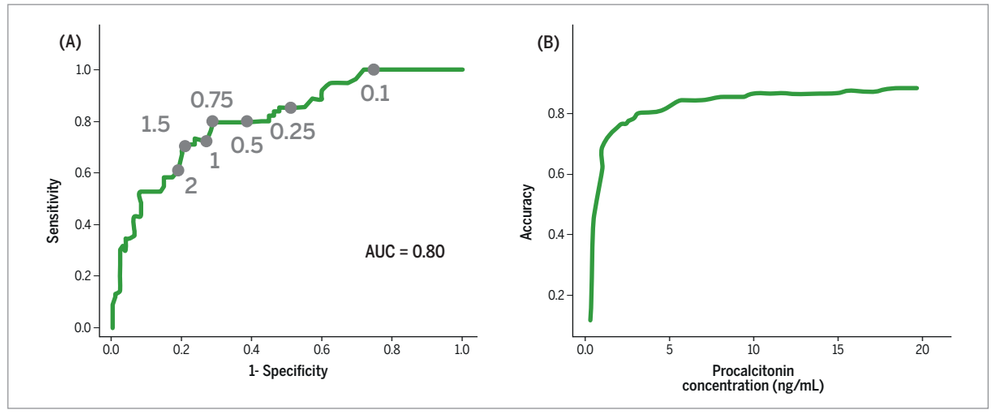
KEY FINDINGS

- PCT concentrations <0.25 ng/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.

PCT-GUIDED ANTIBIOTIC THERAPY IN PEDIATRICS

Figure 1. Discriminatory performance of several procalcitonin cutoffs in identifying children hospitalized without typical bacterial community-acquired pneumonia (CAP)

Adapted from Stockmann C, et al. *J Pediatric Infect Dis Soc.* 2018; 7(1):46-53



(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.

PCT-GUIDED ANTIBIOTIC THERAPY CONSENSUS & PROTOCOLS

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CLINICAL CHEMISTRY AND LABORATORY MEDICINE
2019;57(9):1308-18

Procalcitonin (PCT)-guided Antibiotic Stewardship: An International Experts Consensus on Optimized Clinical Use.

Schuetz P, Beishuizen A, Broyles M, Ferrer R, Gavazzi G, Gluck EH, González Del Castillo J, Jensen JU, Kanizsai PL, Kwa ALH, Krueger S, Luyt CE, Oppert M, Plebani M, Shlyapnikov SA, Toccafondi G, Townsend J, Welte T, Saeed K.

OBJECTIVE

The purpose of this international meeting was to reach agreement on algorithms for use in patients with suspicion of bacterial infection and that are easy to implement in clinical settings.

CONSENSUS PROCESS

The consensus process took place during a 1-day workshop in Berlin in late September 2018. The consensus was developed by a multidisciplinary team of 19 experts on PCT use in clinical practice, from 12 countries mirroring the different medical specialties participating in hospital ABS (antibiotic stewardship) programs.

CONSENSUS OUTCOMES AND UPDATES

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

To simplify practical application, the expert group refined the 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 disease (**Figure 1**) and one for severe disease (**Figure 2**), 0.25 µg/L and 0.5 µg/L, respectively.

Further, guidance on interpretation of PCT results to initiate, withhold or discontinue antibiotic treatment was included.

"...integration of PCT into [antibiotic stewardship] algorithms has the potential to improve the diagnostic and therapeutic management of patients presenting with respiratory illnesses and sepsis"

KEY FINDINGS

- International consensus achieved by a multidisciplinary team of 19 experts on PCT usage in clinical practice.
- PCT has shown promising results to help tailor antibiotic treatment to the individual patient, thereby reducing antibiotic exposure and improving clinical outcomes for patients with acute respiratory infections and sepsis.
- PCT supports the move from standardized care to more personalized treatment decisions, and contributes to the fight against bacterial resistance.

Figure 1. Use of PCT in patients with moderate illness outside the ICU
Adapted from Schuetz P. et al. *Clin Chem Lab Med*. 2019;57(9):1308-18

	Patient with moderate illness outside ICU (Defined by setting specific scores, e.g. qSOFA, MEDS, NEWS)			
Initial clinical assessment (Including microbiology)	**Bacterial infection uncertain**		**Bacterial infection highly suspected**	
PCT result (µg/L)	**<0.25**	**≥0.25**	**<0.25**	**≥0.25**
Probability of bacterial infection based on PCT level?	**Low probability**	**High probability**	**Low probability**	**High probability**
Overall interpretation	**Bacterial infection unlikely**	**Bacterial infection likely**	**Bacterial infection possible**	**Bacterial infection highly likely**
Antibiotic management	Use empiric Abx based on clinical judgement, consider other diagnostic tests	Use Abx based on clinical judgement	Use empiric Abx based on clinical judgement, consider other diagnostic tests	Use Abx based on clinical judgement
Recommendations for follow-up of patients	Use repeated PCT test within 6–24 h to early stop Abx to if PCT still <0.25 µg/L	Use PCT every 24–48 h for monitoring and discontinuation of Abx if PCT <0.25 µg/L or drop by 80%	Consider 2nd PCT test within 24 h to stop Abx if PCT still <0.25 µg/L	Use PCT every 24–48 h for monitoring and discontinuation of Abx if PCT <0.25 µg/L or drop by 80%

*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)

Figure 2. Use of PCT in patients with severe illness in the ICU
Adapted from Schuetz P. et al. *Clin Chem Lab Med*. 2019;57(9):1308-18

	Patient with severe illness in ICU (Defined by setting specific scores, e.g. qSOFA, SOFA, APACHE)			
Initial clinical assessment (Including microbiology)	**Bacterial infection uncertain**		**Bacterial infection highly suspected**	
PCT result (µg/L)	**<0.5**	**≥0.5**	**<0.5**	**≥0.5**
Probability of bacterial infection based on PCT level?	**Low probability**	**High probability**	**Low probability**	**High probability**
Overall interpretation	**Bacterial infection unlikely**	**Bacterial infection likely**	**Bacterial infection possible**	**Bacterial infection highly likely**
Antibiotic management	Use empiric Abx based on clinical judgement, consider other diagnostic tests	Use Abx based on clinical judgement	Use empiric Abx based on clinical judgement, consider other diagnostic tests	Use Abx based on clinical judgement
Recommendations for follow-up of patients	Use PCT within 24–48 h for monitoring and discontinuation of Abx if PCT still <0.5 µg/L	Use PCT every 24–48 h for monitoring and discontinuation of Abx if PCT <0.5 µg/L or drop by 80%	Consider 2nd PCT test within 24 h to stop Abx if PCT still <0.5 µg/L	Use PCT every 24–48 h for monitoring and discontinuation of Abx if PCT <0.5 µg/L or drop by 80%

*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)

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CLINICAL CHEMISTRY AND LABORATORY MEDICINE
2020;58(12):1983-91

Procalcitonin (PCT)-guided Antibiotic Stewardship in Asia-Pacific Countries: Adaptation based on an Expert Consensus Meeting.

Lee CC, Kwaa ALH, Apisarnthanarak A, Feng J-Y, Gluck EH, Ito A, Karuniawati A, Periyasamy P, Pratumvinit B, Sharma J, Solante R, Swaminathan S, Tyagi N, Vu DM, Zirpe K, Schuetz P.

OBJECTIVE

The recent International Experts Consensus on optimal use of procalcitonin (PCT)-guided antibiotic stewardship (AMS) focused mainly on Europe and the United States (see page 28). However, for Asia-Pacific countries, such recommendations may need adaptation due to differences in types of infections, available resources and standard of clinical care. The purpose of this expert consensus meeting for Asia-Pacific countries was to discuss what modifications to the Berlin consensus algorithm may be necessary, and derive adapted algorithms for the Asia-Pacific region.

CONSENSUS PROCESS

During a 1-day workshop in Bangkok on September 21, 2019, a multidisciplinary team of 16 experts from 12 Asia-Pacific countries discussed practical experience with PCT-guided AMS, and the applicability of the Berlin consensus algorithms for the Asia-Pacific region.

CONSENSUS OUTCOMES

The expert group observed that, overall, the existing evidence for PCT-guided AMS in patients with acute respiratory infections and sepsis is also generally valid for Asia-Pacific countries.

The group reached consensus on an approach based on two adapted PCT algorithms, one for critically ill (**Figure 1**) and one for non-critically ill (**Figure 2**) patients. This approach aims to simplify optimal use of PCT in clinical routine in Asia-Pacific countries. Initially, patients should be stratified according to clinical criteria and probability of bacterial infection (uncertainty vs. high suspicion of bacterial infection), followed by a PCT test based on the following cut-offs:

- <0.25 µg/L in non-critically ill patients,
- <0.5 µg/L in critically ill patients indicating low likelihood of bacterial infection.

However, due to an insufficient database on patients with tropical diseases in the Asia-Pacific patient population, the experts do not currently recommend use of these algorithms in such patients. Furthermore, the algorithms should be used in acute infections, but not in patients with chronic infections (e.g. abscess, osteomyelitis, endocarditis). These points are reflected in the adapted algorithms.

CONCLUSIONS

Use of PCT to guide antibiotic stewardship can significantly improve the utilization of antibiotic treatment in Asia-Pacific countries. However, adaptations of existing PCT algorithms are required due to differences in types of infections and routine clinical care. In particular, the lack of scientific data for tropical diseases underlines the need for further research to understand the optimal use of PCT and interpretation of results in such cases.

"Use of PCT to guide antibiotic stewardship in conjunction with continuous education and regular feedback to all stakeholders has high potential to improve the utilization of antibiotic treatment also in Asia-Pacific countries."

KEY FINDINGS

- The expert group agreed that the existing evidence for PCT-guided antibiotic stewardship in patients with acute respiratory infections and sepsis is also largely valid for Asia-Pacific countries.
- The experts decided that two adapted algorithms, one for the critically ill and one for the non-critically ill patient population would be most relevant to optimize use of PCT in clinical routine in Asia-Pacific countries.
- Following patient stratification based on clinical criteria and probability of bacterial infection, PCT should be added to patient assessment based on the following cut-offs:
  <0.25 µg/L in non-critically ill patients,
  <0.5 µg/L in critically ill patients indicating low likelihood of bacterial infection.

Figure 1. Algorithm for use of PCT in critically ill patient populations
Adapted from Lee CC. et al. *Clin Chem Lab Med.* 2020;58(12):1983-91

	Critically ill patients				
Initial clinical assessment (Including microbiology)	**Bacterial infection uncertain**		**Bacterial infection highly suspected**		**Suspected tropical disease****
Initial antibiotic management	**Use empiric Abx based on clinical judgment, consider to do a baseline PCT level and other diagnostic tests**				
Follow-up PCT result (µg/L)	**<0.5 or drop ≥80%**	**≥0.5 or <80%**	**<0.5 or drop ≥80%**	**≥0.5 or <80%**	
Probability of bacterial infection based on PCT kinetics?	**Low probability**	**High probability**	**Low probability**	**High probability**	
Overall interpretation	**Ongoing bacterial infection unlikely**	**Ongoing bacterial infection likely**	**Ongoing bacterial infection unlikely**	**Ongoing bacterial infection highly likely**	
Antibiotic management during follow-up	Consider stopping Abx if clinical situation is favorable	Use repeated PCT or monitoring and discontinuation of Abx if PCT <0.5 µg/L or drop by 80%	Consider stopping Abx if clinical situation is favorable	Consider treatment failure, Monitor PCT for discontinuation of Abx if PCT <0.5 µg/L or drop by 80%	PCT kinetics may help to assess prognosis

*Caution in patients with immunosuppression (including HIV), CF, pancreatitis , trauma, pregnancy, high volume transfusion, PCT-guided stewardship should not be applied to patients with chronic infections (e.g., abscess , osteomyelitis , endocarditis)
**Tropical diseases include, but are not limited to, malaria, dengue lever, hemorrhagic lever, typhus and others

Figure 2. Algorithm for use of PCT in non-critically ill patient populations
Adapted from Lee CC. et al. *Clin Chem Lab Med.* 2020;58(12):1983-91

	Non Critically ill patients				
Initial clinical assessment (Including microbiology)	**Bacterial infection uncertain**		**Bacterial infection highly suspected**		**Suspected tropical disease****
PCT result (µg/L)	**<0.25**	**≥0.25**	**<0.25**	**≥0.25**	
Probability of bacterial infection based on PCT kinetics?	**Low probability**	**High probability**	**Low probability**	**High probability**	
Overall interpretation	**Bacterial infection unlikely**	**Bacterial infection likely**	**Bacterial infection possible**	**Bacterial infection highly likely**	
Antibiotic management	Consider to with hold Abx in non-severe patients*, look for other diagnoses	Use Abx based on clinical judgment	Use empiric Abx based on clinical judgment. Look for other diagnoses	Use Abx	Use Abx based on clinical judgment
Recommendations for follow-up of patients	If clinically indicated, consider 2nd PCT test within 6-24h before sending home	Use repeated PCT or monitoring and discontinuation of Abx if PCT <0.25 µg/L or drop by 80%	Consider 2nd PCT test within 24h to stop Abx if PCT still <0.25 µg/L	Use repeated PCT or monitoring and discontinuation of Abx if PCT <0.25 µg/L or drop by 80%	PCT kinetics may help to assess prognosis

*Caution in patients with immunosuppression (including HIV), CF, pancreatitis , trauma, pregnancy, high volume transfusion, PCT-guided stewardship should not be applied to patients with chronic infections (e.g., abscess , osteomyelitis , endocarditis)
**Tropical diseases include, but are not limited to, malaria, dengue lever, hemorrhagic lever, typhus and others

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JOURNAL OF THORACIC DISEASE
2020;12(SUPPL 1):S5-S15

Role of Procalcitonin Use in the Management of Sepsis.

Gregoriano C, Heilmann E, Molitor A, Schuetz P.

OBJECTIVE

The purpose of this review was to provide an overview about the current knowledge of procalcitonin (PCT) use in the treatment of critically ill patients with sepsis based on existing study results.

REVIEW FINDINGS

This review covered the following aspects of procalcitonin:

- **Procalcitonin as a diagnostic biomarker for bacterial infection and sepsis**
  PCT is one of the most investigated host-directed biomarkers. Its synthesis pathway can vary depending on different inflammatory states. Due to cytokines released during viral infections that inhibit the production of TNF-alpha, PCT synthesis is not induced in most viral infections. Furthermore, PCT has a wide biological range, is rapidly induced following bacterial stimulation and has a long half-life. It therefore has good discriminatory properties for the differentiation between bacterial and viral infections with rapidly available results. PCT per se cannot isolate or detect specific pathogens, but the level of PCT may be useful to estimate the probability of a severe bacterial infection.
- **Procalcitonin as a prognostic biomarker for risk assessment in patients with severe infection and sepsis**
  PCT values correlate with severity of illness and serial measurements have prognostic implications. PCT kinetics over time can improve the monitoring of critically ill patients with sepsis, since decreasing PCT values correlate with good outcomes and increasing values are associated with adverse outcomes, such as mortality.
- **Procalcitonin as a therapeutic biomarker for antibiotic stewardship in patients with severe infection and sepsis**
  In 2017, the US Food and Drug Administration (FDA) approved the use of PCT for antibiotic stewardship. This decision was based on systematic reviews and meta-analyses of randomized controlled trials (RCTs) which analyzed infections of varying severity in different clinical settings ranging from primary care to ICU. These RCTs investigated and demonstrated the efficacy and safety of PCT-guided antibiotic therapy.
- **Practical considerations for use of procalcitonin testing**
  The proACT[1] trial showed low compliance rates with the PCT protocol, indicating a lack of experience by physicians in the use and interpretation of PCT in a clinical context. Repeated education for antibiotic stewardship could help physicians gain more confidence in PCT testing, as confirmed by a retrospective cohort study by Broyles et *al*[2]. Education-based antibiotic stewardship, including the use of PCT measurements, could lead to reduced antibiotic prescriptions and lower resistance rates.
- **Limitations of procalcitonin**
  Very limited data about the use of PCT in immunosuppressed patients including patients with HIV, cystic fibrosis, pancreatitis, trauma, pregnancy and high-volume transfusion is available. Furthermore, certain non-infectious disorders, such as C-cell carcinoma or trauma, can lead to a systemic inflammation resulting in elevated PCT levels. The use of PCT-guided stewardship is not recommended in patients suffering from a chronic infection such as osteomyelitis or endocarditis, since observational studies were unable to identify any benefit and interventional investigations in this context are still lacking.

CONCLUSIONS

Serial PCT measurement and continuous education for antibiotic stewardship could be advantageous for physicians.

[1] Huang DT, et al. *New England Journal of Medicine* 2018;379(3):236-249 • [2] Broyles MR, et al. *Open Forum Infectious Diseases* 2017;4(4):ofx213

"Through education-based antibiotic stewardship, which includes also the use of PCT measurements, a reduction of antibiotic prescriptions and lower resistance rates could be achieved."

KEY FINDINGS

- PCT is the best studied biomarker regarding antibiotic stewardship and has good discriminatory properties to differentiate between bacterial and viral infections.
- PCT values are not intended to replace good clinical practice, but should be used as a complementary tool combined with available clinical and diagnostic parameters.

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

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

Schuetz P, Bretscher C, Bernasconi L, Mueller B.

OBJECTIVE

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.

REVIEW FINDINGS

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;
- 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 B·R·A·H·M·S PCT™ assays (based on B·R·A·H·M·S 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® B·R·A·H·M·S 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 which are not based on B·R·A·H·M·S antibodies may have limited sensitivity at lower levels and require additional validation. Newly developed semi-quantitative point of care assays may be of limited 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.

CONCLUSIONS

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 FINDINGS

- 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.

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ARCHIVES OF INTERNAL MEDICINE
2011;171(15):1322-31

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

Schuetz P, Chiappa V, Briel M, Greenwald JL.

OBJECTIVE

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.

REVIEW FINDINGS

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=4,467 patients) were included: 2 performed in the primary care setting (1,008 patients with LRTI*), 6 in the ED (2,449 patients with CAP** and AECOPD***), and 6 in the ICU (1,010 patients with severe sepsis/septic shock).

REVIEW FINDINGS

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.

CONCLUSIONS

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 (**Figure 1**).

*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 FINDINGS

- Major systematic review of 14 randomized controlled trials (4,467 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 PCT values to determine antibiotic treatment of infections
Adapted from Schuetz P, et al. *Arch Intern Med.* 2011;171(15):1322-31

A LOW-ACUITY NON-PNEUMONIC INFECTIONS (i.e., LOW RISK) IN PRIMARY CARE AND ED SETTINGS

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**
Over ruling 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 MODERATE-ACUITY PNEUMONIC INFECTIONS (i.e., MODERATE RISK) IN HOSPITAL AND ED SETTINGS

EVALUATION AT TIME OF ADMISSION				
PCT result	**<0.1 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**
Over ruling 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**
Over ruling 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 HIGH-ACUITY INFECTIONS (i.e., HIGH RISK) IN ICU SETTINGS

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**
Over ruling 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.

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CURRENT OPINION IN CRITICAL CARE
2013;19(5):453-60

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

Schuetz P, Raad I, Amin DN.

OBJECTIVE

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 with presumed sepsis to safely individualize treatment and patient management decisions.

METHODS

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].

RESULTS

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 .

CONCLUSIONS

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 FINDINGS

- 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.

HEALTH ECONOMICS AND OUTCOMES STUDIES OF PCT

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PLOS ONE
2019;14(4):E0214222

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, Broyles MR, Nguyen HB, Steuten LM.

OBJECTIVE

This study aimed to compare the effectiveness and costs of procalcitonin (PCT)-guided care *versus* standard care to optimize antibiotic prescription in hospitalized patients diagnosed with suspected sepsis or lower respiratory tract infection (LRTI) in the US.

STUDY DESIGN

A previously published health economic decision model was used to compare the costs and the effects of PCT-guided care (**Figures 1 and 2**). The analysis took into account the societal and hospital impact and costs over the length of hospital stay. The main outcomes analyzed were:

- total difference in costs per patient (including treatment costs and productivity losses),
- number of patients with antibiotic resistance or *C. difficile* infections,
- costs per antibiotic day avoided.

RESULTS

Table 1. Results of implementation of a PCT-guided algorithm on main outcomes analyzed
Data extracted from Mewes JC, et al. *PLoS One* 2019;14(4):e0214222

Sepsis Patients	Results
Reduction in antibiotic therapy days	5.83
Reduction in LOS (ICU)	3.6
Reduction of mechanical ventilation days (ICU)	2
Savings per patient cost in PCT Arm VS Standard of Care (SOC)	$11,311
% sepsis patients with Antibiotic Resistance (ABR) was smaller in PCT arm	6.40%
Reduction in *C. difficile* infections	54.80%

CONCLUSIONS

PCT-guided care for hospitalized patients with suspected sepsis and LRTI was associated with:
- a reduction in antibiotic treatment days,
- shorter length of stay on the regular ward and the intensive care unit,
- shorter duration of mechanical ventilation,
- reduced risk of antibiotic-resistant or *C. difficile* infections.

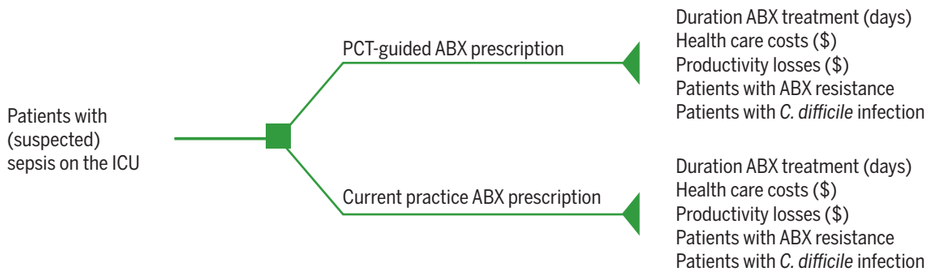
Significant cost-savings were observed in the PCT-guided group *vs.* standard care for both sepsis and LRTI patient populations.

"Using a Procalcitonin-algorithm to guide antibiotic use in sepsis and hospitalised lower respiratory tract infection patients is expected to generate cost-savings to the hospital and lower rates of antibiotic resistance and C.difficile infections."

KEY FINDINGS

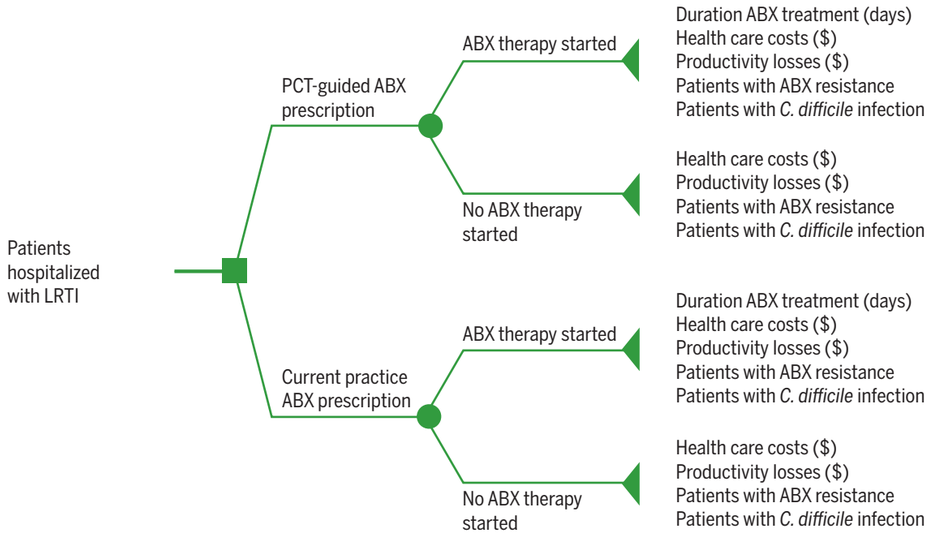
- **In the PCT group, total costs were reduced by 26.0% in sepsis and 17.7% in LRTI (total incremental costs of −$11,311 per patient and −$2,867 per patient respectively) *vs.* standard care.**
- **Using a PCT-guided algorithm can lead to hospital cost-savings and lower rates of antibiotic resistance and *C. difficile* infections.**

Figure 1. Decision tree for patients with sepsis
Adapted from Mewes JC, et al. *PLoS One* 2019;14(4):e0214222



ABX: antibiotics

Figure 2. Decision tree for patients with LRTI
Adapted from Mewes JC, et al. *PLoS One* 2019;14(4):e0214222



ABX: antibiotics

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AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE
2020; DOI.10.1164/RCCM.202004-1201OC

Procalcitonin to Reduce Long-Term Infection-associated Adverse Events in Sepsis: A Randomized Trial.

Kyriazopoulou E, Liaskou-Antoniou L, Adamis G, Panagaki A, Melachroinopoulos N, Drakou E, Marousis K, Chrysos G, Spyrou A, Alexiou N, Symbardi S, Alexiou Z, Lagou S, Kolonia V, Gkavogianni T, Kyprianou M, Anagnostopoulos I, Poulakou G, Lada M, Makkina A, Roulia E, Koupetori M, Apostolopoulos V, Petrou D, Nitsotolis T, Antoniadou A, Giamarellos-Bourboulis EJ.

OBJECTIVE

The objective of this study was to assess the impact of PCT-guided discontinuation of antimicrobials on the incidence of infection-associated adverse events in septic patients.

STUDY DESIGN

This multicenter randomized trial was designed as a real-world pragmatic study. Performed in 7 internal medicine departments in Athens, Greece, the study enrolled 266 patients with lower respiratory tract infections (LRTIs), acute pyelonephritis, primary bloodstream infection, and meeting the Sepsis-3 definitions.

After 24 hours of antimicrobial treatment, patients were randomized into two arms: PCT-guided discontinuation or standard of care (SOC). In the PCT-guided arm, antibiotics were discontinued if ≥80% decrease in PCT level or PCT level ≤0.5 µg/L at day 5 or later. In the SOC arm, duration of antimicrobial treatment followed international guidelines.

Primary outcome was the rate of infection-associated adverse events at day 180. Adverse events were defined as: new case of *C. difficile* infection; new case of multidrug-resistant organism (MRDO) infection; and death associated with either MDRO or *C. difficile* baseline infection. Secondary outcomes were: 28-day mortality, length of treatment (LOT) and hospitalization cost.

RESULTS

- The rate of infection-associated adverse events was 7.2% in the PCT-guidance arm vs 15.3% in SOC arm (p=0.045).
- The 28-day mortality rate was 15.2% in PCT arm vs 28.2% in SOC arm (p=0.02).
- A trend for decreased mortality at day 180 was observed in the PCT arm (30.4%) compared to SOC arm (38.2%), but was not statistically significant.
- The median LOT was 5 days in PCT arm vs 10 in SOC arm (p<0.01).
- Costs were €956.99 in PCT arm vs €1,183.49 in SOC arm (p=0.05).

CONCLUSIONS

The PCT-guidance approach was shown to be effective in reducing the rate of infection-associated adverse events, as well as 28-day mortality, LOT and related cost of hospitalization. In countries with high antimicrobial consumption and high antimicrobial resistance rates, this strategy could be beneficial from a public health standpoint.

"In the PROGRESS trial, we demonstrate for the first time that PCT-guided early discontinuation of antimicrobials in patients with sepsis prevents infection caused by MDRO and/or C. difficile."

KEY FINDINGS

- PROGRESS is the first multicenter randomized trial showing that early discontinuation of antimicrobials in patients with sepsis decreases the incidence of infection-associated adverse events.
- PCT-guided antimicrobial therapy was effective in reducing in-hospital and 28-day mortality.
- PCT-guidance could be a safe strategy with long-term benefits that may have substantial impact on public health.

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OPEN FORUM INFECTIOUS DISEASES
2019;6(11):ofz355

Impact of Procalcitonin Levels Combined with Active Intervention on Antimicrobial Stewardship in a Community Hospital.

Newton JA, Robinson S, Ling CLL, Zimmer L, Kuper K, Trivedi KK.

OBJECTIVE

The objective of this study was to measure the impact of PCT with an antimicrobial stewardship program (ASP) on patient length of stay (LOS) and antimicrobial therapy (ABX) duration in a community hospital.

STUDY DESIGN

Patients with at least 1 PCT value and an ASP recommendation to alter medications were included in the study. Between May 2013 and April 2014, 857 patients were eligible. ASP recommendations were made based upon evidence-based guidelines, clinical experience and PCT results.

RESULTS

Patients were stratified into two groups based upon treating physician acceptance or rejection of ASP guidance (compliers *versus* non-compliers). Patients were also stratified by initial PCT level (normal *versus* elevated). Providers complied with 73.7% of ASP recommendations. LOS, length of ABX after ASP recommendations and total length of ABX were evaluated (**Figure 1**).

Figure 1. Length of stay, duration of antibiotic after ASP recommendation and total duration of ABX therapy stratified by compliance and initial PCT level.
Adapted from Newton JA, et al. *Open Forum Infect*. Dis. 2019;6(11):ofz355

	Normal PCT Level			Elevated PCT Level		
	Compliers (n=380)	Non-compliers (n=144)		Compliers (n=252)	Non-compliers (n=81)	
	Mean (SD)	Mean (SD)	*p* Value	Mean (SD)	Mean (SD)	*p* Value
LOS	7.98 (6.09)	7.77 (6.88)	0.7464	9.17 (7.40)	9.01 (8.76)	0.8537
ABX (days) after ASP recommendation*	2.11 (2.83)	3.64 (4.38)	<0.0001	3.11 (3.89)	4.43 (4.37)	0.0043
Total ABX (days)*	4.64 (3.39)	6.23 (4.75)	<0.0001	5.79 (4.12)	7.12 (5.30)	0.0111

ABX: antimicrobial therapy; SD: standard deviation
*indicates statistically significant difference between groups

CONCLUSIONS

PCT guided recommendations, when accepted by providers, resulted in shorter duration of ABX irrespective of whether PCT values were normal or elevated.

"Procalcitonin has the potential to improve provider decision making and support antimicrobial stewardship through reduction of both unnecessary antibiotic initiation and treatment duration."

KEY FINDINGS

- In a 'real world' setting, compliance with PCT-guided recommendations provided by an ASP can decrease antimicrobial therapy duration.
- Duration of antibiotic therapy after ASP recommendations was significantly shorter (2.5 vs 3.9 days, p<0.0001) in the ASP complier group.
- ASPs play a key role in reducing inappropriate use of antimicrobials.

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LANCET INFECTIOUS DISEASES
2018;18(1):95-107

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

Schuetz P, 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.

OBJECTIVE

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.

STUDY DESIGN

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 primary endpoints were 30-day mortality and setting-specific treatment failure, secondary endpoints were antibiotic exposure, side-effects and length of stay.

RESULTS

The analysis demonstrated significant improvements in patient outcomes for the PCT-guided treatment group. Mortality at 30 days was significantly lower (9% *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. 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). Mean total antibiotic exposure was significantly lower in the PCT-guided group (5.7 days *vs.* 8.1 days, p<0.0001) and, side-effects were also lower (16% *vs.* 22%, p<0.001). No significant differences in length of hospital stay or ICU stay were observed between the two groups.

CONCLUSIONS

This meta-analysis found that implementation of PCT-guided protocols in patients with ARIs led to positive effects on clinical outcomes and reduced antibiotic exposure. Given these positive findings, and the increasing threat of multi-drug resistance, this report strengthens the rationale to use procalcitonin to support antibiotic stewardship decisions in patients with ARIs.

"... [This patient-level 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."

KEY FINDINGS

- This patient-level meta-analysis 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 (5.7 days *vs.* 8.1 days), 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.

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CRITICAL CARE MEDICINE
2018;46(5):691-98

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

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

OBJECTIVE

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.

STUDY DESIGN

Ten randomized controlled trials 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.

RESULTS

A total of 3,489 patients were included in these studies. PCT-guided patients had shorter antibiotic duration compared to controls: (7.35 *vs.* 8.85 days; p<0.001). However, ICU length of stay was not statistically 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).

CONCLUSIONS

In this systematic review and meta-analysis, PCT-guided therapy was found to reduce antibiotic duration with no adverse effects on patient outcomes in adult patients with suspected or confirmed sepsis.

"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 FINDINGS

- 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.

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THE AMERICAN JOURNAL OF MEDICINE
2018;131(2):201.E1-201.E8

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

Walsh TL, 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, Bremmer DN.

OBJECTIVE

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.

STUDY DESIGN

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. the secondary outcomes included duration of IV antibiotics; hospital length of stay (LOS); and percentage of patients with appropriate antibiotic therapy duration.

RESULTS

In the post-PCT guidance group, the primary outcome of antibiotic therapy duration was significantly reduced. Secondary outcomes were also positively impacted in the PCT group (**Table 1**).

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), as shown in **Table 2**. Among this population, therapy duration of therapy was significantly shorter in the low PCT cohort.

CONCLUSIONS

In this real-world study, the implementation of a PCT guidance algorithm led to shorter durations of total antibiotic therapy and shorter hospital length of stay without affecting hospital readmissions.

"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 FINDINGS

- A real world study of PCT-guidance in patients with pneumonia, which showed similar findings to 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.

Table 1. Primary and secondary outcomes
Data extracted from Walsh et al. *Am J Med.* 2018;131(2):201.e1-201.e8

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

LOS: length of stay

Table 2. Outcomes in patients receiving PCT-guided care by PCT level
Data extracted from Walsh et al. *Am J Med.* 2018;131(2):201.e1-201.e8

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

LOS: length of stay

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OPEN FORUM INFECTIOUS DISEASES
2017;4(4):OFX213

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

Broyles MR.

OBJECTIVE

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.

STUDY DESIGN

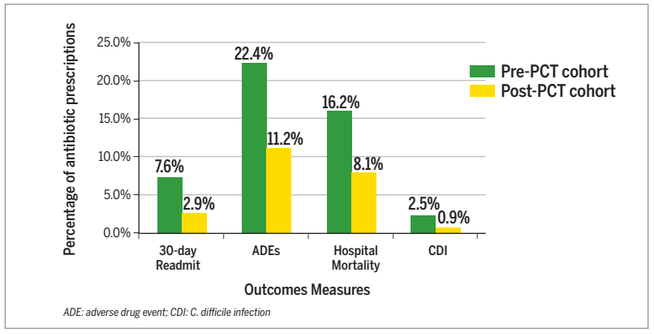
Patient data from four years before and four years after implementation of VIDAS® B·R·A·H·M·S PCT™ testing were collected. A total of 985 patients managed without PCT-guidance (the Pre-PCT cohort) and 1,167 PCT-managed patients (the Post-PCT cohort) were included in the analysis.

RESULTS

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* (CDI) 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 Broyles. *Open Forum Infectious Diseases* 2017;4(4):ofx213



ADE: adverse drug event; CDI: C. difficile infection

CONCLUSIONS

Implementing a PCT-guided antibiotic therapy algorithm in a community healthcare facility with an established stewardship program led to a significant reduction in antibiotic exposure and adverse outcomes. Use of the algorithm, together with thorough clinician education, made improved antibiotic management and outcomes achievable.

"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 FINDINGS

- 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.

CLICK TO ACCESS ARTICLE

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, Kadri SS, Cao Z, Robinson SB, Lipkin C, Bozzette SA.

OBJECTIVE

This study evaluated the impact of PCT testing performed on the first day of ICU admission in critically ill adult patients with suspected or documented sepsis, with the aim of providing real-world data on healthcare utilization and cost.

STUDY DESIGN

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.

RESULTS

A total of 33,569 PCT managed patients were compared to 98,543 propensity-matched non-PCT patients. The differences observed between the PCT-guided group and the comparison group for the main outcomes are shown in **Figure 1**.

Figure 1. Average Differences Between the Two Groups

Data extracted from Balk RA, et al. *Chest* 2017;151(1):23-33

Outcome	Mean Adjusted Value	*p* value
Total LOS (days)	-1.2	<0.001
ICU LOS (days)	-0.2	0.031
Total Cost ($)	-$2,759	<0.01
ICU Cost ($)	-$1,310	<0.001
Pharmacy Cost ($)	-$331	0.002
Antibiotic Cost ($)	-$70	0.074
Lab Cost ($)	$81	0.002
Total Antibiotic Exposure (days)	-0.7	0.006

CONCLUSIONS

Use of PCT testing on ICU admission was associated with reduced antibiotic exposure, shorter hospital and ICU length of stay, and significant cost-savings for the hospital, ICU, and pharmacy.

"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 FINDINGS

- 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.

NOTES

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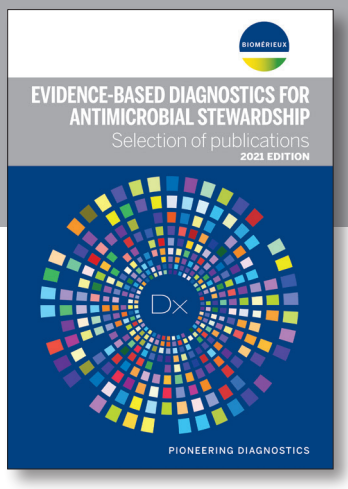

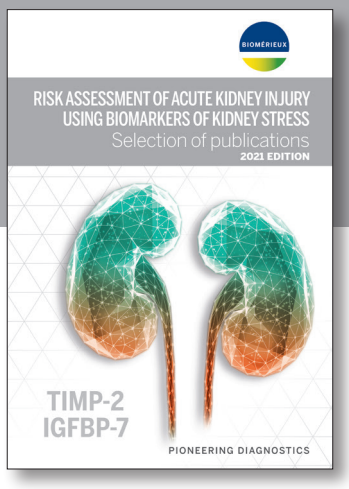

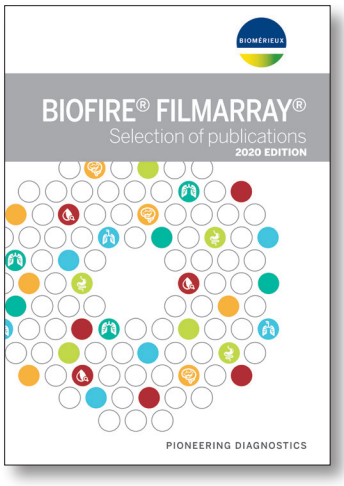

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