BIOMÉRIEUX

PROCALCITONIN-GUIDED ANTIBIOTIC THERAPY

Selection of publications

2024 EDITION

PIONEERING DIAGNOSTICS

“Up to 50% of antimicrobials are suboptimally prescribed, contributing to adverse events, increased costs, and antimicrobial resistance” [1]

“Antimicrobial pressure and resulting antimicrobial resistances are a major public health issue as well as a daily struggle in the management of patients with severe infectious diseases, especially in intensive care units where antibiotic exposure is high”[2]

“For adults with an initial diagnosis of sepsis or septic shock and adequate source control where optimal duration of therapy is unclear, we suggest using procalcitonin AND clinical evaluation to decide when to discontinue antimicrobials over clinical evaluation alone”[3]

For quote and Introduction references, see page 33

INTRODUCTION

Across the treatment spectrum from primary care to the emergency department and critical care, acute respiratory tract illnesses and suspected sepsis often prompt initiation of empiric antibiotic treatment. Yet, in many cases a bacterial pathogen cannot be detected and viruses may indeed account for a large proportion of respiratory illnesses.[4,5] The same is true in patients presenting with a febrile illness, where inflammatory or viral illnesses may account for a significant proportion of cases. Despite technological advances and the wider availability of rapid molecular diagnostics,[6] **antibiotics are often over-prescribed** due to concerns about bacterial coinfections and therefore the safety of withholding antibiotics. Additionally, once started, physicians often use prolonged antibiotic courses due to the lack of well validated clinical parameters providing proof that the infection has resolved and antibiotics can be stopped. **Unnecessarily long treatment durations** often also result from the use of fixed antibiotic regimens advocated by practice guidelines.

Individualizing antibiotic treatment therefore has potential to **improve antibiotic stewardship efforts** to encourage judicious and correct usage of these agents and mitigate the emergence of multi-drug resistant pathogens, which without a doubt, is one of the most urgent threats to global health and directly linked to antibiotic overuse.[7]

Herein, the integration of **host response markers** which correlate with bacterial infection into clinical care has high potential to improve individual antibiotic decisions in patients. Among such host-response markers, **procalcitonin (PCT)** has generated much interest as it more specifically correlates with bacterial infection compared to traditional markers and shows a more favorable kinetic profile allowing its use for prognosis and for assessing response to treatment.[8-10]

Today, a growing body of evidence-based literature supports **the use of PCT to improve the clinical management of patients with suspicion of bacterial infection and to contribute to antibiotic stewardship initiatives.**[10] 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 .[11-13] 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.[14]

PCT should not be used as a substitute for good clinical practice, but rather be part of the **overall assessment of a patient**.[3] Decisions pertaining to the initiation and discontinuation of antibiotic treatment remain strongly dependent on an assessment of all available clinical and diagnostic parameters, including a thorough assessment of the patient and the severity of the illness. Furthermore, the use of PCT should not delay or impede the initiation of empirical treatment in high risk situations. However, host response markers like PCT remain the best line of defense against diagnostic uncertainty and antibiotic overuse and further research is needed to explore the optimal use of biomarkers in combination with pathogen-directed tests.

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CONTENTS

PCT FOR ANTIBIOTIC THERAPY GUIDANCE

PCT IN GUIDELINES AND CONSENSUS STATEMENTS

HEALTH ECONOMICS AND OUTCOMES STUDIES OF PCT

CONTENTS

ADDITIONAL RECOMMENDED READING

PCT FOR ANTIBIOTIC THERAPY GUIDANCE

CLICK TO ACCESS ARTICLE

LANCET INFECTIOUS DISEASES
2023;23(4):484-495

Efficacy and Safety of Azithromycin versus Placebo to Treat Lower Respiratory Tract Infections associated with Low Procalcitonin: A Randomised, Placebo-controlled, Double-blind, Non-inferiority Trial.

Tsalik EL, Rouphael NG, Sadikot RT, Rodriguez-Barradas MC, McClain MT, Wilkins DM, Woods CW, Swamy GK, Walter EB, El Sahly HM, Keitel WA, Mulligan MJ, Tuyishimire B, Serti E, Hamasaki T, Evans SR, Ghazaryan V, Lee MS, Lautenbach E; TRAP-LRTI Study Group; Antibacterial Resistance Leadership Group.

OBJECTIVE

This study, the TRAP-LRTI (Targeted Reduction of Antibiotics using Procalcitonin – Lower Respiratory Tract Infections) trial, aimed to compare the efficacy and safety of azithromycin versus placebo to treat lower respiratory tract infections (LRTIs) in patients with low procalcitonin (PCT) levels (≤0.25ng/mL).

STUDY DESIGN

Randomized, double-blinded, placebo-controlled, non-inferiority multicenter clinical trial conducted at 5 health centers in the USA between December 8, 2017 and March 9, 2020.

Adults aged ≥18 years with clinically suspected non-pneumonia LRTI & symptom duration from 24 hours to 28 days were enrolled at clinics or emergency departments.

Participants with a PCT concentration of 0.25 ng/mL or less were randomly assigned (1:1) to receive oral azithromycin (n=249) or matching placebo (n=250).

The primary outcome was efficacy of azithromycin versus placebo in terms of clinical improvement at day 5 in the intention-to-treat population. The non-inferiority margin was −12·5%. Assessment was based on: 1) clinical improvement and 2) the Desirability Of Outcome Ranking (DOOR) and the Response Adjusted for Days of Antibiotic Risk (RADAR).

RESULTS

- In total, 499 patients were enrolled (out of 691 assessed for eligibility) and randomly assigned to receive azithromycin (n=249) or placebo (n=250).
- Primary outcome of clinical improvement: at day 5, placebo treatment was not non-inferior to azithromycin. Clinical improvement at day 5 was observed in 148 (63%, 95% CI 54 to 71) of 238 participants with full data in the placebo group and 155 (69%, 61 to 77) of 227 participants with full data in the azithromycin group in the intention-to-treat analysis (between-group difference −6%, 95% CI −15 to 2). The 95% CI for the difference did not meet the non-inferiority margin **(Table 1).**
- At day 11, placebo treatment was non-inferior to azithromycin and at day 28, there were mixed findings **(Table 1).**
- However, the DOOR-RADAR analysis accounting for azithromycin-related solicited adverse events and antibiotic exposure showed placebo treatment to be superior **(Figure 1).**

CONCLUSIONS

Low procalcitonin levels can be used to identify adults with lower respiratory tract infections who are unlikely to benefit from antibiotic therapy especially when accounting for the harms associated with unnecessary antibiotic use.

"Clinicians should weigh these factors (clinical improvement, reduced adverse events, and lower antibiotic use) when deciding whether to use procalcitonin as a guide for antibiotic initiation."

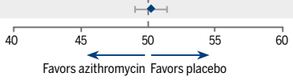
Table 1. Rates of clinical improvement by timepoint and analysis population.
Reproduced with permission from Elsevier. Tsalik EL, *et al. Lancet Infectious Diseases* 2023;23(4):484-495

	Participants with clinical improvement	Between-group difference	Non-inferiority*
Day 5 Intention to treat population			
Azithromycin group (n=249)	155 (69% [61 to 77])	-	-
Placebo group (n=250)	148 (63% [54 to 71])	-6% (-15 to 2)	No
Per-protocol population			
Azithromycin group (n=204)	136 (70% [62 to 79])	-	-
Placebo group (n=221)	136 (65% [57 to 74])	-5% (-14 to 4)	No
Day 11 Intention to treat population			
Azithromycin group (n=249)	187 (81% [74 to 87])	-	-
Placebo group (n=250)	184 (76% [70 to 83])	-4% (-12 to 3)	Yes
Per-protocol population			
Azithromycin group (n=211)	174 (80% [73 to 87])	-	-
Placebo group (n=225)	177 (77% [70 to 83])	-4% (-11 to 4)	Yes
Day 28 Intention to treat population			
Azithromycin group (n=249)	202 (88% [83 to 93])	-	-
Placebo group (n=250)	194 (82% [77 to 86])	-7% (-13 to 0)	No
Per-protocol population			
Azithromycin group (n=210)	185 (88% [83 to 93])	-	-
Placebo group (n=223)	184 (82% [77 to 87])	-6% (-12 to 1)	Yes

Data are n (% [95% CI]) or % (95% CI).
*Non-inferiority of placebo was concluded if the lower bound of the 95% CI for the between-group difference in proportions was greater than -12.5%.

Figure 1. Clinical improvement and solicited adverse events at day 5.
Reproduced with permission from Elsevier. Tsalik EL, *et al. Lancet Infectious Diseases* 2023;23(4):484-495

	Azithromycin group (n=249) n (%)	Placebo group (n=250) n (%)	DOOR probability (95% CI)
DOOR			49% (44-54)
Absence of clinical improvement			
Any qualifying event	72 (29%)	90 (36%)	46% (42-51)
Absence of improvement in at least two symptoms or signs	40 (16%)	45 (18%)	49% (46-52)
Deterioration in any sign or symptom	47 (19%)	60 (24%)	47% (44-51)
Presence of fever in day preceding or at visit	0 (0%)	1 (<1%)	50% (49-50)
Medically attended visit for persistent of worsening lower respiratory tract infection	10 (4%)	18 (7%)	48% (46-50)
Solicited adverse events			
Any qualifying event	107 (43%)	88 (35%)	54% (50-58)
Abdominal pain	59 (24%)	41 (16%)	54% (50-57)
Vomiting	15 (6%)	12 (5%)	51% (49-53)
Diarrhoea	65 (26%)	61 (24%)	51% (47-55)
Allergic reaction	10 (4%)	9 (4%)	50% (48-52)
Candidiasis	10 (4%)	8 (3%)	50% (49-52)
Severity of solicited adverse events			
Mild	62 (25%)	51 (20%)	52% (49-56)
Moderate	40 (16%)	33 (13%)	51% (48-54)
Severe	5 (2%)	4 (2%)	50% (49-51)



KEY FINDINGS

- The trial concluded that, at day 5, it is unclear whether antibiotics are indicated for patients with LRTI and a low PCT concentration.
- However, at later timepoints, low PCT levels were shown to safely identify adults with LRTI who are unlikely to benefit from antibiotic therapy, especially when accounting for the harms associated with unnecessary antibiotic use.

CLICK TO ACCESS ARTICLE

LANCET GASTROENTEROLOGY AND HEPATOLOGY
2022;7(10):913-921

A Procalcitonin-based Algorithm to Guide Antibiotic Use in Patients with Acute Pancreatitis (PROCAP): A Single-centre, Patient-blinded, Randomised Controlled Trial.

Siriwardena AK, Jegatheeswaran S, Mason JM; PROCAP investigators.

OBJECTIVE

Distinguishing inflammation from bacterial infection in patients with acute pancreatitis is a clinical challenge. Since procalcitonin (PCT) is able to distinguish infection from inflammation, this study (PROCAP) tested the hypothesis that use of a PCT-based algorithm to guide initiation, continuation, and discontinuation of antibiotics could lead to reduced antibiotic use without adverse effects in patients with acute pancreatitis.

STUDY DESIGN

Pragmatic, single-center (Manchester, UK), patient-blinded, randomized controlled trial (RCT). Participants aged 18 years or older with a clinical diagnosis of acute pancreatitis were randomly assigned (1:1) to PCT-guided care or usual care.

In the PCT-guided care group, PCT testing was performed on days 0, 4, 7 and then weekly. Guidance was to stop or not start antibiotics following a test value of less than 1·0 ng/mL and to start or continue antibiotics following a test value of 1·0 ng/mL or more.

In the usual care group any decision to use antibiotics was preceded by measurement of PCT.

Primary outcome: antibiotic use during the time from first hospital admission to discharge.

RESULTS (Table 1)

- Between July 29, 2018, and November 13, 2020, 260 patients were enrolled and randomly assigned to a treatment group (132 to PCT-guided care and 128 to usual care).
- Full protocol adherence was achieved in 92 (70%) patients in the PCT-guided care group, with 24 cases of clinician over-ride of the algorithm.
- In the PCT-guided care group, 59 (45%) of patients were prescribed antibiotics compared with 79 (63%) in the usual care group (adjusted risk difference −15·6% [95% CI −27·0 to −4·2]; *p*=0·0071).
- The odds ratio for the treatment effect was 0·49 (95% CI 0·29 to 0·83; *p*=0·0077).
- The mean number of days of antibiotic use per patient was significantly lower in the PCT-guided care group than in the usual care group: 4·5 (10·5) vs. 5·8 (10·6) with adjusted risk difference −1·16 (95% CI −2·10 to −0·22; *p*=0·015).
- No significant difference was observed between the 2 groups in terms of the number of clinical infections or hospital-acquired infections per patient.
- In the PCT-guided care group, 4 (3%) patients died vs. 3 (2%) patients in the usual care group, and all deaths were related to underlying severe pancreatitis.
- There was no difference in adverse events between the 2 groups.

CONCLUSIONS

PROCAP is the largest RCT to date of the use of a PCT algorithm to guide antibiotic use in patients with acute pancreatitis. PCT-guided care was shown to reduce antibiotic use without increasing infection or harm in patients with acute pancreatitis. PCT-based algorithms to guide antibiotic use should be considered in the care of this group of patients and be incorporated into future guidelines on the management of acute pancreatitis.

"Our findings showed that compared with usual care, procalcitonin-guided care reduced the probability of being prescribed an antibiotic and reduced the mean number of days of antibiotic use without differences in mortality, infections, adverse events, length of stay, quality of life, or cost."

PCT FOR ANTIBIOTIC THERAPY GUIDANCE

Table 1. Primary and Secondary Outcomes according to Treatment Group.

Reproduced with permission from Elsevier. Siriwardena AK,*et al. Lancet Gastroenterology and Hepatology* 2022;7(10):913-921

	PCT-guided care (n=132)	Usual care (n=128)	Adjusted difference (95% CI); *p* value*
Antibiotic use	59 (45%)	79 (62%)	-15.6% (-27.0 to -4.2); 0.0071
Prophylactic use excluded	41 (31%)	60 (47%)	-14.2% (-24.4 to -4.1); 0.0061
All-cause mortality	4 (3%)	3 (2%)	0.69% (-3.24 to 4.62); 0.73
Days of antibiotic use	4.5 (10.5)	5.8 (10.6)	-1.16 (-2.10 to -0.22); 0.015
Clinical infections	0.39 (1.02)	0.27 (0.80)	0.046 (-0.086 to 0.177); 0.50
Hospital-acquired infections	0.24 (0.74)	0.11 (0.46)	-0.005 (-0.055 to 0.045); 0.84
Total length of hospital stay (days)	13.6 (18.8)	10.7 (12.5)	0.9 (-0.7 to 2.6); 0.28
Cost (£)	£7,050 (14,375)	£4,734 (7,465)	£373 (-297 to 1,043); 0.28

Data are n (%) or mean (SD) except where otherwise stated. * *p* values are produced using adjusted generalized linear models.

Table 2. Adverse Events according to Treatment Group.

Reproduced with permission from Elsevier. Siriwardena AK,*et al. Lancet Gastroenterology and Hepatology* 2022;7(10):913-921

	Procalcitonin-guided care (n=132)	Usual care (n=128)
None	119 (90%)	110 (86%)
Any adverse event	13 (10%)	18 (14%)
Not severe	4 (3%)	7 (5%)
Severe	9 (7%)	11 (9%)
Expected	8 (6%)	7 (5%)
Unexpected	5 (4%)	11 (9%)
Resolved	12 (9%)	15 (12%)
Resolved with sequelae	1 (1%)	3 (2%)

KEY FINDINGS

- Use of PCT can support decision-making around antibiotic prescribing and reduce antibiotic use in patients with acute pancreatitis, without increasing infection or harm.
- PCT-based algorithms should be incorporated into future guidelines for management of acute pancreatitis.

CLICK TO ACCESS ARTICLE

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

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

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):819-827

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 less at 19.6% for the PCT-guided group vs. 25% for the standard of care group (p=0.0122) and mortality at 1 year was 34.8% for the PCT group vs. 40.9% for standard of care (p=0.0158).
- A median reduction of antibiotic costs in the PCT-guided group was 34 Euros per patient (p=0.0006).

CONCLUSIONS

This large multi-center study in critically ill patients shows that PCT concentrations help physicians in deciding whether 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

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

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.

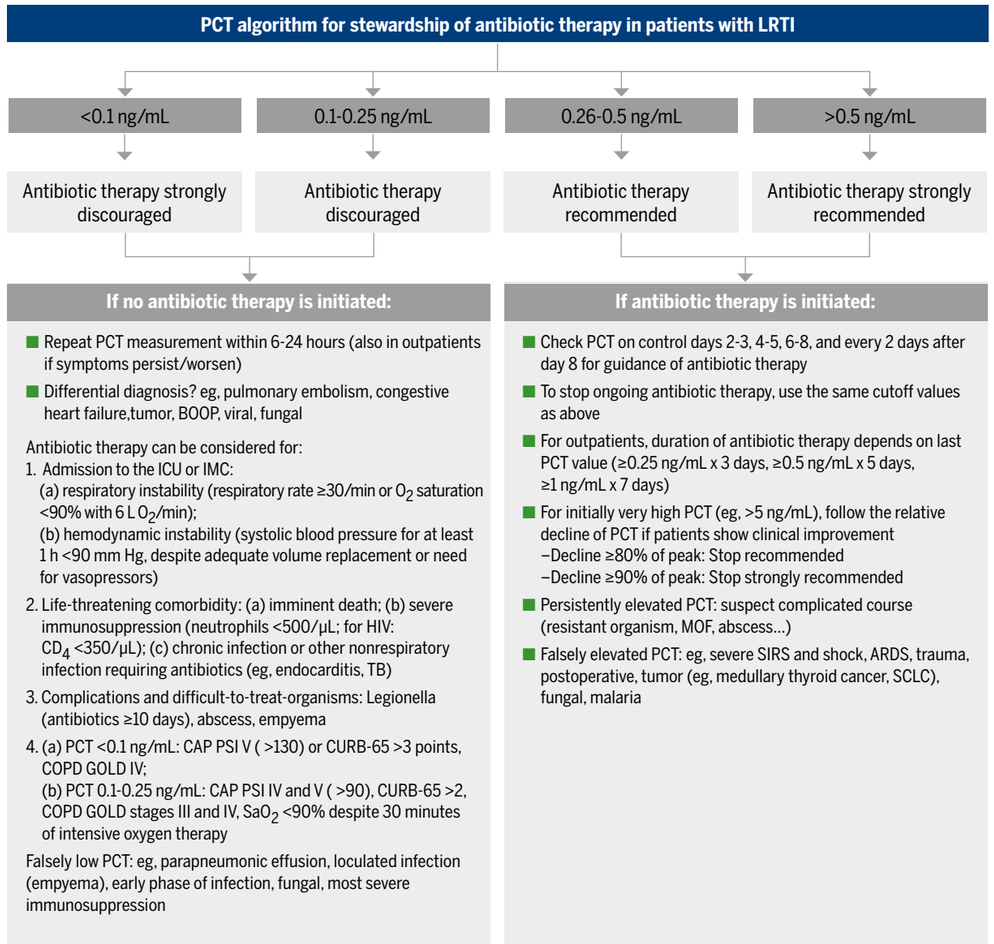
"We demonstrate that good compliance with the PCT algorithm is possible in real-life conditions but has to be reinforced to achieve optimal benefit."

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® B·R·A·H·M·S PCT™ (bioMérieux) and KRYPTOR (Thermo Fisher) demonstrated similar PCT results. VIDAS® B·R·A·H·M·S PCT™ showed ease-of-use in different settings (ED, primary care).**

PCT FOR ANTIBIOTIC THERAPY GUIDANCE

Figure 1: PCT Algorithm for Antibiotic Stewardship in patients with LRTI - ProREAL
Reproduced with permission from American Medical Association. Albrich WC *et al. Arch Intern Med.* 2012;172(9):715-722



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.

CLICK TO ACCESS ARTICLE

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

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.

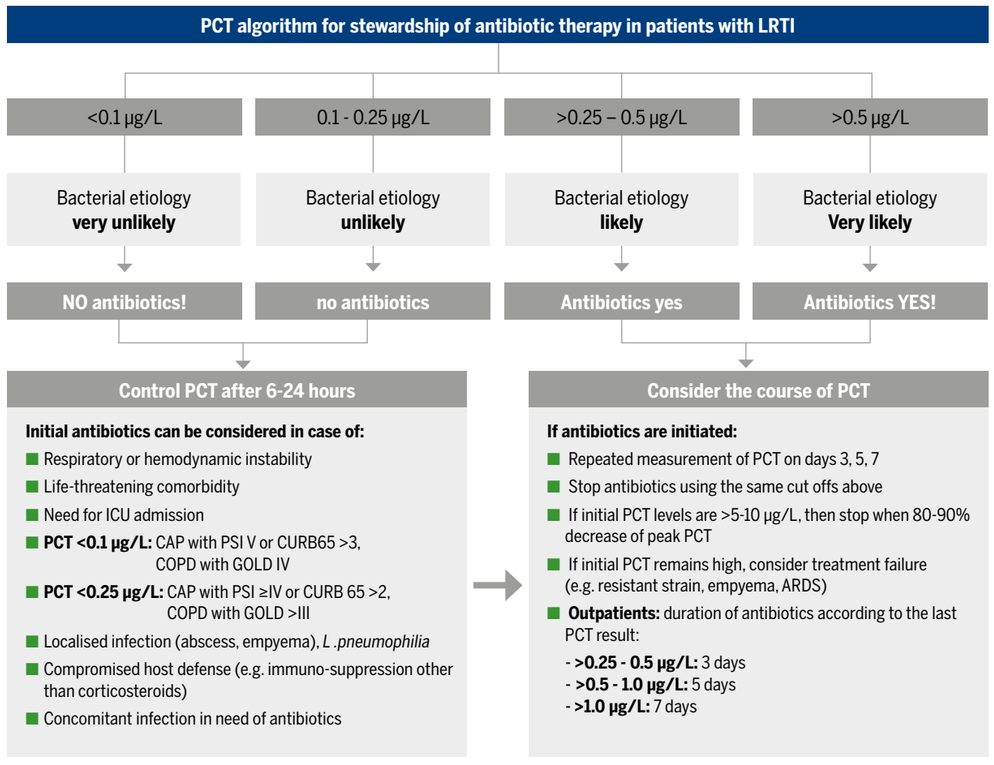
"PCT guidance will have substantial clinical and public health implications to reduce antibiotic exposure and associated risks of adverse effects and antibiotic resistance."

KEY FINDINGS

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

PCT FOR ANTIBIOTIC THERAPY GUIDANCE

Figure 1: PCT Algorithm for Antibiotic Stewardship in patients with LRTI – ProHOSP.
Reproduced with permission from the American Medical Association. Schuetz P, *et al. JAMA* 2009;302(10):1059-1066



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

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BMC MEDICINE
2015;13:104

Procalcitonin and Pyuria-based Algorithm Reduces Antibiotic Use in Urinary Tract Infections: A Randomized Controlled Trial.

Drozdov D, Schwarz S, Kutz A, Grolimund E, Rast AC, Steiner D, Regez K, Schild U, Guglielmetti M, Conca A, Reutlinger B, Ottiger C, Buchkremer F, Haubitz S, Blum C, Huber A, Buergi U, Schuetz P, Bock A, Fux CA, Mueller B and Albrich WC.

OBJECTIVE

Since urinary tract infections (UTIs) are one of the most common indications for antibiotic therapy, the impact of any reduction in treatment duration is important. This study aimed to investigate whether an algorithm based on procalcitonin (PCT) and quantitative pyuria could safely reduce the duration of antibiotic therapy in patients with UTIs.

STUDY DESIGN

Single-center, factorial design, randomized controlled open-label trial, enrolling immunocompetent adults with community-acquired non-catheter-related UTI presenting to the emergency department of a tertiary-care 600-bed hospital in northwestern Switzerland between April 2012 and March 2014,

Patients were randomly assigned to either the PCT-pyuria-based algorithm group or the control group. Clinical presentation was used to guide initiation and duration of antibiotic therapy according to current guidelines in the control group, or using the PCT-pyuria-based algorithm in the PCT-pyuria group.

Primary endpoint was overall antibiotic exposure within 90 days.

Secondary endpoints included duration of the initial antibiotic therapy, persistent infection 7 days after end of therapy and 30 days after enrollment, recurrence and rehospitalizations within 90 days.

RESULTS

- In the study, 125 (76% women) were enrolled in the intention-to-treat (ITT) group and 96 patients with microbiologically confirmed UTIs were enrolled in the per protocol (PP) group, of which 84 (67%) patients had a febrile UTI, 28 (22%) had bacteremia, 5 (4%) died, and 3 (2%) were lost to follow-up.
- Primary outcome: overall antibiotic exposure within 90 days was shorter in the PCT-pyuria group than in the control group (median 7.0 [IQR, 5.0–14.0] vs. 10.0 [IQR, 7.0–16.0] days, p=0.011) in the ITT analysis.
- Secondary outcomes: duration of initial antibiotic therapy was shorter in the PCT-pyuria group, and mortality, rates of persistent infections, recurrences, and rehospitalizations were similar in both groups.

CONCLUSIONS

Implementation of a PCT-pyuria-based algorithm into clinical workflows is practicable and can help determine optimal length of antibiotic therapy and avoid antibiotic overuse. The PCT-pyuria-based algorithm significantly reduced antibiotic exposure in UTI patients when compared to current guidelines without apparent negative effects on clinical outcomes.

"A PCT-pyuria-based algorithm reduced antibiotic exposure by 30% when compared to current guidelines without apparent negative effects on clinical outcomes."

KEY FINDINGS

- **A PCT-pyuria-based algorithm resulted in a 30% reduction in antibiotic exposure in patients with urinary tract infections.**

PCT IN GUIDELINES AND CONSENSUS STATEMENTS

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EUROPEAN RESPIRATORY JOURNAL
2023;61:2200735

ERS/ESICM/ESCMID/ALAT Guidelines for the Management of Severe Community-acquired Pneumonia.

Martin-Loeches I, Torres A, Nagavcj B, Aliberti S, Antonelli M, Bassetti M, Bos L, Chalmers JD, Derde L, de Waele J, Garnacho-Montero J, Kollef M, Luna C, Menendez R, Niederman M, Ponomarev D, Restrepo M, Rigau D, Schultz MJ, Weiss E, Welte T, Wunderink R.

OBJECTIVE

To develop the first international guidelines for managing severe community-acquired pneumonia (sCAP) with the aim of providing guidance on the most effective treatment and management strategies for adult patients with sCAP.

STUDY DESIGN

An expert group comprised of 18 European and 4 non-European experts and 2 methodologists from the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and Latin American Thoracic Association (ALAT) worked together to develop the first international guidelines for sCAP.

Using the ERS methodology for guideline development, the panel addressed 8 key clinical questions for sCAP diagnosis and treatment using the PICO (Patients, Intervention, Comparison, Outcomes) format. Systematic literature searches were performed in several databases and whenever possible, meta-analyses were performed for evidence synthesis.

The quality of evidence was assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluation). Evidence to Decision frameworks were used to determine the direction and the strength of the guideline recommendations, with strong recommendations described as "we recommend" and conditional recommendations as "we suggest".

KEY RECOMMENDATIONS

Recommendations covered diagnosis, antibiotics, organ support, biomarkers, and co-adjuvant therapy in sCAP, and also recommendations for or against specific treatment interventions **(Table 1).**

FUTURE RESEARCH PRIORITIES

Three priorities were identified:

1. Clinical features that would help distinguish aspiration pneumonia from chemical pneumonitis.
2. Determination of treatment duration, particularly if short courses would be beneficial even in patients with sCAP on invasive mechanical ventilation.
3. Biomarkers that would help distinguish aspiration pneumonia from chemical pneumonitis.

CONCLUSIONS

These international guidelines provide evidence-based clinical practice recommendations for sCAP, as well as demonstrating current knowledge gaps and making recommendations for future research.

"In these international guidelines, ERS, ESICM, ESCMID, and ALAT provide evidence-based clinical practice recommendations for diagnosis, empirical treatment, and antibiotic therapy for sCAP, following the GRADE approach."

KEY FINDINGS

- **First published guidelines for patients with sCAP.**
- **These recommendations will benefit physicians caring for critically ill patients and help standardize the current treatment and management of sCAP.**

Table 1. Eight questions and recommendations

Reproduced from Martin-Loeches I, *et al. Eur Respir J.* 2023;61:2200735

	QUESTION	RECOMMENDATION	QUALITY OF EVIDENCE
1	In patients with sCAP, should rapid microbiological techniques be added to current testing of blood and respiratory tract samples?	If the technology is available, we **suggest** sending a lower respiratory tract sample (either sputum or endotracheal aspirates) for multiplex PCR testing (virus and/or bacterial detection) whenever non-standard sCAP antibiotics are prescribed or considered.	! VERY LOW
2	In hypoxemic patients with sCAP, can either NIV or HFNO be used initially— rather than supplemental standard oxygen administration—to avoid intubation and reduce mortality?	In acute hypoxemic respiratory failure not needing immediate intubation, we **suggest** using HFNO instead of standard oxygen. NIV might be an option in certain patients with persistent hypoxemic respiratory failure not needing immediate intubation, irrespective of HFNO.	! VERY LOW ! LOW
3	When using initial empirical therapy for sCAP, should a macrolide or fluoroquinolone be used as part of combination therapy, to reduce mortality and adverse clinical outcomes?	We **suggest** the addition of macrolides, not fluoroquinolones, to beta-lactams as empirical antibiotic therapy in hospitalized patients with sCAP.	! VERY LOW
4	**In patients with sCAP, can serum PCT be used to reduce the duration of antibiotic therapy and improve other outcomes in comparison to standard of care not guided by serial biomarker measurements?**	**We suggest the use of PCT to reduce the duration of antibiotic treatment in patients with sCAP.**	! LOW
5	Should oseltamivir be added to standard therapy in patients with sCAP and confirmed influenza?	We **suggest** the use of oseltamivir for patients with sCAP due to influenza confirmed by PCR. When PCR is not available to confirm influenza, we **suggest** the use of empirical oseltamivir during the influenza season.	! VERY LOW ! VERY LOW
6	Does the addition of steroids to antibiotic therapy in specific sCAP populations lead to better outcomes in comparison to when steroid therapy is not used?	In patients with sCAP, we **suggest** the use of corticosteroids if shock is present.	! LOW
7	Does the use of a prediction score for drug-resistant pathogens lead to more appropriate therapy and improved outcomes (mortality, treatment failure, duration of antibiotic therapy, prolonged ICU stay)?	We **suggest** integrating specific risk factors (eventually computed into clinical scores) based on local epidemiology and previous colonization to guide decisions regarding drug-resistant pathogens (excluding those immunocompromised) and empirical antibiotic prescription in sCAP patients.	! MODERATE
8	Do patients with sCAP and aspiration risk factors have better outcomes (mortality, length of stay, treatment failure) if treated with a risk-based therapy regimen instead of standard sCAP antibiotics?	In patients with sCAP and aspiration risk factors, we **suggest** standard CAP therapy regimen and not specific therapy targeting anaerobic bacteria.	GOOD PRACTICE

! Conditional recommendation !! Strong recommendation

Strong recommendations are worded as "we recommend", while conditional recommendations are worded as "we suggest".
CAP: community-acquired pneumonia; HFNO; high-flow nasal oxygen; ICU: intensive care unit; NIV: non-invasive ventilation; PCR: polymerase chain reaction; PCT: procalcitonin.

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JOURNAL OF APPLIED LABORATORY MEDICINE
2023;8(3):598-634

AACC Guidance Document on the Clinical Use of Procalcitonin.

Chambliss AB, Patel K, Colón-Franco JM, Hayden J, Katz SE, Minejima E, Woodworth A.

OBJECTIVE

The Guidance Document aims to provide evidence-based guidance on how to best use procalcitonin (PCT) across various clinical settings and patient populations to improve patient outcomes. It addresses 10 key questions **(Table 1)** regarding key aspects of PCT-guided management of patients with suspected sepsis and/or bacterial infections, particularly respiratory infections. The document explores the evidence for PCT utility for antimicrobial therapy decisions and outcomes prediction. It also discusses analytical and preanalytical considerations for PCT analysis and confounding factors that may affect the interpretation of PCT results.

The guidance is intended for both clinical and laboratory stakeholders, and in particular those caring for adult and pediatric patients with suspected sepsis and respiratory infections (e.g., physicians/assistants, nurses, pharmacists, laboratorians).

STUDY DESIGN

Detailed review of English-language literature conducted for PCT studies in adult (≥100 patients), pediatric, and neonatal populations. The study size involved 31,580 patients at multiple sites. Inclusion criteria were patients with sepsis in the intensive care unit, patients with LRTI, patients evaluated for single PCT measurement or PCT clearance, use in pediatrics.

CONCLUSIONS

Evidence to support PCT testing to guide antibiotic discontinuation is compelling in the critically ill and in some LRTIs. However, it is lacking in other clinical scenarios, and is limited in pediatric and neonatal populations.

Data on the utility of PCT to guide antibiotic initiation and does not demonstrate a clear benefit. In pediatric and neonatal populations, some studies have established a role for PCT-guided protocols in reducing antibiotic exposure, however, the utility of PCT has not yet been well-studied in preterm infants. While elevations in PCT generally correlate with poor prognosis and outcomes, no consistent PCT concentration(s) have been established to predict mortality.

The utility of PCT is optimized when the test is used in conjunction with antimicrobial stewardship programs, and results are interpreted by a multidisciplinary team of laboratorians, pharmacists and infectious disease providers, using interpretative algorithms and clinical decision support systems.

"Successful implementation of clinical PCT requires a multidisciplinary effort among laboratorians, pharmacists, and infectious disease providers."

KEY FINDINGS

- There is a vast amount of compelling evidence to support the use of PCT to guide antibiotic discontinuation, particularly in the critically ill and in some LRTIs.
- B·R·A·H·M·S PCT KRYPTOR (Thermo Fisher) is identified as the gold standard reference method, as it was used in most initial clinical trials which established the current clinical decision cut-offs.
- Improved outcomes are more likely to be achieved when PCT is used in conjunction with antimicrobial stewardship programs, institutional interpretive algorithms, and clinical decision support tools.
- Interpretation of PCT results requires guidance from multidisciplinary care teams of clinicians, pharmacists, and clinical laboratorians.

Table 1. 10 Key Questions around PCT.
Adapted from Chambliss AB, *et al. J Applied Lab Med.* 2023;8(3):598-634

1.	Can PCT results be utilized to inform treatment decisions in both initiation and cessation of antimicrobial therapy in adult patients with sepsis or respiratory infections?
2.	Is PCT an accurate predictor of outcomes (mortality, respiratory failure, shock) in adult populations?
3.	Can PCT results be utilized to inform treatment decisions in both initiation and cessation of antimicrobial therapy in neonatal and pediatric patients with sepsis or respiratory infections?
4.	Is PCT an accurate predictor of outcomes (e.g., mortality, respiratory failure, shock) in pediatric populations?
5.	When and how often should PCT be measured? Which cutoff(s) should be used?
6.	How should PCT be incorporated into antimicrobial stewardship efforts?
7.	What preanalytical factors affect PCT results and/or interpretation?
8.	What FDA-approved methods are available to measure PCT and how do they compare?
9.	Are clinical decision points (cutoffs) comparable across PCT assays?
10.	What are possible confounding factors for the interpretation of PCT results?

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CLINICAL CHEMISTRY AND LABORATORY MEDICINE
2020;58(12):1983-1991

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
Reproduced from Lee CC. *et al. Clin Chem Lab Med.* 2020;58(12):1983-1991. CC BY 4.0

	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
Reproduced from Lee CC. *et al. Clin Chem Lab Med.* 2020;58(12):1983-1991 CC BY 4.0

	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 withhold 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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CLINICAL CHEMISTRY AND LABORATORY MEDICINE
2019;57(9):1308-1318

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

- 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

	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

	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)

HEALTH ECONOMICS AND OUTCOMES STUDIES OF PCT

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ANTIMICROBIAL STEWARDSHIP HEALTHCARE EPIDEMIOLOGY
2023;3(1):E107

Antimicrobial Stewardship, Procalcitonin Testing, and Rapid Blood-Culture Identification to Optimize Sepsis Care in Critically Ill Adult Patients: A Quality Improvement Initiative.

Sligl WI, Chen JZ, Wang X, Boehm C, Fong K, Crick K, Garrido Clua M, Codan C, Dingle TC, Gregson D, Prosser C, Sadrzadeh H, Yan C, Chen G, Tse-Chang A, Garros D, Doig CJ, Zygun D, Opgenorth D, Conly JM, Bagshaw SM.

OBJECTIVE

This quality improvement (QI) initiative assessed the impact of combining antimicrobial stewardship programs (ASP) with standardized procalcitonin (PCT) testing and rapid molecular blood culture identification (BCID) on clinical outcomes and health-resource utilization in critically ill adult patients with sepsis.

STUDY DESIGN

Prospective, real-world, pragmatic pre-and post-implementation QI study. Between 2017 and 2018, adult patients with confirmed or suspected sepsis (Sepsis-3)[1] admitted to 2 academic, multidisciplinary ICUs in Canada, were prospectively enrolled. Each unit had a 12-week baseline period (phase 1) and an intervention period (phase 2).

In the ASP intervention, physicians and pharmacists conducted prospective audit and feedback (PAF) on all prescribed antimicrobials within 1-3 days of ICU admission and 3-5 days after. PCT testing (VIDAS® B·R·A·H·M·S PCT™) was performed daily for up to 7 days or until ICU discharge. Clinical decision support with evidence-informed stopping and continuation rules were available. Rapid molecular BCID (BIOFIRE® FILMARRAY® Blood Culture Identification Panel) was performed on all positive blood cultures 7 days a week.

Primary outcome: in-hospital mortality. **Secondary outcomes:** clinical outcomes, ICU antimicrobial utilization, and health-resource utilization.

RESULTS

- A total of 727 patients were included (phase 1, n = 342 and phase 2, n = 385).
- No significant difference in hospital mortality between the phases (25.4% vs 26.5%; *p*=.75), nor for clinical outcomes, use of mechanical ventilation, vasoactive support, or renal replacement therapy.
- ICU stay was similar, but hospital stay was significantly shorter in phase 2 (mean difference, 5.06; 95% CI, 4.46–5.84; *p*=.017).
- Antibacterial utilization was significantly lower in phase 2 (7.3% reduction; *p*=.010) and piperacillin-tazobactam use was reduced by 17.6% (*p*=.038).
- ASP assessments showed that antimicrobial usage could be optimized in 35% of patients.
- PCT testing helped clinicians make confident decisions on antimicrobial usage, with 36% discontinuation when levels were below 0.25 ng/mL.
- 6% of patients were bacteremic. BCID accurately identified the species in 76% of cases and 71% faster than standard lab protocols. Preliminary susceptibilities were available 28.6 hours sooner than standard laboratory testing, particularly for drug-resistant organisms.

CONCLUSIONS

Bundling ASP, PCT, and BCID did not impact sepsis mortality, but was found to be safe and acceptable, and led to a reduction in antimicrobial treatment and hospital length of stay.

"Based on these findings, we advocate for ASPs in all ICUs providing care for septic patients. Adjunctive PCT measurements may be useful in further risk stratifying patients and increasing clinician confidence for antibiotic discontinuation."

KEY FINDINGS

- PCT aided in antimicrobial streamlining and/or discontinuation and may have increased confidence in decision making for clinicians.
- Implementation of bundled ASP, PCT, and BCID significantly reduced antimicrobial therapy and length of stay.
- The authors therefore advocate for ASPs in all ICUs providing care for septic patients.

1. Sepsis 3: defined in The Third International Consensus Definitions for Sepsis and Septic Shock (SEPSIS 3) as an acute change in total SOFA score >2 points consequent to the infection.

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CURRENT MEDICAL RESEARCH AND OPINION
2020;36(9):1529-1532

ProCommunity: Procalcitonin Use in Real-world US Community Hospital Settings.

DeSear KE, Thompson-Leduc P, Kirson N, Chritton JJ, Ie S, Van Schooneveld TC, Cheung HC, Ou S, Schuetz P.

OBJECTIVE

To assess the impact of a procalcitonin (PCT)-based antibiotic stewardship program on antibiotic use in US community hospitals.

STUDY DESIGN

Retrospective, observational, matched cohort study: de-identified patient data from electronic patient health records were retrieved from 47 hospitals from a large US community hospital system spanning 20 states. Six hospitals were included in the PCT cohort (in-house PCT testing) and 41 in the Control cohort (no PCT testing available for ordering or sent out tests with routine turnaround times >2 days).

In total, 2,424 patients from treatment hospitals were included in the PCT cohort and 4,848 patients from control hospitals were included in the Control cohort.

Primary outcome: antibiotic exposure during the hospital stay, measured in days of antibiotic therapy. A single calendar day with multiple agents was counted as multiple days of therapy. **Secondary outcomes:** included hospital length of stay (LOS), ICU LOS, 30-day readmissions, in-hospital mortality and diagnosis of acute kidney injury (AKI) based on ICD-10 code.

RESULTS

- Patients in the PCT cohort had a statistically significant reduction of 1.47 fewer antibiotic days (9.1 vs. 8.5 days, 95%CI: -2.72; -0.22, *p*=0.021).
- No statistically significant difference in length of stay or adverse clinical outcomes except for an increase in acute kidney injury in the PCT cohort (odds ratio=1.26, 95%CI: 1.01; 1.58, *p*=0.038).

Table 1. Patient Outcomes in the PCT and Control Cohorts.

	PCT cohort [A] *N* = 1480	Control cohort [B] *N* = 1480	Multivariable results [A] vs. [B]	95% CI	*p* value
Length of AB treatment (days)	8.6 (6.9)	9.1 (8.1)	AMD: −1.50	(−3.27, 0.27)	.10
Length of hospital stay (days)	6.0 (3.7)	6.2 (4.2)	AMD: −0.68	(−1.26, −0.09)	.02*
Length of stay in the ICU (days)	1.3 (2.8)	1.2 (2.9)	AMD: −0.01	(−0.25, 0.24)	.96
30 day readmission	197 (13.3)	208 (14.1)	OR: 0.95	(0.71, 1.26)	.71
Mortality	48 (3.2)	85 (5.7)	OR: 0.44	(0.18, 1.11)	.08
Acute kidney injury	299 (20.2)	347 (23.4)	OR: 0.78	(0.54, 1.14)	.20

* Significant at the 5% level. AMD: Adjusted mean difference; AB: Antibiotics; CI: Confidence interval; ICU: Intensive care unit; OR, Odds ratio; PCT, Procalcitonin; SD, Standard deviation.

CONCLUSIONS

Use of a PCT-based protocol with on-site testing, education and pharmacy support was associated with fewer days of antibiotic therapy in patients with respiratory infections and sepsis in real-world practice in US community hospitals.

Furthermore, this intervention was considered to be safe as there were no differences in hospital length of stay, length of stay in the ICU, 30-day readmissions, or in-hospital mortality.

"Patients with respiratory infections and sepsis in hospitals utilizing a procalcitonin-based protocol coupled with education received fewer days of antibiotic therapy."

KEY FINDINGS

- Real-world study comparing US community hospitals with a PCT-based protocol, including on-site testing, education and pharmacist support versus control hospitals, where PCT was not readily available.
- The use of a PCT-based protocol was associated with a reduction in days of antibiotic therapy in patients with respiratory infections and sepsis in real-world practice.

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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 MDRO 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) **(Figure 1).**
- 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 €1183.49 in SOC arm (p=0.05).

CONCLUSIONS

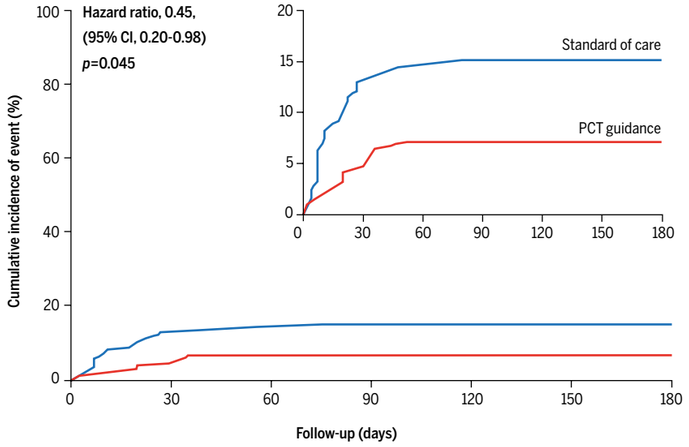
The PCT-guidance approach was shown to be effective in reducing the rate of infection-associated adverse events, as well as 28-day mortality, LOT and related cost of hospitalization. In countries with high antimicrobial consumption and high antimicrobial resistance rates, this strategy could be beneficial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

Figure 1: Kaplan-Meier curve for primary outcome: rate of infection-associated adverse events in the PCT-guidance group compared to standard-of-care group after 180 days.



NOTES

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Other resources available on Procalcitonin-Guided Antibiotic Therapy

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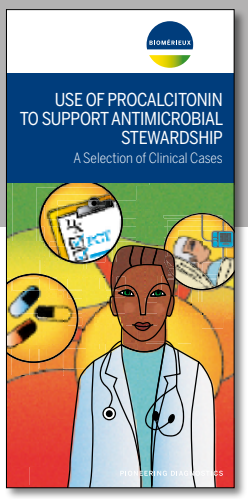

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