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Using Procalcitonin to Guide Antibiotic Therapy

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Procalcitonin levels rise in response to systemic inflammation, especially of bacterial origin. Multiple randomized controlled trials have demonstrated that procalcitonin-based algorithms can safely reduce antibiotic use in 2 clinical scenarios. First, in stable, low-risk patients with respiratory infections, procalcitonin levels of $<0.25 \mu\text{g/L}$ can guide the decision to withhold antibiotics or stop therapy early. Second, in critically ill patients with suspected sepsis, clinicians should not initially withhold antibiotics, but procalcitonin levels of $<0.5 \mu\text{g/L}$ or levels that decrease by $\geq 80\%$ from peak can guide discontinuation once patients stabilize. The recent stop antibiotics on procalcitonin guidance study (SAPS), the largest procalcitonin trial to date, demonstrated reduction in both antibiotic exposure and mortality in critically ill patients. Although procalcitonin is ready for routine use, future research should examine optimal strategies for implementation in hospitals, its real-world impact on clinical outcomes and costs, its applicability to immunocompromised patients, and the generalizability of trials to the US population.

Keywords. antibiotic stewardship; biomarkers; procalcitonin; respiratory infections; sepsis.

Up to 30%–50% of antibiotics given to hospitalized patients may be unnecessary [1]. Treatment courses commonly exceed recommended durations or are targeted towards colonizing or contaminating microorganisms [2]. Antibiotic overprescription has fueled the emergence of antibiotic-resistant bacteria as well as unnecessary drug adverse events and propagation of *Clostridium difficile* infection [3]. This global public health threat has stimulated national calls for hospitals to improve antibiotic prescribing practices and implement stewardship programs. However, in the face of imperfect diagnostic tools, clinicians are reluctant to withhold antibiotics when infection is suspected. This pressure is compounded by national quality measures compelling clinicians to immediately start antibiotics in potentially septic patients, even when the diagnosis is uncertain [4]. Subsequent antibiotic de-escalation can be challenging because 40% or more of patients with sepsis never have a pathogen identified [5].

Additional tools to help guide antibiotic prescribing are thus sorely needed. Biomarkers of bacterial infection are attractive because they can provide objective data to augment clinicians' intuition in starting, withholding, or stopping antibiotics. Of the various biomarkers, procalcitonin has been the most extensively studied. This review will focus on the literature supporting

procalcitonin's utility as a biomarker of bacterial infection and its role in guiding antibiotic therapy in adult patients.

PROCALCITONIN AS A BIOMARKER FOR BACTERIAL INFECTION AND SEPSIS

Procalcitonin is a precursor hormone of calcitonin that is undetectable in healthy states, but it is upregulated by cytokines released in response to bacterial infections [6, 7]. Conversely, procalcitonin production is blocked by interferon-gamma, a cytokine released in response to viral infections [8]. Procalcitonin has been used in Europe for many years and was also approved for use in the United States by the US Food and Drug Administration (FDA) as a diagnostic aid for sepsis in 2005. It also gained an FDA indication in 2016 for serial use to assess sepsis progression and 28-day mortality risk. Several different procalcitonin assays exist, but all demonstrate good concordance at clinically relevant cutoffs [9].

Serum procalcitonin levels rise rapidly in response to systemic inflammatory insults, with peak levels that correlate with the intensity of the stimulus. Procalcitonin has a short half-life (25–30 hours), and levels decline rapidly with resolution of inflammation [6, 10]. These properties make it potentially useful in helping decide whether to start antibiotics and when to stop antibiotics in a clinically improving patient. The kinetics also explain the prognostic value of both the initial procalcitonin level and subsequent trends [11]. The nonbinary nature of the test also means that different procalcitonin thresholds differ in their sensitivity and specificity, while allowing for potential variation in algorithms used to guide antibiotic therapy.

Although procalcitonin is more specific for bacterial infections than other inflammatory markers such as C-reactive protein [12], false positives can occur. Major stressors that cause

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systemic inflammation, such as severe trauma, circulatory shock, surgery, burns, inhalation injury, and pancreatitis, can also elevate procalcitonin levels, possibly through gut translocation of lipopolysaccharide or other bacterial products [13]. False negatives can also occur, notably in contained localized infections such as mediastinitis, empyema, or abscesses, or if procalcitonin is drawn too early in the course of infection [14].

The performance of procalcitonin as a diagnostic biomarker for sepsis in intensive care unit (ICU) patients has been examined in several studies and summarized in a recent meta-analysis by Wacker et al [15]. This meta-analysis pooled 30 studies, with a total of 3244 patients, and found moderate accuracy (overall sensitivity of 77% and specificity of 79%), with substantial heterogeneity between studies. However, procalcitonin levels are significantly higher in culture-positive sepsis versus culture negative-sepsis, and thus diagnostic performance may be better in the former group of patients [5, 16]. Furthermore, in critically ill patients with microbiologically documented infection, procalcitonin levels differ by site of infection, with the highest levels in those with positive blood cultures and lowest with pulmonary cultures [17]. Unfortunately, it is in the septic patients where no organism is identified that accurate biomarkers of infection would be most clinically helpful. Attempts to characterize the accuracy of procalcitonin in these patients are hampered by the lack of a true gold standard for diagnosing sepsis, because even experienced clinicians often disagree on whether or not patients were septic in retrospect [18]. It is similarly impossible to characterize procalcitonin's accuracy in pneumonia, because the absence of positive cultures does not rule out bacterial infection or coinfection when viral pathogens are identified.

Because of the lack of a reliable reference standard for identifying bacterial pneumonia and sepsis, particularly in culture-negative patients, the utility of procalcitonin cannot be determined through observational studies alone. However, numerous randomized intervention studies have examined whether procalcitonin-based algorithms can help clinicians decide whether to start or stop antibiotic therapy, without adversely impacting patients through delayed antibiotic therapy or inadequate treatment courses. These studies have primarily demonstrated efficacy in 2 clinical scenarios: adult patients with suspected respiratory infections, and critically ill adults with any type of suspected infection. Improving antibiotic use in these 2 clinical scenarios carries the potential for significant benefit given that respiratory infections are the most common indication for antibiotics in hospitalized patients and antibiotic use is most prevalent in ICUs [19].

PROCALCITONIN TO GUIDE ANTIBIOTIC THERAPY FOR RESPIRATORY INFECTIONS

Randomized controlled trials that have shown that procalcitonin guidance can help safely decrease antibiotic exposure in

patients with suspected or proven respiratory infections are summarized in Table 1. Christ-Crain et al [20] first demonstrated this in a single hospital in Switzerland in patients who presented to the emergency department with suspected lower respiratory tract infections. Procalcitonin was used to help determine whether not to initiate antibiotics, with a cutoff threshold of 0.25 µg/L. The procalcitonin group had a 47% reduced rate of antibiotic exposure, with no difference in laboratory or clinical outcomes. Follow-up trials in the same hospital, using similar procalcitonin algorithms, demonstrated efficacy in safely reducing antibiotic exposure in patients hospitalized for suspected community-acquired pneumonia and exacerbations of chronic obstructive pulmonary disease [21, 22].

The largest study to date examining procalcitonin for respiratory infections, the Procalcitonin Guided Antibiotic Therapy and Hospitalisation in Patients With Lower Respiratory Tract Infections (ProHOSP) study, was a multicenter randomized controlled trial involving 1359 adults at 6 hospitals in Switzerland who presented to the emergency department with any type of suspected respiratory tract infection [23]. Investigators in this study tested the utility of procalcitonin to inform both treatment initiation as well as discontinuation. As in prior studies, clinicians were encouraged to withhold antibiotics for patients with procalcitonin values of ≤ 0.25 µg/L. The study then required repeat procalcitonin testing on days 3, 5, 7, and at discharge. The investigators also recommended stopping antibiotics if procalcitonin levels decreased by $\geq 80\%$ when the initial procalcitonin was > 5 – 10 µg/L. Clinicians were allowed to overrule the algorithm and start antibiotics in patients with respiratory or hemodynamic instability, pneumonia due to *Legionella pneumophila*, or other risk factors for poor outcomes regardless of procalcitonin level. The procalcitonin group had a significantly lower mean duration of antibiotics (5.7 vs 8.7 days), with no difference in adverse events (including death, ICU admission, and recurrent infection). The procalcitonin algorithm also safely facilitated earlier antibiotic discontinuation in the subgroup of patients with confirmed community-acquired pneumonia, including those with documented bacteremia. Overall, 75% of patients in the procalcitonin group received any antibiotics, vs 88% in the control group. The algorithm was overruled by the physician based on their clinical judgment in only 9.2% of cases.

Although the trials studying procalcitonin for respiratory infections have generally focused on patients presenting to the emergency room (or in some cases the outpatient setting [24, 25]), one study demonstrated efficacy of procalcitonin in safely guiding antibiotic discontinuation in ICU patients with ventilator-associated pneumonia [26]. A subsequent Cochrane review concluded that procalcitonin guidance for respiratory patients in a variety of settings (including the emergency

Table 1. Procalcitonin Randomized Controlled Trials for Respiratory Tract Infections in Adult Patients

First Author (Year) [Reference] Trial Name	Setting (Country)	Number and Type of Infection	PCT Algorithm	Exclusion Criteria	Antibiotic Reduction Outcomes	Clinical Outcomes
Christ-Crain (2004) [20]	1 hospital (Switzerland)	243 patients with LRTI	Initiation only: antibiotics strongly discouraged ($<0.1 \mu\text{g/L}$), discouraged ($0.1\text{--}0.25$), encouraged ($0.25\text{--}0.5$), strongly encouraged (≥ 0.5). Repeat PCT after 6–24 hours if antibiotics withheld	Severely immunocompromised, cystic fibrosis, active tuberculosis, hospital-acquired pneumonia	47% reduction in antibiotic use ($P < .0001$)	No difference (including hospital mortality or long-term mortality at mean 5.3 months, hospital or ICU LOS, laboratory outcomes)
Christ-Crain (2006) [21] ProCAP	1 hospital (Switzerland)	302 patients with CAP	Initiation and Discontinuation: antibiotics strongly discouraged ($<0.1 \mu\text{g/L}$), discouraged ($0.1\text{--}0.25$), encouraged ($0.25\text{--}0.5$), strongly encouraged (≥ 0.5). Repeat PCT after 6–24 hours if antibiotics withheld, and at days 4, 6, and 8	Severely immunocompromised, cystic fibrosis, active tuberculosis, hospital-acquired pneumonia	52% relative risk of antibiotic exposure and median 5 vs 12 days of antibiotic treatment ($P < .001$ for both)	No difference (including mortality, ICU admission, treatment success, laboratory outcomes)
Stolz (2007) [22]	1 hospital (Switzerland)	208 patients with COPD exacerbation	Initiation only: antibiotics discouraged ($<0.1 \mu\text{g/L}$), discouraged if clinically stable ($0.1\text{--}0.25$), encouraged (>0.25). Repeat PCT after 6–24 hours if antibiotics withheld	Immunosuppression, asthma, cystic fibrosis, infiltrates on chest radiograph, psychiatric illness	56% relative risk of antibiotic exposure; 40% vs 72% overall antibiotic use ($P < .0001$ for both)	No difference (including death, treatment success, hospital LOS, ICU admission, improvement in FEV1 at 14 days and 6 months, 6 month rehospitalization rate, mean time to next exacerbation)
Briel (2008) [25]	53 outpatient physicians in (Switzerland)	458 outpatients with acute respiratory tract infections	Initiation and Discontinuation: antibiotics strongly discouraged ($\leq 0.1 \mu\text{g/L}$), discouraged ($0.1\text{--}0.25$), encouraged (>0.25). Repeat PCT after 6–24 hours if antibiotics withheld	Antibiotics within prior 28 days, psychiatric disorders, severe immunosuppression, cystic fibrosis, active tuberculosis, need for immediate hospitalization	72% decrease in antibiotic use (95% CI, 66%–78%)	No difference in activity restriction at 14 days, or ongoing symptoms or relapsing infection at 28 days
Kristoffersen (2009) [45]	3 hospitals (Denmark)	223 patients with LRTI	Initiation only: antibiotics discouraged ($<0.25 \mu\text{g/L}$), encouraged ($0.25\text{--}0.5$), and strongly encouraged (≥ 0.5). Single PCT measurement	None described	Mean 5.1 vs 6.8 days of antibiotic therapy ($P = .007$)	No difference (including hospital LOS, ICU admission, hospital mortality)
Schuetz (2009) [23] ProHOSP	6 hospitals (Switzerland)	1359 patients with LRTI	Initiation and Discontinuation: antibiotics strongly discouraged ($\leq 0.1 \mu\text{g/L}$), discouraged ($0.1\text{--}0.25$), encouraged ($0.25\text{--}0.5$), strongly encouraged (≥ 0.5). Repeat PCT after 6–24 hours if antibiotics withheld, and at days 3, 5, 7, and discharge	Active intravenous drug use, severe immunosuppression, life-threatening comorbidities, hospital-acquired pneumonia, chronic infection requiring antibiotics	Mean 5.7 vs 8.7 days of antibiotic therapy (relative change, –34.8%; 95% CI, –40.3% to –28.7%)	No difference (composite of 30-day adverse outcomes including death, ICU admission, and disease-specific complications, and recurrent LRTI); less frequent antibiotic-associated adverse events (19.8% vs 28.1%)
Burkhardt (2010) [24]	15 primary care practices (Germany)	550 patients with mild respiratory tract infection	Initiation only: no antibiotics ($<0.25 \mu\text{g/L}$) or yes antibiotics (≥ 0.25)	Recent antibiotics, chronic liver disease, recent major surgery, autoimmune or systemic inflammatory disorders, dialysis, medullary C-cell carcinoma	21.5% vs 36.7% of patients received antibiotics	No difference in significant health impairment after 14 days
Long (2011) [46]	1 hospital (China)	172 patients with low-risk CAP (discharged from ED)	Initiation only: antibiotics strongly discouraged ($\leq 0.1 \mu\text{g/L}$), discouraged ($0.1\text{--}0.25$), encouraged (>0.25). Repeat PCT after 6–12 hours if antibiotics withheld	Pregnancy, antibiotics started ≥ 48 hours before enrollment, immunocompromised, withholding of life-support, active tuberculosis	55% relative risk of antibiotic exposure ($P = .003$); median 5 vs 7 days of antibiotic treatment ($P < .001$)	No difference (all survived at 4 weeks, with similar clinical and laboratory outcomes)
Tang (2013) [47]	1 hospital (China)	225 patients with asthma exacerbation	Initiation only: antibiotics strongly discouraged ($\leq 0.1 \mu\text{g/L}$), discouraged ($0.1\text{--}0.25$), encouraged (>0.25). Repeat PCT after 6–8 hours if initial PCT <0.25	Recent antibiotics, other bacterial infections, pneumonia on chest radiograph, other chronic respiratory disease, severe organ dysfunction	46.1% vs 74.8% of patients received antibiotics ($P < .001$)	No difference (including asthma control, secondary ED visits, hospital readmission, additional steroids or antibiotics, FEV ₁)

Table 1. Continued

First Author (Year) [Reference] Trial Name	Setting (Country)	Number and Type of Infection	PCT Algorithm	Exclusion Criteria	Antibiotic Reduction Outcomes	Clinical Outcomes
Branche (2015) [48]	1 hospital (United States)	300 patients with nonpneumonic LRTI	Initiation only: antibiotics strongly discouraged (≤ 0.1 $\mu\text{g/L}$), discouraged (0.1–0.25), encouraged (0.25–0.5), strongly encouraged (≥ 0.5). PCT inter- vention arm coupled with viral PCR testing.	Definitive infiltrates on chest radiograph, immunosuppression, hypotension, ICU requirement, $\geq 15\%$ peripheral bands, conditions known to increase PCT, antibiot- ics before admission	No difference overall, but less antibi- otics in algo- rithm-adherent patients (2.0 vs 4.0 days; $P = .004$)	No difference in adverse events (no deaths in either arm; same median hospital LOS and number of posthospitalization healthcare visits)

Abbreviations: CAP, community-acquired pneumonia; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ED, emergency department; FEV₁, forced expiratory volume at 1 second; ICU, intensive care unit; LOS, length of stay; LRTI, lower respiratory tract illness; PCR, polymerase chain reaction; PCT, procalcitonin.

department, ICU, and primary care settings) resulted in a significant reduction in total antibiotic exposure (median 4 days vs 8 days), with no difference in mortality or rates of treatment failure [27].

PROCALCITONIN TO GUIDE ANTIBIOTIC THERAPY IN CRITICALLY ILL PATIENTS

Compared with stable patients with respiratory infections, it is less realistic that clinicians will withhold antibiotics in critically ill patients with suspected infection, regardless of procalcitonin results. This is reasonable in light of the imperfect sensitivity of procalcitonin for bacterial sepsis, and the potential to miss severe infections if only looking at a single measurement taken early in the course of disease. Thus, in randomized controlled trials examining the ICU patient population (summarized in Table 2), procalcitonin has generally been used as an aid to discontinue therapy after clinical stabilization. Procalcitonin cutoffs to stop antibiotics in ICU patients have been higher (0.5 $\mu\text{g/L}$, or even greater in some studies) than cutoffs used for stable patients with respiratory tract infections (0.25 $\mu\text{g/L}$). Small, single-center studies in medical-surgical or surgical ICUs in Switzerland and Germany first demonstrated that procalcitonin used in this manner could safely reduce antibiotic therapy in patients with suspected sepsis [17, 28, 29].

The first large multicenter study, the PROcalcitonin to Reduce Antibiotic Treatments in Acutely ill patients (PRORATA) trial, was conducted in 5 academic hospitals in France and included 621 adult patients with suspected bacterial infection at admission or during their stay in the ICU [30]. This study was unique in the ICU-based trials in that the algorithm included an initial procalcitonin to help assess whether to start antibiotics in addition to subsequent daily procalcitonin levels to help decide when to stop antibiotics. The cutoff procalcitonin value for discontinuation was <0.5 $\mu\text{g/L}$ or a decrease from peak value by $\geq 80\%$. Overall, more than 80% of patients were retrospectively adjudicated to have microbiologically or clinically documented

infection. The procalcitonin group had significantly more days at 28 days without antibiotics (14.3 days vs 11.6 days) and an overall 23% relative reduction in days of antibiotic exposure (mean 10.3 vs 13.3 days). The algorithm was overruled in 53% of cases (a much higher rate than in ProHOSP). The most common reason for nonadherence was physician reluctance in stopping antibiotic therapy in patients with low procalcitonin levels but ongoing clinical instability. The study showed noninferiority for 28-day and 60-day mortality, with no difference in other clinical outcomes. However, many critics were concerned about the trend towards higher 60-day mortality seen in the procalcitonin group (30.0% vs 26.1%), even though it did not meet the 10% noninferiority boundary set by the trial. Although none of the 60-day deaths in the procalcitonin group appeared to be attributable to relapsed or recurrent infection, this finding has made some critical care clinicians reticent to use procalcitonin in this way.

The next multicenter randomized controlled trial, the ProGUARD study, was conducted in 11 Australian ICUs and enrolled 400 adult patients with suspected sepsis [31]. The algorithm was much more conservative than PRORATA, because it advised stopping antibiotics if procalcitonin was <0.1 $\mu\text{g/L}$ or levels decreased by $>90\%$ from baseline (vs 0.5 $\mu\text{g/L}$ or $\geq 80\%$ decline in PRORATA). The control arm explicitly included antimicrobial stewardship guidance. There was a nonsignificant trend towards decreased antibiotic use in the procalcitonin group (median treatment duration of 9 vs 11 days, $P = .58$), with no difference in clinical outcomes, despite high ($>97\%$) protocol compliance. The more conservative procalcitonin threshold used may explain the lack of benefit compared with PRORATA. In addition, the study was likely underpowered because it was designed to detect an ambitious reduction of antibiotic therapy by 3.75 days.

The largest trial to date was the Stop Antibiotics on Procalcitonin guidance Study (SAPS), a multicenter randomized trial in patients with suspected infection admitted to the ICU in 3 university medical centers and 12 teaching

Table 2. Procalcitonin Randomized Controlled Trials for Infections in Critically Ill Adult Patients

First Author (Year) [Reference] Trial Name	Setting (Country)	Number and Type of Infection	PCT Algorithm	Exclusion Criteria	Antibiotic Reduction Outcomes	Clinical Outcomes
Nobre (2008) [17]	1 Medical-Surgical ICU (Switzerland)	79 patients with severe sepsis/septic shock	Discontinuation only: stop antibiotics if PCT decreased 90% from initial value, but not before day 3 (if baseline <1 µg/L) or day 5 (if baseline ≥1)	Organisms or conditions requiring prolonged duration of therapy, severe viral or parasitic infections, antibiotics started ≥48 hours before enrollment, severely immunocompromised, withholding of life support	4 day reduction in median duration of antibiotic therapy ($P = .003$)	No difference in mortality and recurrent infection; reduced ICU LOS by 2 days ($P = .03$)
Hochreiter (2009) [28]	1 Surgical ICU (Germany)	110 patients with suspected or confirmed sepsis	Discontinuation only: stop antibiotics if PCT <1 µg/L or decrease to 25%–35% of initial value over 3 days	Antibiotics started before ICU admission, therapy limitation due to goals of care	Mean 5.9 vs 7.9 days ($P < .001$)	No difference (treatment success, ICU LOS, SOFA score, hospital mortality)
Schroeder (2009) [29]	1 Surgical ICU (Germany)	27 patients with severe sepsis	Discontinuation only: stop antibiotics if PCT <1 µg/L or decrease to <35% of initial value over 3 days	Antibiotics started before ICU admission	Mean 6.6 vs 8.3 days ($P < .001$)	No difference (SAPS II or SOFA score, ICU stay, hospital mortality)
Stolz (2009) [26] ProVAP	7 ICUs in 3 hospitals (Switzerland, United States)	101 patients with ventilator-associated pneumonia	Discontinuation only: after 72 hours, antibiotic cessation strongly encouraged (<0.25 µg/L), encouraged (0.25–0.5 or decrease by ≥80%), discouraged (≥0.5 or decrease by <80%), strongly discouraged (>1)	Pregnant, enrolled in another trial, immunosuppressed, coexisting extrapulmonary infection requiring antibiotics for >3 days	13 vs 9.5 antibiotic-free days alive 28 days after ventilator-associated pneumonia onset (overall 27% reduction in antibiotic therapy, $P = .038$)	No difference (mechanical ventilation-free days, ICU-free days alive, hospital LOS, 28-day mortality)
Boudama (2010) [30] PRORATA	5 medical ICUs and 2 surgical ICUs (France)	621 patients with suspected infection	Initiation and Discontinuation: antibiotics strongly discouraged (<0.25 µg/L), discouraged (0.25–0.5), encouraged (0.5–1), strongly encouraged (≥1) (daily PCT measurements). Discontinuation also if PCT decreased ≥80% from peak	Pregnancy, bone marrow transplant, or neutropenic, infections requiring long-term antibiotics, poor chance of survival, and do-not-resuscitate orders	Mean 11.6 vs 14.3 days of therapy ($P < .0001$)	No difference in noninferiority analysis (28-day and 60-day mortality), but trend towards increased 60-day mortality (+3.8%). No difference in infection relapse or superinfection, mechanical ventilation, ICU and hospital LOS
Anname (2013) [49]	8 ICUs (France)	58 patients with culture-negative severe sepsis	Initiation and Discontinuation: withhold or stop antibiotics (<0.25 µg/L); antibiotics strongly discouraged (0.25–0.5), recommended (0.5–5), strongly recommended (≥0.5). Higher cutoffs used for postsurgical patients	Pregnancy, severe burns, trauma, cardiac arrest, postorthopedic surgery, neutropenic, withholding of life-supportive therapies, indisputable clinical infection, antibiotic exposure ≥48 hours before ICU admission	Nonsignificant trend: 67% vs 81% of patients on antibiotics at day 5 ($P = .24$)	No difference in day 5 mortality, ICU or hospital LOS or mortality, SOFA score at day 3 or 5 (but study terminated early due to low incidence of eligible patients)

Table 2. Continued

First Author (Year) [Reference] Trial Name	Setting (Country)	Number and Type of Infection	PCT Algorithm	Exclusion Criteria	Antibiotic Reduction Outcomes	Clinical Outcomes
Shehabi (2014) [31] ProGUARD	11 ICUs (Australia)	394 patients with suspected sepsis	Discontinuation only: stop antibiotics if PCT <0.1 µg/L, or 0.1–0.25 and infection is highly unlikely, or subse- quent PCT declines >90% from baseline (daily PCT measurements)	Antibiotics for surgical pro- phylaxis or proven infec- tion requiring >3 weeks of therapy, fungal or viral infections, immunosup- pressed, cardiac surgery or trauma or heat stroke within 48 hours, medullary thyroid or small cell lung cancer, not expected to survive, pregnancy	Nonsignificant trend: median 9 vs 11 days of antibiotic therapy (<i>P</i> = .58)	No difference (ventilation time, ICU and hospital LOS, hospital and 90-day mortality)
de Jong (2016) [32] SAPS	ICUs at 15 hospitals (Netherlands)	1546 patients with suspected or proven infection	Discontinuation only: stop antibiotics if PCT decreased to ≥80% of peak value, or ≤0.5 µg/L (daily PCT measurements)	Antibiotics for prophylaxis only or gut decontam- ination, expected ICU stay <24 hours, severe immunosuppression, severe viral or parasitic or tuberculosis infections, moribund, chronic infec- tion (eg, endocarditis)	Median antibiotic consumption of 7.5 vs 9.3 daily defined doses (<i>P</i> < .0001), median treatment dura- tion 5 vs 7 days (<i>P</i> < .0001)	Decreased 28-day mor- tality (20% vs 25%, <i>P</i> = .0122) and 1-year mortality (36% vs 43%, <i>P</i> = .0188). No differ- ence in hospital and ICU LOS or requirement for additional antibiotics within 28 days. But 5% vs 3% rate of reinfec- tion by same pathogen (<i>P</i> = .0492)
Bloos (2016) [50] SISPCT	33 ICUs (Germany)	1089 patients with severe sepsis or septic shock	Discontinuation or “Alert”: PCT measured on days 0, 1, 4, 7, 10, and 14. On day 4: change antibiotics or intensify source control efforts if PCT not decreased by ≥50% from baseline value. Other days: stop antibiotics if PCT <1 or decreased by ≥50% from previous value. (2 × 2 factorial study design with sodium selenite administration and PCT arms)	Pregnancy or lactation, selenium intoxication, infections with long recommended treatment durations, immunocom- promised, imminent death or treatment limitations	4.5% reduction in antibiotic exposure per 1000 ICU days (823 days vs 862 days) (<i>P</i> = .02)	No difference in 28-day mortality (25.6% vs 28.2%, <i>P</i> = .34), no dif- ferences in procedures for infection source control or diagnosis

Abbreviations: ICU, intensive care unit; PCT, procalcitonin; LOS, length of stay; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment score.

hospitals [32]. Importantly, this trial was conducted in the Netherlands, a country known to have judicious antibiotic prescribing practices. Baseline procalcitonin measurements were obtained around time of initiation of antibiotics and each day until ICU discharge or 3 days after systemic antibiotics were stopped. The algorithm in SAPS was similar to PRORATA, as clinicians were advised to stop antibiotics if procalcitonin was ≤0.5 µg/L or if it decreased by ≥80% of peak value. Unlike PRORATA, the algorithm was not designed to encourage or discourage antibiotic initiation at the time of suspected infection.

Overall, the procalcitonin group had significantly lower median antibiotic consumption: 7.5 vs 9.3 defined daily doses

and 5 vs 7 median days of treatment. As expected in this country with low antibiotic prescribing rates, treatment durations were lower in both arms compared with ProGUARD and PRORATA. Although this was designed as a noninferiority study, the procalcitonin group had statistically significant lower mortality at 28 days (20% vs 25% in control group, *P* = .0122) and at 1 year (36% vs 43%, *P* = .0188). There was 53% physician adherence to the algorithm within 48 hours. As in PRORATA, the main reason for nonadherence was concern about stopping antibiotics when the patient was not yet clinically stable. Although clinical outcomes were generally superior (mortality) or no different (hospital and ICU length of stay and requirement for additional courses of antibiotics within 28 days), 5% of the procalcitonin

group required a second course of antibiotics for proven reinfection by the same pathogen, vs 3% in the standard care group ($P = .0492$).

Despite the mild increase in reinfection seen in the intervention arm, the SAPS trial provides the strongest evidence to date that procalcitonin algorithms can be used to help safely decrease antibiotic exposure in critically ill patients, even when baseline antibiotic treatment courses are fairly short. More importantly, SAPS alleviated the concerning trend towards higher mortality seen in the PRORATA trial. Although the reasons for the lower mortality were not explicitly studied, the study authors speculated that high procalcitonin levels may lead physicians to feel reassured about their initial diagnosis of sepsis, whereas low procalcitonin levels may lead physicians to seek noninfectious diagnoses at an earlier stage than they would otherwise and thus treat patients' true causes of illness sooner [32]. In addition, antibiotic reduction may decrease adverse effects, selection of resistant pathogens, and *C difficile*.

LIMITATIONS AND AREAS FOR FUTURE RESEARCH

Despite the strength of evidence described above, there are several limitations to these studies that clinicians should be aware of before using procalcitonin in their own practice. First, in all procalcitonin-based trials, treatment group blinding is impossible, so the possibility of treatment bias cannot be ruled out. Randomized controlled trials are also accompanied by education and close guidance to physicians on how to apply the procalcitonin algorithms. Despite this, protocol adherence in the ICU-based trials has typically been approximately 50%. How closely physicians outside of clinical trials adhere to evidence-based algorithms is unclear. Large, ideally prospective studies are thus needed to examine the way procalcitonin is being used as well as its impact in real-world situations. Future studies quantifying procalcitonin impact should also examine its effects on antibiotic-associated adverse reactions, *C difficile* infections, and antibiotic resistance. Cost-effectiveness should also be carefully evaluated; so far, however, several small studies do suggest a net positive benefit in terms of reduction of overall costs of care [33–35]. One retrospective propensity-matched observational study using a large US database also suggested that procalcitonin testing on ICU admission was associated with lower hospital and ICU length of stay and costs [36].

Second, the optimal strategy for implementing procalcitonin algorithms in hospitals to maximize compliance and its impact on antibiotic use, outcomes, and cost remains unknown. Procalcitonin algorithms may not be well understood or trusted by front-line clinicians, and lessons can be learned from the literature showing that rapid diagnostics for bloodstream infections have greatest impact on patients and resource utilization when integrated with an antibiotic

stewardship program that receives results in real-time and can intervene [37]. Furthermore, although the SAPS trial shows that procalcitonin can reduce antibiotic exposure when baseline treatment courses are already short, it remains to be seen whether similar results can be achieved simply by shortening global duration of treatment recommendations and implementing rigorous antibiotic stewardship programs. This is particularly relevant in light of recent randomized controlled trials and guidelines supporting shorter treatment courses for various infections [38–40].

Third, immunocompromised patients have generally been excluded from randomized controlled trials. However, evidence exists that procalcitonin is still a sensitive marker of sepsis in these patients [41]. Given that immunocompromised patients account for a substantial amount of antibiotic use, future research is required to determine whether procalcitonin algorithms can help safely guide therapy in this patient population. Furthermore, optimal diagnostic cutoff points for sepsis may be higher in surgical versus medical patients with sepsis [42]. Surgical patients were a minority of cases in the large ICU-based trials, and it is unclear whether different algorithms should be applied in these patients. Other patient populations that have generally been excluded, but in whom guidance regarding antibiotic therapy duration would be valuable, include pregnant patients, patients with cystic fibrosis, and those with infections generally treated with prolonged antibiotic courses (such as osteomyelitis or endocarditis).

Fourth, although the procalcitonin cutoffs used for respiratory tract infections and ICU patients has been generally consistent (0.25 µg/L and 0.5 µg/L, respectively), there have been slight variations in the algorithms in different studies. As demonstrated by the ProGUARD study, where the procalcitonin cutoff level for discontinuing antibiotics was a conservative 0.1 µg/L, the benefit of procalcitonin may depend on what algorithm is used. At this point, however, it seems reasonable for hospitals to adopt the algorithms used in the largest studies for respiratory infections (ProHOSP) and ICU patients (PRORATA and SAPS). Future studies should aim (1) to explore the comparative effectiveness of different algorithms to optimize the use of procalcitonin and (2) to demonstrate whether procalcitonin guidance is safe and effective for all types of suspected or proven infections in non-ICU patients, not just those with respiratory infections.

Finally, most of the trials have been conducted in Europe. Thus, the generalizability of these findings to the US population has not yet been clearly demonstrated. However, the Procalcitonin Antibiotic Consensus (ProACT) study, a US-based multicenter trial, is underway and hopefully will help close this particular knowledge gap [43]. This trial is similar to the ProHOSP study and aims to study the effect of a procalcitonin algorithm in noncritically ill adult patients presenting to the emergency department with lower respiratory

tract infections. A positive result from ProACT, and a study replicating SAPS in the United States, would undoubtedly go a long way in reassuring US-based practitioners about the safety and efficacy of procalcitonin for antibiotic guidance in the ICU.

PROCALCITONIN AS AN ALERT TOOL TO GUIDE ANTIBIOTIC ESCALATION

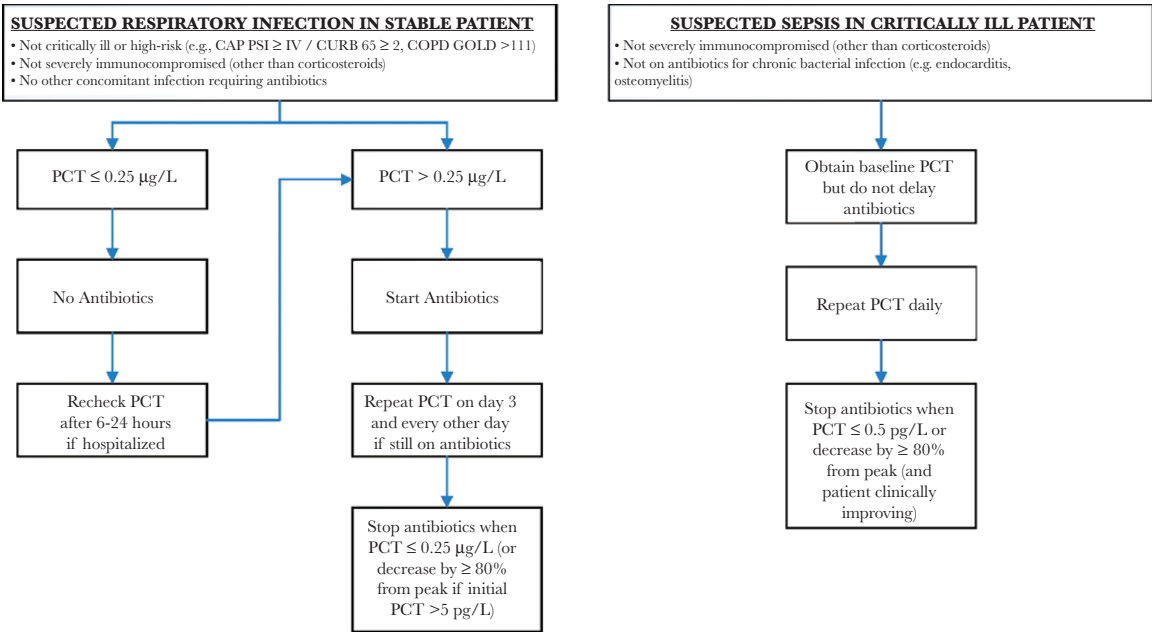
Although most of the ICU-based trials to date have focused on using procalcitonin as a tool to guide antibiotic discontinuation, there has also been interest in using procalcitonin-in-based screening to alert physicians to worsening sepsis. The Procalcitonin and Survival Study (PASS) was a randomized controlled trial at 9 university hospitals in Denmark that enrolled 1200 adults within 24 hours of ICU admission, regardless of whether or not infection was initially suspected, and measured daily procalcitonin levels [44]. If procalcitonin levels were $\geq 1.0 \mu\text{g/L}$ and not decreasing at least 10% from prior day, clinicians were required to increase the spectrum of antibiotic coverage and/or intensify infection diagnostic efforts. The study showed no benefit in 28-day mortality. Although the intervention increased the number of cultures taken and broad-spectrum antibiotic use, it did not improve time to appropriate antibiotics, except in patients with blood-stream infections. There was evidence of harm with increased

ICU length of stay and increased rates of mechanical ventilation, vasopressor use, and renal injury.

SUMMARY AND RECOMMENDATIONS

Procalcitonin has been extensively studied as a biomarker of bacterial infection, and most studies suggest good but imperfect diagnostic performance. However, based on over a dozen randomized controlled trials, it can be a useful aid to guide antibiotic therapy in the following 2 scenarios (summarized in Figure 1):

- 1. *Non-critically ill patients with suspected or proven respiratory infection.* Procalcitonin can be safely used at a cutoff of $<0.25 \mu\text{g/L}$ to withhold antibiotics in stable, low-risk patients with suspected respiratory infections. If antibiotics are given, procalcitonin can help inform early discontinuation of antibiotics based on serial measurements, even in those with documented bacterial infections.
- 2. *Critically ill patients with suspected infection/sepsis.* Clinicians are understandably reluctant to withhold antibiotics when sepsis is first suspected in unstable patients, regardless of procalcitonin levels, but serial procalcitonin measurements can be used at a cutoff of $<0.5 \mu\text{g/L}$ or $\geq 80\%$ decrease in peak level to help guide early antibiotic discontinuation once patients stabilize. Using procalcitonin in this fashion is safe, even in



Notes:
• If PCT levels do not decline despite therapy, consider treatment failure (e.g., inadequate antibiotic therapy or source control)
• PCT algorithms apply to patients with clinically confirmed infections as well as those in whom infection was never proven
• PCT algorithms can be used as a clinical decision aid but should never override clinical judgment

Figure 1. Suggested algorithms for using procalcitonin to guide antibiotic therapy in stable patients with respiratory infections and critically ill patients with sepsis. CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PCT, procalcitonin; PSI, Pneumonia Severity Index.

those with documented infections, and the largest trial to date (SAPS) suggests that it may even reduce mortality.

CONCLUSIONS

Clinicians must remember that false positives and negatives can occur with procalcitonin testing and that sepsis is a complex and heterogeneous syndrome. In most of the procalcitonin trials, overruling of the algorithm was allowed and in fact common in the ICU-based studies, underscoring the fact that procalcitonin should not replace clinical judgment. Clinicians should also be aware of the patients typically excluded from trials, particularly severely immunocompromised patients. However, when used properly as a clinical decision aid, the evidence is robust that procalcitonin can be a powerful antibiotic stewardship tool.

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