Procalcitonin
Where Are We Now?

Bachar Hamade, MD, MSc[a,b], David T. Huang, MD, MPH[c,*]

KEYWORDS

• Sepsis • Respiratory tract infection • Procalcitonin • Antibiotics • Mortality

KEY POINTS

- Procalcitonin is a biomarker generally elevated in bacterial infections but not viral.
- Procalcitonin guidance may aid physicians in modestly decreasing antibiotic use in critically ill patients.
- However, impact in settings with low baseline antibiotic use may be muted, and the effect on antibiotic resistance is unclear.
- As with troponin and all tests, procalcitonin requires extensive observational and interventional studies to best determine its role.

History

Procalcitonin (PCT) is a protein that consists of 116 amino acids and is the peptide precursor of calcitonin. Calcitonin is initially biosynthesized as PCT, which, under normal conditions, is found in low levels in the circulation ($\leq$0.1 ng/mL).[1,2]

PCT was first described as a marker of bacterial infection in 1993 when high concentrations of calcitonin-like immunoreactivity were detected in the blood of patients with extrathyroid diseases.[3] Using a monoclonal immunoradiometric assay for calcitonin precursors, investigators measured the serum concentrations of PCT

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Dedication: Dedicated to Jia Liu.

[a] Department of Emergency Medicine, American University of Beirut Medical Center, 2nd Floor, Cairo Street, Beirut, Lebanon; [b] Department of Critical Care Medicine, University of Pittsburgh Medical Center, 3550 Terrace Street, Room 651, Scaife Hall, Pittsburgh, PA 15261, USA; [c] Departments of Critical Care Medicine and Emergency Medicine, The MACRO (Multidisciplinary Acute Care Research Organization) and CRISMA (Clinical Research, Investigation, and Systems Modeling of Acute illness) Centers, University of Pittsburgh, 3550 Terrace Street, Room 606B, Scaife Hall, Pittsburgh, PA 15261, USA
* Corresponding author.
E-mail address: huangdt@upmc.edu

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in 79 children with bacterial and viral infections. They found serum PCT levels to be very high (6–53 ng/mL) in patients with severe invasive bacterial infections when compared with patients with mild local bacterial infections or viral infections (0.1–1.5 ng/mL); additionally, they noticed that the PCT levels decreased rapidly during antibiotic therapy and that calcitonin levels were normal in all patients irrespective of PCT levels. They concluded that PCT levels are increased during bacterial septic conditions and that serum concentrations are correlated with severity of microbial invasion.

A 1994 study also found PCT levels increase in response to bacterial infection, by injecting healthy volunteers with endotoxin and measuring serial PCT levels.[4] Levels were detectable at 4 hours, peaked at 6 hours, and maintained a plateau through 8 and 24 hours before they began to decrease, thus, exhibiting a half-life of 24 hours.[4,5] Several other studies also demonstrated superior diagnostic accuracy of PCT for sepsis compared with other markers, and additionally showed PCT itself is a mediator of the deleterious effects of systemic infection.[6,7]

Subsequently, PCT has received substantial interest as a potential marker of infection to assess the presence, clearance, and eradication of infection; predict mortality; and guide antibiotic management.

This review describes a conceptual framework for biomarkers using lessons from the history of troponin, applies this framework to PCT with a review of observational studies and randomized trials in and out of the intensive care unit (ICU), and concludes with clinical recommendations and thoughts on how to test a test.

LESSONS FROM TROPONIN

The evolution of PCT as a marker of sepsis is similar to the evolution of biomarkers of other disease processes. One biomarker used in everyday practice, and specifically in cardiac disease processes, is troponin. Here we discuss how troponin came to be the dominant cardiac injury marker.

Up until the early 1990s, creatine kinase muscle/brain (CKMB) was the biomarker of choice for diagnosing acute coronary syndromes (ACS) and cardiac ischemia. However, CKMB had both imperfect sensitivity to detect myocardial injury and imperfect specificity, with increased levels also noted in patients with skeletal muscle injury and renal failure.[8] Troponin is a contractile protein released into the circulation after loss of integrity of myocardial cell membranes and is undetectable in the serum of healthy people.[9] Several observational studies began to show the potential usefulness of troponin as a prognostic indicator in ACS. They showed that patients with unstable angina (ACS without biomarker elevation) who had negative values of CKMB but positive troponin values, had subsequently higher rates of myocardial infarction and cardiac events, as well as increased mortality.[9–11] Other observational studies also showed that patients with negative CKMB and positive troponin also exhibited worse echocardiographic findings and wall motion abnormalities,[12] and had worse cardiac pathology at autopsy.[13] Going beyond prognostication, other studies suggested that troponin could be of potential value in identifying patients that would benefit from specific treatments. For example, long-term anticoagulation was found to be associated with reduced infarction and death only in patients with positive troponin values,[14] and similar beneficial long-term outcomes were observed in patients with positive troponin placed on antiplatelet agents.[15] These observational studies were followed by interventional trials such as the randomized trial of 2220 patients by Morrow and colleagues[16] that demonstrated troponin identified ACS patients that would benefit from an early invasive strategy compared with a conservative strategy.

Currently, troponin is the gold standard cardiac biomarker, and critical care clinicians and investigators often wish we had a similar tool for sepsis. In the midst of our "troponin envy," we should recognize, however, that even troponin is not perfect. A recent editorial by a prominent troponin investigator noted that even now, "integration of troponin…-with clinical decision pathways…remains an area of active investigation" and that "what represents a significant change in troponin remains contentious."[17]

Nonetheless, there are several lessons to be learned from the history of troponin. Clinically, it is clear a thoughtful clinician is needed to decide when to order a test in the first place, and then how to interpret the test, to avoid, as has been stated for troponin, an "erosion of the importance of the clinical findings [and] the electrocardiogram."[18] Academically, it is clear many studies are needed, both observational and interventional, to fully understand the true clinical usefulness of a test, with a particular focus on understanding the discordance between the old and new tests. Ideally, a goal standard is available to help understand the discordance. In the case of troponin and CKMB, serial echocardiograms were used as a clinical gold standard for true myocardial infarction, "which kept [cardiology investigators] out of the logic loop of simply comparing 2 blood tests and trying to prove one is better by seeing who could shout louder."[19] Finally, and most important, any test needs to be tied to a treatment strategy to improve outcomes.

Overall, we should be clear and specific in what exactly we want a biomarker, or any test, to do. First, one could imagine a biomarker aiding in identification, both to detect occult cases early, as well as rule out. Second, a test that predicted the development of a condition could be useful, by prompting a clinician to order additional preventive measures. However, outcome prediction may of minimal use, as noted by another prominent troponin researcher who wrote that it is "easy to show prognosis…[yet] difficult to show prognostic value"[18] For example, whether or not your patient has a 30% mortality risk (based on routinely available data and your clinical judgment) or a 60% mortality risk (based on the additive value of a novel prognostic test), both scenarios represent a high risk, and you will likely offer maximal therapy in both scenarios. Third, the ideal test would also be able to guide treatment, with a subsequent improvement in outcomes.

Applying this framework to sepsis is challenging (**Table 1**). Sepsis is defined as life-threatening organ dysfunction owing to a dysregulated host response to infection.[20]

Table 1
Potential roles of a novel biomarker in sepsis, a clinical syndrome of infection and organ dysfunction

	Infection	Organ Dysfunction
Identify	Yes/No Etiology	No usefulness, as organ dysfunction defined clinically
Predict	Development—potential value in prompting increased preventive measures Outcomes—limited value unless huge change in predictive likelihood	
Guide treatment	Start, stop, or change antibiotics	Fluids—limited usefulness beyond existing hemodynamic monitoring technologies Organ support—can, and should, any novel test alter a clinician's judgment as to when to intubate, start vasopressors, start dialysis, etc?
Improve outcomes	The hardest bar to cross; troponin required multiple observational and interventional studies to determine clinical role	

The greatest challenge is that, unlike in ACS, there is no gold standard for infection or sepsis. The ideal biomarker would identify the presence or absence of infection, etiology, and some measure of antibiotic resistance and microbial burden. However, organ dysfunction is defined clinically via known guidelines such as Sepsis-3, thus, obviating any nonresearch role for a novel test in defining organ dysfunction.[21] With respect to guiding treatment, a biomarker could conceivably aid in deciding when to start, stop, or change antibiotics, but it is difficult to imagine a biomarker having incremental value in guiding fluid management beyond existing hemodynamic monitoring technologies, or aiding in deciding when to offer organ support beyond clinician judgment and routinely available data. For example, it would seem unlikely for a clinician to decide to intubate a patient based on a biomarker. Finally, improving outcomes is a high bar to cross, requiring multiple rigorous studies, as was done with troponin.

EVIDENCE: OBSERVATIONAL STUDIES

Identification

Several studies have examined the diagnostic usefulness of PCT both in and out of the ICU for multiple conditions (**Table 2**). Overall, most, but not all, studies have found PCT to have good performance characteristics for the identification of bacterial infection and sepsis.

A 2013 systematic review and meta-analysis by Wacker and colleagues[22] of PCT as a diagnostic marker of sepsis in critically ill patients included 30 observational ICU and

Table 2
Selected recent observational studies across a variety of conditions

Authors, Year	Type of Study	Sample Size (n)	PCT Cut-Off (ng/mL)	Identification
El-Solh et al,[36] 2011	Prospective observational	65	Multiple thresholds	Aspiration pneumonia
Maisel et al,[35] 2012	Prospective, international	1641	<0.25	Reduces pneumonia diagnosis uncertainty by 82%
Hattori et al,[23] 2014	Retrospective	1331	>0.9	+ Blood cultures
Laukemann et al,[24] 2015	Observational cohort	1083	>0.1	+ Blood cultures
Rast et al,[33] 2015	Observational quality control	48	>0.25	100% specificity for distinguishing erysipelas from deep venous thrombosis
Facy et al,[30] 2016	Prospective, multicenter observational	501	>0.25	Postoperative intra-abdominal infection
Rodriguez et al,[34] 2016	Prospective, multicenter, observational	972	<0.29	Excludes bacterial coinfection in influenza patients
Sharma et al,[26] 2016	Prospective	100	>7	Identifies cardiac surgery patients with infection
Dominguez-Comesana E et al,[29] 2017	Prospective observational	120	>0.45 on postoperative day 3	Postoperative intra-abdominal infection after colon surgery

non-ICU studies. The authors included articles that investigated PCT for the differentiation of sepsis from noninfectious inflammation, and had a well-defined reference standard for sepsis based on national medical society definitions. Pooled sensitivity and specificity were 0.77 (95% confidence interval [CI], 0.72–0.81) and 0.79 (95% CI, 0.74–0.81), respectively. The authors concluded PCT is a potentially helpful marker for identification of sepsis, when carefully interpreted within the context of the clinical presentation.

Two large emergency department (ED) studies demonstrated that PCT was a useful marker in excluding bacteremia and predicting severe bacteremia.[23,24] In the ICU, PCT and potentially change in PCT[25] were found to be a predictor of bacterial infection in the surgical population.[26,27] PCT was also able to predict anastomotic leaks[28] and infection after colorectal surgery[29,30] as well as mesenteric ischemia after cardiac surgery.[31] Other small outpatient and ED studies showed the diagnostic usefulness of PCT in identifying infection in patients with rheumatoid arthritis,[32] and differentiating erysipelas from deep vein thrombosis.[33] However, a study by Facy and colleagues[30] showed that C-reactive protein (CRP) outperformed PCT in detecting postoperative infections.

The diagnostic ability of PCT to indicate infection was also demonstrated in observational studies of respiratory diseases. In a large prospective, multicenter ICU study in patients with H1N1 influenza, a PCT of less than 0.29 ng/mL had a 94% negative predictive value for excluding bacterial coinfection, and outperformed CRP.[34] In the ED, the BACH study prospectively examined 1641 patients with a chief complaint of dyspnea and found PCT increased the accuracy of diagnosing pneumonia, particularly in cases with diagnostic uncertainty, such as in patients with concomitant acute heart failure.[35] In patients with acute heart failure, a PCT of greater than 0.21 ng/mL was associated with increased mortality if not treated with antibiotics. However, other observational studies have shown less impressive performance characteristics; for example, a study by El-Solh and colleagues[36] concluded that PCT had poor ability to differentiate aspiration pneumonia from pneumonitis.

Prediction

Several observational studies assessed the prognostic ability of PCT (**Table 3**). A 2015 systematic review and meta-analysis of PCT in predicting mortality in sepsis included 23 observational studies with 3944 patients. Studies had different PCT cut-offs, but all

Table 3
Selected observational studies of PCT predicting outcome

Authors, Year	Type of Study	Sample Size (n)	PCT Cut-Off (ng/mL)	Prediction
Bloos et al,[44] 2011	Multicenter observational	175	>0.6	Increased mortality in ventilator associated pneumonia
Jain et al,[42] 2014	Prospective observational	54	>7	Increased mortality
Sager et al,[45] 2017	Multinational prospective observational	6970	>0.5	Increased mortality
Schuetz et al,[46] 2017	Multicenter prospective observational	858	Delta-PCT >80% by day 4	Increased mortality

measured PCT serially. The authors found that elevated PCT and nonclearance of PCT were associated with increased mortality in septic patients with pooled relative risks of 2.60 (95% CI, 2.05–3.30) and 3.05 (95% CI, 2.35–3.95), respectively.[37] A small prospective study showed that a PCT of greater than 2.0 ng/mL was associated with ICU admission and 30-day mortality in patients with health care associated pneumonia,[38] and another study found similar associations and additionally showed a value of greater than 0.85 ng/mL predicted *Streptococcus pneumoniae* infection.[39] Other small prospective ICU studies showed elevated PCT levels at admission were associated with increased mortality in patients with sepsis,[40–42] infective endocarditis,[43] and community-acquired or ventilator-associated pneumonia.[44] The 2 largest studies were the TRIAGE[45] and MOSES[46] studies. TRIAGE was a multicenter prospective observational study of 6970 undifferentiated adult medical patients presenting to the EDs of 3 tertiary-care hospitals in Switzerland, France, and the United States. Irrespective of presenting diagnosis and independent of underlying infection, PCT was a strong and independent predictor of 30-day mortality, with an increased mortality as well as ICU admission and hospital readmission seen with higher PCT values. PCT also improved the prognostic accuracy of the quick sequential organ failure assessment score.[20] Similarly, the ED- and ICU-based MOSES study of 858 patients showed that, when the PCT did not decrease by more than 80% from baseline to day 4, the 28-day mortality doubled.

Guiding Treatment and Improving Outcomes

There have been several publications reporting either conceptual PCT guidance based on retrospective analysis of observational data, or actual implementation of a hospital protocol with PCT guidance. One single-center study assessed multiple clinical scores and biomarkers and concluded that the combination of a clinical score and PCT could potentially decrease unnecessary blood cultures with minimal false-negative rates.[24] Similarly, an observational Japanese study suggested that theoretic PCT guidance could safely decrease antibiotic duration in community-acquired pneumonia from 12.6 to 8.6 days,[47] and an observational Spanish study suggested PCT guidance might reduce antibiotic duration in secondary peritonitis.[48] Other studies have implemented a PCT guided protocol, and then used a before/after design to determine impact. A French study of 245 patients with an exacerbation of chronic obstructive pulmonary disease found a PCT protocol was associated with a decrease in antibiotic initiation, but not duration, with 60% physician compliance with the protocol.[49] Finally, some outcome prediction studies have suggested that like lactate clearance, PCT clearance could be used to identify treatment failure, and thus guide treatment.[50] However, not all studies concur, with some finding that PCT kinetics fail to predict treatment response, such as in perioperative abdominal infection with septic shock.[51]

Overall, although most of the observational literature of PCT suggest potential clinical usefulness, good performance characteristics alone are insufficient, with the central issue for PCT, or any biomarker or test, that it be tied to a treatment decision. For infection and sepsis, the lack of a gold standard is challenging, with the microbial etiology unknown for most cases of pneumonia, and even with septic shock, approximately 30% to 40% of such cases are culture negative.[52–54] To circumvent this issue, pioneering Swiss investigators developed a PCT treatment guideline, tested this guideline in a randomized trials, and thus used patient outcomes as the gold standard.[55] In the following section, we discuss the most recent systematic reviews and metanalysis of RCTs of adult patients admitted to ICUs with a diagnosis of sepsis, where antibiotic duration and mortality were compared between a PCT-guided

intervention arm and a usual care arm (Table 4). We then individually cover the largest of these ICU trials, as well as the 2 largest ED trials.

EVIDENCE: RANDOMIZED, CONTROLLED TRIALS

A 2018 systematic review and meta-analysis examined 10 RCTs containing 3489 ICU patients to estimate the efficacy (antibiotic duration) and safety (mortality, ICU length of stay) of PCT guidance for suspected or confirmed sepsis.[56] Most trials used a cut-off of 0.5 ng/mL to recommend antibiotic cessation among patients with sepsis or when PCT levels had decreased by 80% to 90% from peak. Two trials were excluded from the efficacy analysis as their antibiotic metric differed from the other 8 (one of the excluded trials showed no antibiotic reduction, the other showed antibiotic reduction with PCT guidance); both were included in the safety analysis.[57,58] The review concluded PCT guidance reduced antibiotic duration by 1.49 days (7. days 35 vs 8.85 days), with no adverse impact on mortality or length of ICU stay.

Another 2018 meta-analysis had a slightly different methodology and focus. The authors used individual patient data from 4482 ICU patients with infection and sepsis from 11 randomized trials to primarily assess the impact of PCT guidance on mortality within 30 days.[59] None of the individual trials were powered for mortality, except for one trial that showed no significant difference.[60] This meta-analysis reported PCT guidance reduced mortality (21.1% vs 23.7%; adjusted odds ratio; 0.89; 95% CI, 0.8–0.99), and decrease antibiotic duration by 1.19 days (9.3 days vs 10.4 days), with no difference in length of ICU or hospital stay.

The most recent 2019 systematic review and meta-analysis focused on PCT-guided antibiotic discontinuation and mortality in ICU patients, and sought to resolve and understand the discrepant mortality findings of prior meta-analyses. The authors analyzed 16 RCTs with 5158 patients and found that PCT-guided antibiotic discontinuation was associated with decreased mortality (risk ratio, 0.89; 95% CI, 0.83–0.97) and antibiotic duration (mean difference of 1.31 days). However, the authors noted these findings represented low-certainty evidence with a high risk of bias, and that decreased mortality was not found in patients with sepsis, trials with high PCT-guidance algorithm adherence, and trials that used PCT-guidance algorithms without CRP.[61]

Overall, the systematic reviews found a decrease of 1.0 to 1.5 antibiotic days with the use of PCT-guided antibiotic therapy in ICU patients, with a null or small survival benefit, and no evidence of harm.

For greater detail, we next review the 4 largest individual RCTs done in critically ill patients of PCT antibiotic guidance, where the primary goal was antibiotic reduction.

Table 4
Selected systematic reviews and meta-analysis comparing PCT-guided antibiotic therapy versus control in patients with sepsis

Authors, Year	Number of Trials	Number of Patients	Outcome in PCT Group Compared with Control
Iankova et al,[56] 2018	10	3489	No effect on mortality, 1.49 reduction in days on antibiotics
Wirz et al,[59] 2018	11	4482	Decreased mortality, 1.19 reduction in days on antibiotics
Pepper et al,[61] 2019	16	5158	Decreased mortality, 1.31 reduction in days on antibiotics, low certainty of evidence with a high risk of bias

- Bouadma and colleagues[62] (2010): ProRATA
  - Prospective, randomized, parallel-group, open-label trial in 7 ICUs in France
  - Dates of enrollment: June 2007 to May 2008
  - Population: Critically ill patients with suspected bacterial infection, who had not received antibiotics for more than 24 hours
  - N = 621 (PCT n = 307, control n = 314)

Enrolled patients were mostly medical (90%), and patients with neutropenia or infections where long-term antibiotic therapy is standard (eg, endocarditis) were excluded. PCT was assessed daily until antibiotic treatment was finished. Investigators were encouraged to discontinue antibiotics when PCT levels were less than 80% of peak, or less than 0.5 μg/L. This guidance was not followed in 219 episodes. Mortality met the noninferiority margin of 10%; however, the point estimates for mortality were higher in the PCT group versus the control group (30.0% vs 26.1% at 60 days, respectively). There was no difference in the proportion of patients with emerging multidrug-resistant bacteria from clinically obtained specimens (17.9% vs 16.6%).

- Shehabi and colleagues[63] (2014): ProGUARD
  - Multicenter, prospective, single-blind, randomized controlled trial in 11 ICUs in Australia
  - Dates of enrollment: March 2011 to December 2012
  - Population: Critically ill patients with suspected bacterial infection, receiving antibiotics, and with 2 or more systemic inflammatory response syndrome criteria
  - N = 394 (PCT n = 196, control n = 198)

PCT was measured at randomization and then daily until ICU discharge or up to 7 days, whichever came first. The PCT algorithm recommended antibiotic cessation for a PCT of less than 0.1 ng/mL, 0.1 to 0.25 ng/mL and infection deemed highly unlikely, or if PCT levels decreased by more than 90% from baseline. The primary outcome of median number of antibiotic days at day 28 did not differ between arms (9 days; interquartile range, 6–21 days) versus 11 days (interquartile range, 6–22 days), nor did the 90-day mortality (35% vs 31%). Compared with other ICU trials, this trial used a very low PCT cut-off to recommend antibiotic cessation. PCT was not measured after ICU discharge, however median ICU length of stay (6 days; interquartile range, 3–10 days) was shorter than the median number of antibiotic days. These 2 factors may have contributed to the lack of significant antibiotic reduction.

- Bloos and colleagues[60] (2016): SISPCT
  - Multicenter, placebo-controlled, randomized 2 × 2 factorial trial in 33 ICUs in Germany
  - Dates of enrollment: November 2009 to June 2013
  - Population: Adults admitted to the ICU with a diagnosis of severe sepsis or septic shock
  - N = 1089 (PCT n = 552, control n = 537)

This trial was the only RCT powered for mortality. Patients were randomized to PCT antibiotic guidance or usual care, as well as to intravenous sodium selenite or placebo. PCT was measured on days 0, 1, 4, 7, 10, and 14, and PCT guidance sought to both optimize antibiotic therapy and source control (if PCT had not decreased by ≥50% from baseline), as well as discontinue antibiotics (if on day 7 or later, PCT was ≤1 ng/mL, or ≥50% lower compared with the previous value). PCT guidance did

not decrease mortality or antibiotic costs, but was associated with a 4.5% decrease in antibiotic exposure (823 days vs 862 days, antibiotic exposure per 1000 ICU days).

- de Jong and colleagues[64] (2016): SAPS
  - Multicenter randomized controlled trial in 15 ICUs in the Netherlands
  - Dates of enrollment: September 2009 to July 2013
  - Population: Critically ill patients receiving antibiotics with suspected or proven infection
  - N = 1546 (PCT n = 761, control n = 785)

The SAPS trial tested the potential superiority of PCT guidance for antibiotic exposure, and the potential noninferiority for mortality and recurrent infection. PCT was measured daily until ICU discharge or until 3 days after antibiotics were stopped, and the protocol recommended antibiotic discontinuation when PCT decreased by 80% or more from peak, or was 0.5 ng/mL or lower. There was a significant decrease in median number of antibiotic days in the PCT group (5 days) compared with the control group (7 days) with an absolute difference of 1.2 days (95% CI, 0.65–1.78; $P<.0001$).

The authors also reported an unexpected finding of a lower 28-day mortality (20% vs 25%), and postulated that PCT levels may have aided in consideration of alternative diagnoses when low, and optimization of infection management when persistently high. A meta-analysis by Pepper and colleagues[61] noted that, if 9 patients in the intervention arm changed from survived to died, the survival benefit would no longer have been statistically significant.

We summarize all ICU trials comparing PCT antibiotic guidance to usual care in **Table 5**. Overall, most, but not all, trials showed a modest reduction in antibiotic exposure, patients were predominantly medical, and PCT algorithm cut-offs varied widely between trials. Only 1 trial showed increased mortality.[65]

The 2 largest non–ICU-based trials of PCT antibiotic guidance are the ProHOSP[75] and ProACT[76] trials. Both enrolled adult ED patients with lower respiratory tract infection (LRTI).

- Schuetz and colleagues[75] (2009): ProHOSP
  - Multicenter, randomized, controlled trial in 6 EDs in Switzerland
  - Dates of enrollment: October 2006 to March 2008
  - Population: adult ED patients with LRTIs
  - N = 1359 (PCT n = 671, control n = 688)

Antibiotics were strongly discouraged for a PCT of less than 0.1 ng/mL, discouraged for a PCT of 0.25 ng/mL or less, encouraged for a PCT of greater than 0.25 ng/mL, and strongly encouraged for a PCT of greater than 0.5 ng/mL. PCT was measured in hospitalized patients after 6 to 24 hours, and on days 3, 5, and 7. PCT guidance was enforced by requiring the treating physician to follow Web-based instructions on the study website before registering and entering baseline data. Physicians could overrule PCT guideline recommendations only after consulting with the coordinating center, for critical illness, or for legionella infection. Overall adverse outcomes were similar between groups (15.4% PCT, 18.9% control); and met the a priori noninferiority margin of 7.5%. The mean antibiotic duration differed between groups (5.7 days PCT vs 8.7 days control). The authors concluded PCT guidance decrease antibiotic exposure without adverse effects in LRTI. The results of smaller but similar trials conducted between 2004 and 2016 were summarized in a 2018 meta-analysis of 4090 trials from 11 trials, and found PCT guidance in LRTI resulted in shorter mean antibiotic use (mean difference, −2.15 days) with no adverse effect on mortality or length of stay.[77] The ProACT trial was published in 2018, and not included in this meta-analysis.

Table 5
ICU RCTs comparing PCT-guided algorithm antibiotic administration with usual care

Authors, Year	Sample Size	PCT Algorithm for Antibiotic Cessation (ng/mL)	Mean Antibiotic Duration	Mortality
Nobre et al,[66] 2008	79	<0.25 or >90% change if initial level ≥1.0	12.3 (PCT), 13.5 (control)	21% (PCT), 20% (control)
Hochreiter et al,[67] 2009	110	<1.0; ≥65%–75% change from initial level and current level>1.0	5.9 (PCT), 7.9 (control)	26% (PCT), 26% (control)
Schroeder et al,[68] 2009	27	≤1.0; ≥65%–75% change from initial level	6.6 (PCT), 8.3 (control)	21% (PCT), 23% (control)
Stolz et al,[69] 2009	101	After 72 h <0.25; between 0.25 and 0.5 with a decrease ≥80% from day 0	27% reduction	16% (PCT), 24% (control)
Bouadma et al,[62] 2010	621	<0.5; >80% change from peak	10.3 (PCT), 13.3 (control)	21% (PCT), 20% (control)
Jensen et al,[70] 2011	1200	<1.0 for ≥3 d	6 (PCT), 4 (control) [median values]	31.5% (PCT), 32% (control)
Layios et al,[57] 2012	509	<0.5	NA	22% (PCT), 21% (control)
Qu et al,[71] 2012	71	<0.5 on day 3	10.89 (PCT), 16.06 (control)	Not mentioned
Annane et al,[72] 2013	62	<0.5	4.7 (PCT), 4.0 (control)	23% (PCT), 32% (control)
Deliberato et al,[73] 2013	81	<0.5; >90% change from peak	15.5 (PCT), 17.3 (control)	2% (PCT), 10% (control)
Oliviera et al,[74] 2013	94	Initial <1.0, day 4 <0.1; initial ≥1.0, day 5 decrease of ≥90%	7.0 (PCT), 6.0 (CRP)	32.7% (PCT), 33.3% (CRP)
Shehabi et al,[63] 2014	394	<0.1; <0.10–0.25 if infection unlikely; >90% change from baseline level	11.7 (PCT), 13.0 (control)	11% (PCT), 8% (control)
Najafi et al,[58] 2015	60	≤0.5	NA	17% (PCT), 13% (control)
Bloos et al,[60] 2016	1089	<1; >50% change from baseline	4.5% reduction	25.6% (PCT), 28.2% (control)
de Jong et al,[64] 2016	1545	≤0.5; >80% change from peak	5.7 (PCT), 7.3 (control)	20% (PCT), 25% (control)
Daubin et al,[65] 2018	302	<0.1	5.2 (PCT), 5.4 (control)	20% (PCT), 14% (control)

- Huang and colleagues[76] (2018): ProACT
  - Multicenter, randomized, controlled trial in 14 EDs in the United States
  - Dates of enrollment: November 2014 to May 2017
  - Population: adult ED patients with LRTIs
  - N = 1656 (PCT n = 826, control n = 830)

ProACT used the same PCT guidance cut-offs and serial measurements used in ProHOSP, and guidance was deployed using quality improvement principles, with extensive use of education, prompts, and feedback. Overall adverse outcomes were similar between the groups (11.7% vs 13.1%) and met the a priori noninferiority margin of 4.5%. However, there was no difference between groups in mean antibiotic days by day 30 (4.2 days PCT vs 4.3 days control). In patients with acute bronchitis, antibiotic prescription in the ED seems to be lower in the PCT group versus control group (17.3% vs 32.1%), even after adjustment for multiple comparisons. However, this finding was a secondary outcome of a subgroup. The authors concluded provision of a PCT guideline to ED and hospital clinicians did not decreased antibiotic use among patients with suspected LRTI. The authors speculated that potential reasons for the lack of difference included limited incremental information from PCT to guide decision making (because PCT was associated with antibiotic prescription in both groups, as well as clinical signs and symptoms), PCT-guided decisions to withhold antibiotics in the ED and hospital were overruled in the outpatient setting, lower control group antibiotic use compared with that in ProHOSP, and lower clinician adherence to PCT guidance than in ProHOSP. Notably, control group antibiotic use was lower than U. norms, with less than one-third of acute bronchitis patients in ProACT receiving antibiotics, versus approximately 70% in multiple large US studies.[78–80]

CURRENT USE

Between 2007 and 2015, PCT use in US ICUs increased from 0.0% to 11.7%, compared with CRP use, which only increased by 3% during that time. Currently, PCT is ordered in 1 of every 20 adult US patients in hospitals found in the Premier Healthcare Database.[81] A retrospective study of patients with sepsis in US ICUs registered in the Premier Healthcare Database found that 18% had PCT measured and 30% had serial PCT measurements.[82] Another retrospective study of 933,591 patients with sepsis showed an increase in PCT use compared with CRP, and that multiple PCT measurements were associated with more interventions such as ICU admission, and use of vasopressors and mechanical ventilation.[83]

National authorities and medical societies have reached varying conclusions about PCT guidance in LRTI and sepsis. The US Food and Drug Administration first approved PCT as an aid, in conjunction with other laboratory findings and clinical assessments, to predict which patients on their first day of ICU admission would progress to sepsis and septic shock. Subsequently, the US Food and Drug Administration also approved serial PCT as an aid to predict risk of 28-day mortality in critically ill patients with sepsis and septic shock. In 2017, the US Food and Drug Administration cleared the expanded use of PCT to help ED or hospital clinicians determine if antibiotics should be started or stopped in patients with LRTI, and stopped in patients with sepsis.[84] In 2016, the US Agency for Healthcare Research and Quality concluded PCT had moderate strength evidence for reducing antibiotic prescription in uncomplicated acute respiratory tract infections, with low strength evidence for safety.[85] In 2015, the United Kingdom National Institute for Health and Care Excellence concluded that there was insufficient evidence for use of PCT in sepsis,[86,87] and in 2016 the Infectious Diseases Society of America did not recommend PCT to guide antibiotic initiation in

suspected hospital- or ventilator-associated pneumonia.[84] The current international 2016 Surviving Sepsis Campaign guidelines suggested that PCT could be used to support shortening antibiotic duration in patients with sepsis, and in patients who initially seemed to have sepsis but subsequently had limited clinical evidence of infection (weak recommendation, low quality of evidence).[88,89] The Infectious Diseases Society of America did not endorse these guidelines, stating that they failed to provide specific recommendations that providers can follow, and noting that their interpretation of the RCT literature is that PCT guidance for antibiotic duration is feasible and safe in critically ill patients with infections.[86]

Although disparate evidence and recommendations are common in medicine, what should hospitals and clinicians do today? We believe that in hospitals similar to those in ProACT—tertiary care academic centers with a relatively low baseline antibiotic use for LRTI—PCT guidance, even if deployed using extensive education, will have a minimal impact. It is possible that PCT guidance, combined with a robust antibiotic stewardship program, may have a greater impact. However, an antibiotic stewardship program alone might be sufficient in decreasing antibiotic use. It is also possible that PCT guidance in hospitals with more liberal use of antibiotics for LRTI may have a greater impact. However, simpler interventions such as basic education might also be impactful in such settings. For critically ill patients in the ICU and those with sepsis, we believe PCT should not be used for antibiotic initiation decisions, but could play a modest role in shortening antibiotic duration. However, the increased attention to antibiotic overuse and stewardship, and evidence-based movement toward shorter antibiotic courses, may limit incremental opportunity for PCT to further shorten duration. The most current meta-analyses in fact have only found a reduction of 1.0 to 1.5 antibiotic days from PCT guidance in the ICU. Although any decrease is laudable, the impact of a 1.0- to 1.5-day decrease in antibiotic duration on the ultimate target of antibiotic resistance is unclear. At the individual clinician level, we concur with the basic precepts of the Choosing Wisely Campaign, which urges thoughtful consideration of when to order tests and how to use their results. We recommend that should a physician choose to order PCT, that it be ordered in cases of clinical uncertainty so as to have the greatest chance of changing management, that the physician be prepared to follow the PCT guidance recommendation, and that above all traditional means of diagnosis and assessment should continue to be used, with PCT as only 1 part of clinical decision making.

HOW DO YOU TEST A TEST?

We should recognize that the story of PCT is not unique, and the generic question of how to prove a test is useful—or not—applies to all diagnostics in all fields. For example, it took decades to realize that the routine use of pulmonary artery catheters in the ICU was unnecessary,[90] and authorities still disagree on the optimal timing of mammograms for breast cancer screening,[91–93] as well as prostate-specific antigen testing for prostate cancer screening.[94] More recently, B-type natriuretic peptide–guided treatment was found to minimally change management in congestive heart failure and did not improve outcomes, in hospitals with expertise in heart failure and robust usual care.[95] Conversely, advanced testing has had positive impact in some areas, such as use of computed tomography scan screening to decrease lung cancer mortality, and use of a novel gene expression array to safely avoid chemotherapy use in breast cancer.[96,97] We believe that, as with troponin, not only PCT, but all tests, require extensive observational and interventional studies to best determine their role. Several currently enrolling trials of PCT guidance will aid in this determination (**Table 6**).

Table 6
Ongoing PCT clinical trials

Title	ClinicalTrials.gov Identifier	Study Type	Aim
A Clinical Trial of Procalcitonin-guided Antimicrobial Therapy in Sepsis (PROGRESS)	NCT03333304	Randomized prospective open-label clinical trial	Can 1 PCT-guided rule of stop antimicrobials decrease the incidence of infections by *C difficile* and multidrug-resistant bacteria
Biomarker Guided Antibiotic Treatment in Community-Acquired Pneumonia (BIO-CAP)	NCT03146182	Randomized prospective parallel assignment open-label clinical trial	To determine the efficacy of CRP and PCT based guidelines vs standard of care in reducing duration of antibiotic exposure in hospitalized patients with community-acquired pneumonia
A Randomized Double-Blinded, Placebo-Controlled Trial of Antibiotic Therapy in Patients with Lower Respiratory Tract Infection (LRTI) and a Procalcitonin Level (TRAP-LRTI)	NCT03341273	Randomized double-blinded placebo controlled noninferiority multicenter clinical trial	Compare the efficacy of azithromycin vs placebo on day 5 in patients with suspect LRTI and PCT levels $\leq$0.25 ng/mL

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