Sepsis Biomarkers
Value and Limitations

Use of biomarkers has flourished in many fields of medicine, and there is no doubt they will have an increasingly important role to play in patient management in the future.

Sepsis biomarkers have three principal applications. First, they can be used to rule out infection. It is often believed that these markers can help identify the presence of infection, but this is not their real value. Indeed, no sepsis biomarker can be entirely specific for infection, because similar pathways can be activated in the absence of an infection; for example, in situations such as trauma or surgery (1). It is rather the negative predictive value, suggesting absence of infection, that can be most useful, encouraging the physician to withhold antibiotics or to discontinue them sooner rather than later. This use of biomarkers has been demonstrated in many studies during the last 10 years, from the initial landmark study by Christ-Crain and colleagues, showing that the use of procalcitonin (PCT) levels could reduce antibiotic therapy in suspected lower tract infections (2), to the more recent analysis of the Procalcitonin Guided Antibiotic Therapy and Hospitalisation in Patients with Lower Respiratory Tract Infections (ProHOSP) study, which showed that PCT use could decrease antibiotic prescription in patients with heart failure presenting to an emergency department (3). Importantly, and in the same context (that biomarkers can be useful to rule out, rather than rule in, infection), a sepsis marker should not be used to escalate antibiotic therapy; this approach has been shown to be associated with increased organ failure (4).

Second, sepsis biomarkers are also markers of disease severity, which is information that can be useful in patient triage, and especially when making decisions about possible intensive care unit admission (5). PCT is a particularly good severity marker in sepsis, with levels well related to mortality rates (6).

Third, repeated measurements can be helpful to evaluate a patient's clinical course and, therefore, suggest a need for treatment review if levels are not decreasing. A substantial decline in sepsis markers can be used to encourage earlier discontinuation of antibiotic therapy (7, 8).

Could this latter application be used to create simple algorithms to guide patient management? In this issue of the *Journal*, Shehabi and colleagues (pp. 1102–1110) temper our enthusiasm about this possibility (9). In a fairly large study of almost 400 patients enrolled in 11 Australian intensive care units, use of an algorithm that included a PCT cutoff value of 0.1 ng/ml for stopping antibiotics did not influence the total duration of antibiotic therapy.

The study was well-designed and conducted, so the quality of the data is not in question. Why, then, did this approach, based on a sound underlying principle, not work? Were the negative results perhaps related to the chosen cutoff value? Would another threshold have resulted in more positive findings? This proposition is far from established. This study may simply just represent another failure of a simple protocol to influence outcomes, particularly when the standard level of care is already good, as was probably the case in these Australian centers.

Should we, therefore, write off PCT measurements? Of course not. It is, in fact, reassuring to see that PCT levels were higher in patients with positive than in those with negative cultures, and that the time course of PCT levels was strongly associated with outcome. Hence, these blood tests make sense. The study, rather, reminds us of the complexity of the problem. The underlying concept is valid, in that the duration of antibiotic therapy should not be identical in all patients, not only because the virulence of the microorganism and the site of infection will influence response to antibiotics but also because the host immune response may vary among patients; this is precisely why monitoring a marker of the patient's response can be important. However, the decision to stop antibiotic therapy should be based on a composite of bacteriological information, source of infection, duration of antibiotic therapy, clinical evolution (including fever and organ function), and the time course of biomarker levels. Within the complex framework of sepsis, attempting to influence our strategies using a specific cutoff value of a single biomarker is unlikely to be effective; the key message is that a sepsis biomarker should never be used alone to dictate patient management.

Among the more than 170 sepsis markers that have been proposed (10), PCT is one of the best, and it is certainly the most widely studied, but there is nothing magic about it, and it is definitely not perfect. Combining information collected from several biomarkers may be more useful (11), and adding circulating biomarker levels to information about the cellular response (12) and the degree of cell activation (13) may be a valuable future approach to help optimize our anti-infective strategies. ■

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Narrowing in on Early Cystic Fibrosis Lung Disease

Cystic fibrosis (CF) lung disease is characterized by chronic infection and inflammation of the airways, bronchiectasis, and progressive lung function decline (1). Although the widespread implementation of newborn screening programs for CF enables diagnosis during the first weeks of life, detecting the onset of lung disease in infants and young children remains challenging (2). Overt respiratory symptoms among children with CF are minimal, and monitoring techniques used in older patients, such as spirometry and sputum cultures, are not directly translatable to younger patients. During the last several years, the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) study has transformed our understanding of early CF lung disease. The AREST CF study enrolls infants diagnosed with CF by newborn screening and is following them longitudinally, with annual infant lung function testing (until age 2–3 years), bronchoalveolar lavage (BAL), and chest computed tomography; the first participants have now been followed for more than a decade. Through this structured protocol, the AREST CF investigators have provided vital insight into just how early CF disease pathogenesis begins. The AREST CF study was the first to show that radiographic evidence of lung disease, specifically bronchiectasis and air trapping, is present in infancy (3, 4) and, once identified, tends to persist or progress (5). In a landmark study, Sly and colleagues found that neutrophil elastase detected in BAL fluid at 3 months was associated with an increased risk for bronchiectasis at 12 and 36 months (6). The AREST CF study also demonstrated that infant lung function measures are already abnormal by 6 months (7), and that isolation of specific microbes from BAL fluid is associated with both lower lung function (8) and more rapid spirometric decline in the first 2 years of life (9). Despite these advances in detection of early disease, current therapeutic options for infants and young children remain comparatively limited.

In this issue of the *Journal*, Ramsey and colleagues (pp. 1111–1116) extend their follow-up of the AREST CF cohort, providing the first depiction of the natural history of CF lung disease from diagnosis by newborn screening into school age (10). The investigators recorded lung function results from 56 school-aged children with CF who underwent early BAL, lung function testing, and computed tomography scanning during the first 2 years of life. A small comparison group of 18 healthy children also had spirometry performed in infancy and at school age. Children with CF had, on average, 8% lower $FEV_{0.75}$ (equivalent to FEV_1 in older patients) than healthy control patients. Early life factors (before 2 years) were examined to identify factors that predicted lower lung function in school age among the patients with CF. Isolation from BAL fluid of pathogens frequently associated with CF (labeled "pro-inflammatory pathogens" and including *Pseudomonas aeruginosa, Staphylococcus aureus, Haemophilus influenzae, Streptococcus pneumoniae*, and *Aspergillus*) and free neutrophil elastase were associated with lower $FEV_{0.75}$ in univariate analyses. In a multivariate analysis, only the detection of abundant pathogens ("infection") remained significantly associated with school age lung function, suggesting infection is the major driver of airway inflammation and damage. Thus, early airway infection appears to have an important and lasting effect on obstructive lung disease. Although other investigators have demonstrated the persistence of abnormal lung function from infancy to preschool or early school age (11–13), this is the first study to demonstrate that lower airway pro-inflammatory pathogens during infancy are associated with this persistent lung function deficit.

Importantly, the investigators found no association of respiratory symptoms during the first 2 years with lower lung function in early childhood, emphasizing the clinically silent nature of early lung damage. The lack of observed association of respiratory hospitalization days in the first 2 years with early childhood lung function contrasts with the report of Byrnes and colleagues (14), who found that early-life pulmonary exacerbations were associated with lower lung function at age 5 years in the Australasian Cystic Fibrosis Bronchoalveolar Lavage Study cohort (15). This discrepancy is likely a result of different study populations and definitions of pulmonary exacerbations. Interestingly, in the current study, treatment with prophylactic antistaphylococcal antibiotics during the first 2 years of life was associated with higher school age lung function in univariate, but not multivariate, analyses; in addition, the treated infants did not have lower rates of infection or inflammation during infancy. Thus, the mechanism by which antibiotic prophylaxis might improve lung function is unclear, and in this observational study, the detected effect may

ORIGINAL ARTICLE

Procalcitonin Algorithm in Critically Ill Adults with Undifferentiated Infection or Suspected Sepsis

A Randomized Controlled Trial

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Abstract

Rationale: The role of procalcitonin (PCT), a widely used sepsis biomarker, in critically ill patients with sepsis is undetermined.

Objectives: To investigate the effect of a low PCT cut-off on antibiotic prescription and to describe the relationships between PCT plasma concentration and sepsis severity and mortality.

Methods: This was a multicenter (11 Australian intensive care units [ICUs]), prospective, single-blind, randomized controlled trial involving 400 patients with suspected bacterial infection/sepsis and expected to receive antibiotics and stay in ICU longer than 24 hours. The primary outcome was the cumulative number of antibiotics treatment days at Day 28.

Measurements and Main Results: PCT was measured daily while in the ICU. A PCT algorithm, including 0.1 ng/ml cut-off, determined antibiotic cessation. Published guidelines and antimicrobial stewardship were used in all patients. Primary analysis included 196 (PCT) versus 198 standard care patients. Ninety-three patients in each group had septic shock. The overall median (interquartile range) number of antibiotic treatment days were 9 (6–21) versus 11 (6–22), $P = 0.58$; in patients with positive pulmonary culture, 11 (7–27) versus 15 (8–27), $P = 0.33$; and in patients with septic shock, 9 (6–22) versus 11 (6–24), $P = 0.64$; with an overall 90-day all-cause mortality of 35 (18%) versus 31 (16%), $P = 0.54$ in the PCT versus standard care, respectively. Using logistic regression, adjusted for age, ventilation status, and positive culture, the decline rate in log(PCT) over the first 72 hours independently predicted hospital and 90-day mortality (odds ratio [95% confidence interval], 2.76 [1.10–6.96], $P = 0.03$; 3.20 [1.30–7.89], $P = 0.01$, respectively).

Conclusions: In critically ill adults with undifferentiated infections, a PCT algorithm including 0.1 ng/ml cut-off did not achieve 25% reduction in duration of antibiotic treatment.

Clinical trial registered with http://www.anzctr.org.au (ACTRN12610000809033)

Keywords: procalcitonin; sepsis; infection; critically ill; intensive care

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*Participating centers and associated investigators are listed before the References.

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At a Glance Commentary

Scientific Knowledge on the Subject: Use of procalcitonin (PCT) algorithms has been associated with reduced antibiotic exposure in different patient populations, including the critically ill.

What This Study Adds to the Field: A PCT algorithm with a cut-off of 0.1 ng/ml did not reduce antibiotic treatment days by 25% or more in heterogeneous patients in the intensive care unit with undifferentiated infection and/or presumed sepsis. Baseline PCT, however, differentiated sepsis severity and bacteremia within 72 hours. The decline in PCT over the first 72 hours independently predicted hospital and 90-day mortality. Thus, in the context of critical illness, investigations into the usefulness of PCT in septic patients could adopt a broader focus than just antibiotic deescalation.

Sepsis and bacterial infections account for more than 50% of intensive care (ICU) admissions. However, the diagnosis of sepsis and related infections is clinically challenging, and more than 70% of all ICU patients receive antibiotics (1). Definitions, such as the 2001 international consensus conference definition of sepsis (2), rely on a constellation of physiological changes that occur with systemic inflammation. The diagnostic accuracy of these definitions has been shown to be supoptimal, with calls for better precision and timely diagnosis and treatment (3, 4). There are limitations associated with microbiological testing in the intensive care setting (5). Thus, it is no surprise that inappropriate initial empirical antimicrobial therapy occurs in at least one-third of patients with sepsis, with a significant increase in mortality and hospital stay (6–8).

The use of novel biomarkers to improve the accuracy and early diagnosis of sepsis is an attractive strategy (9, 10). Among sepsis biomarkers, procalcitonin (PCT), a precursor of calcitonin, has been most widely studied to guide antibiotic prescription in septic patients, including the critically ill (11–16).

The use of a PCT-based intervention for antimicrobial escalation in septic ICU patients led to higher use of broad-spectrum antibiotics, longer mechanical ventilation, higher need for dialysis, and longer ICU stay (17). In contrast, the use of a PCT-guided deescalation algorithm in septic patients with respiratory infections, including those treated in the ICU, was associated with lower antibiotic exposure without increase in mortality or treatment failure (18). Fewer randomized controlled trials (RCTs), however, investigated the effect of PCT-guided algorithms on antibiotic prescription in the intensive care setting. The current Surviving Sepsis Guidelines suggests that low PCT values can assist clinicians to discontinue empiric antibiotics in patients who appear septic with no further evidence of infection (low level of evidence, GRADE 2C) (19). Adding to the uncertainty of the usefulness of PCT in the critically ill, the lack of a universally accepted cut-off value (20–23) has reduced clinicians' confidence and led to poor protocol compliance with study protocol (16).

Previous studies used different cutoff values based on the population investigated. For respiratory infections, cutoff values of 0.1 and 0.25 ng/ml were used in primary and emergency care setting. In the ICU setting, values of 0.25, 0.5, and as high as 2 ng/ml were used (22). Given the uncertainty surrounding the role of PCT in the critically ill and the lack of agreement on a universal cut-off, we planned a multicenter RCT to investigate whether a PCT algorithm with a low cut-off value of 0.1 ng/ml can reduce antibiotic exposure in academic and regional ICUs compared with standard care, including therapeutic guidelines and antimicrobial stewardship (24, 25). We also planned to investigate the predictive value of the initial plasma PCT level in determining the site of infection and the severity of sepsis in undifferentiated infections and the survival prognostic value of serial PCT levels in heterogeneous critically ill patients admitted to the ICU with presumed infection, sepsis, or septic shock.

Methods

Study Design

This prospective, single-blind, randomized, controlled, investigator-initiated trial was conducted in 11 ICUs in Australia between March 2011 and December 2012. The study protocol was approved by a New South Wales Lead Human Research and Ethics Committee (HREC/09/SVH/103) and ethics committees at all participating sites. Prospective written informed consent was obtained from all patients or a legally authorized representative. Data were collected by professional research personnel at each site and entered into a central secured database at the Clinical Informatics and Data Management Unit, Department of Epidemiology and Preventive Medicine, Monash University and analyzed by a blinded biostatistician at Monash University, Melbourne, Australia. The study was monitored by an independent data safety and monitoring committee, with no interim analysis performed.

Population

Patients older than 18 years of age, admitted to ICU within the previous 72 hours,

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receiving parenteral and/or enteral antibiotics for a suspected bacterial infection (2) (with two or more systemic inflammatory response syndrome criteria) and expected to remain in the ICU for longer than 24 hours were eligible. Exclusion criteria were patients receiving antibiotics for surgical prophylaxis or with proven bacterial infection requiring more than 3 weeks' antibiotic therapy, isolated systemic fungal or systemic viral infection in the absence of bacterial infection, neutropenia with a neutrophil count less than 1,000 cells/μl, receiving immunosuppressive agents, cardiac surgery or trauma or heat stroke within 48 hours, medullary thyroid or small cell lung cancer, subject not expected to survive to hospital discharge, or known pregnancy.

Randomization and Study Process

Patients were variable block randomized 1:1 via a secured central study website into either a PCT-guided (PCT group) or clinician-guided (standard care [STDC]) group. Randomization was stratified according to the presence of septic shock (defined by the receipt of inotropes and/or any vasopressors within the previous 24 h).

PCT was measured at randomization and daily thereafter in all patients until ICU discharge or up to 7 days, whichever came first. In the PCT group, clinicians can order additional PCT levels after Day 7 at their discretion. Daily PCT results were made available to the treating clinician for patients randomized to the PCT group. For the STDC group, clinicians were blinded to the PCT levels, and results were faxed directly to the Clinical Informatics and Data Management Unit. Antibiotic prescription in both the STDC and PCT groups was according to the Australian Antibiotics Therapeutic Guidelines (24) and the antimicrobial stewardship (implemented by infectious diseases twice-weekly rounds and on need consultations). The algorithm was implemented only in the ICU.

Most participating ICUs (8/11) had not used PCT for antibiotic guidance before the study. Treating clinicians were allowed to overrule the algorithm as clinically indicated.

The PCT algorithm:

1. Cease antibiotics if:
   a. Initial or any subsequent PCT is negative, level < 0.10 ng/ml
   b. Initial or any subsequent PCT is borderline, level 0.10–0.25 ng/ml, and infection is highly unlikely
   c. Subsequent PCT level declined more than 90% from baseline, and
2. Assess antibiotic appropriateness and/or adequacy of source control if PCT level at 48 hours is $>70\%$ of baseline value.

Baseline data included: patient demographics (age, sex, weight); 24-hour prerandomization Acute Physiology and Chronic Health Evaluation (APACHE) II (26) score, at randomization Sequential Organ Failure Assessment score (SOFA) (27), chronic comorbidities, ICU admission source, suspected infection source, and interventions (mechanical ventilation, vasopressor support, intravascular catheters). Postrandomization data collection included all daily antimicrobial prescriptions including dosage throughout the hospital stay and confirmed microbiological isolates during ICU stay. Patients were followed to 90 days for survival. Compliance with PCT-guided algorithm was monitored by the Coordinating Center.

The plasma PCT assays were performed using automated immunoassay analyzers.

Outcome Measures

The primary outcome is time to antibiotic cessation at 28 days, hospital discharge, or death, whichever came first after randomization, We have also assessed antibiotic-free days at Day 28 after randomization. Subgroup analysis, prospectively defined, included patients with sepsis, septic shock, positive culture, negative culture, bacteremia, and pulmonary isolate.

The main secondary outcome was the number of antibiotic daily defined

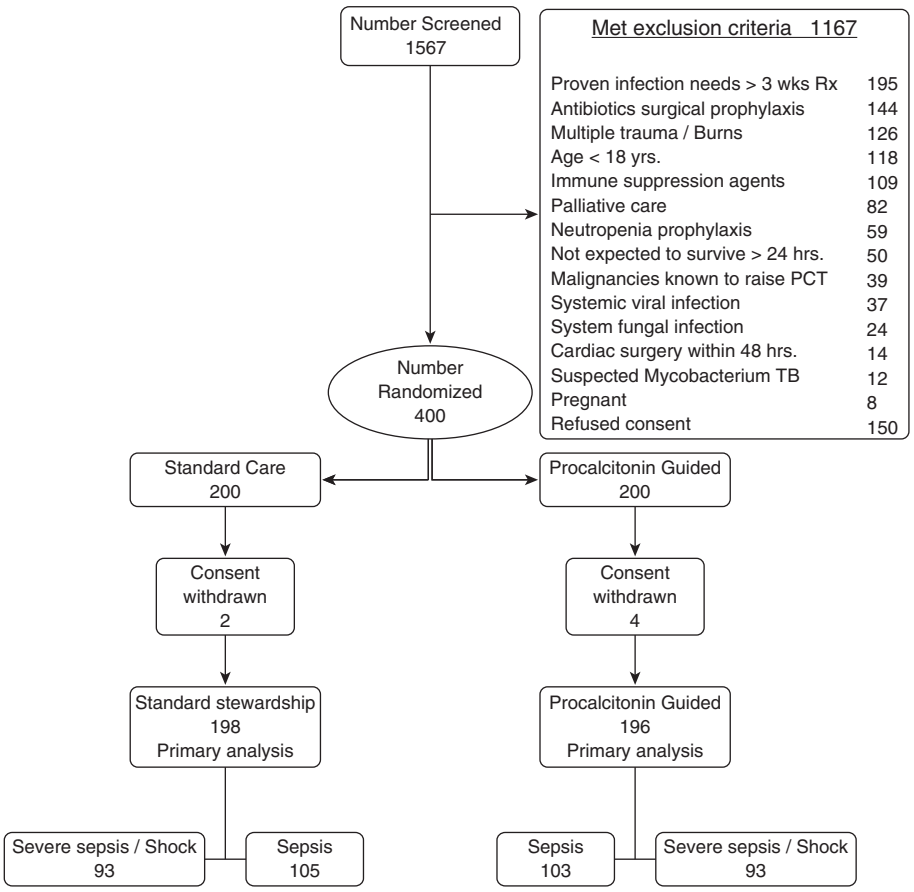

Figure 1. Patient flow diagram. The main exclusions met are shown, with 9.6% due to consent refusal. Six patients withdrew consent, leaving 394 patients for full analysis, with 47.2% of the entire population stratified with septic shock. There was no loss to follow-up at 90 days. PCT = procalcitonin; TB = tuberculosis; wks Rx = weeks of treatment.

doses (DDD) at Day 28. Other secondary outcomes included ICU and hospital length of stay and mortality and 90-day all-cause mortality. Additional *a priori* outcomes included the relationship between baseline (taken at randomization) PCT and sepsis severity, microbiologically confirmed infections within 72 hours, and the predictive value of baseline and serial PCT of mortality. Safety endpoints included readmission, emergence of resistant microorganisms, and the number of algorithm violations.

Statistical Analysis

Sample size calculations were derived from the findings of Schuetz and colleagues (14) in which patients with lower respiratory tract infections treated with a PCT-based algorithm showed a 35% (29–40%) reduction in antibiotic exposure. Assuming a median baseline exposure level of 9 days and an SD of 6 days, with 165 patients per group, this study had greater than 90% power to detect a clinically relevant reduction in duration of antibiotic usage of 25% (9.0 vs. 6.7 d). As duration of antibiotic usage is unlikely to follow a normal distribution, in accordance with Lehmann (28) this figure was inflated by 15%. To further account for potential dropout or loss to follow-up (anticipated to be <5%), a total of 400 subjects were recruited.

All variables were assessed for normality and log transformed if appropriate. Comparisons of proportions were performed using Chi-square tests for equal proportion or Fisher exact tests where numbers were small. Continuous normally distributed variables were compared using student tests and presented as mean (SD), whereas nonnormally distributed variables were compared using Wilcoxon rank-sum tests and presented as median (interquartile range [IQR]). Days of antibiotic therapy and the total DDDs were censored at death, discharge, or Day 28, whichever came first. Time to antibiotic cessation between groups was compared using a log-rank test and presented as median (IQR). To account for potential baseline imbalances, time to antibiotic cessation was adjusted for age, sex, and baseline PCT using Cox proportional hazard regression model and presented as hazard ratios (95% confidence interval [CI]). Changes in log PCT over time were modeled using generalized linear modeling, fitting main effects for group, time, and an interaction between group and time to ascertain if groups behaved differently over time. Similarly, the relationship between log PCT (taken shortly after randomization) and positive blood cultures was also examined using generalized linear modeling with results reported as geometric means (95% CI). The decline in log PCT during the first 72 hours was determined by fitting linear regression for each patient. The relationship between 90-day mortality and the change in log PCT over the first 72 hours was determined using logistic regression, with results reported as odds ratios (OR) (95% CI). All patients (including deaths) with a hospital length of stay less than 72 hours were excluded from this analysis.

To adjust for potential confounders, multivariable logistic regression analysis was performed using both stepwise selection and backward elimination procedures with variable inclusion criteria set at $P < 0.05$. Variables considered for model inclusion were participating hospital, principal diagnosis, age, APACHE II (26) (with age component removed) score, APACHE III diagnostic category, positive blood culture within the first 72 hours, ventilation (first 72 h), use of vasopressors (first 72 h), baseline PCT, sepsis type (sepsis vs. septic shock), surgical status, and the change in log PCT over the first 72 hours. A sensitivity analysis was then performed on hospital mortality using the same variables. Sensitivities and negative predictive values (NPV) were determined by

Table 1. Baseline Characteristics and Demographic Data

Characteristics	PCT Guided (*n = 196*)	Standard (*n = 198*)
Age, mean (SD)	63.1 (14.9)	65.8 (15.5)
Male, n (%)	93 (47)	119 (60)
Weight, mean (SD)	79.5 (25.3)	80.6 (24.9)
APACHE II,* mean (SD)	21.2 (7.8)	20.9 (7.1)
SOFA score total,† median (IQR)	6 (3–9)	6 (3–8)
PCT > 0.1 ng/ml, n (%)	169/180 (94)	166/176 (94)
PCT > 0.25 ng/ml, n (%)	157/180 (89)	156/176 (87)
Admission source, n (%)		
Emergency department	84 (43)	99 (50)
General ward	54 (28)	50 (25)
Operating room emergency	19 (10)	23 (12)
Operating room elective	5 (3)	0 (0)
Other ICU	2 (1)	4 (2)
Other hospital	32 (16)	22 (11)
Site of suspected infection, n (%)		
Pulmonary	86 (44)	84 (42)
Intraabdominal	20 (10)	38 (19)
Urinary tract	13 (7)	18 (9)
Blood stream	6 (3)	5 (3)
Others	7 (4)	7 (4)
Unidentified	64 (33)	46 (23)
Chronic comorbidities, n (%)		
Congestive heart failure	18 (9)	17 (9)
Chronic pulmonary disease	52 (27)	47 (24)
Diabetes mellitus + insulin	11 (6)	11 (6)
Diabetes type II	32 (16)	44 (22)
Chronic kidney disease	15 (8)	24 (12)
Hepatic impairment/failure	3 (2)	4 (2)
Cancer	18 (9)	19 (10)
Stroke	7 (4)	12 (6)
Ventilated at randomization, n (%)	94 (48)	91 (46)
Vasopressors at randomization, n (%)	93 (48)	93 (47)
Central venous catheter	153 (78)	140 (71)
Arterial catheter	175 (89)	182 (92)

Definition of abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II (26); ICU = intensive care unit; IQR = interquartile range; PCT = procalcitonin; SOFA = Sepsis-related Organ Failure Assessment (27).

*APACHE II scores recorded using worst values over previous 24 hours from time of study enrollment.

†SOFA recorded with worst values at enrollment.

fitting logistic regressions with results reported with 95% CI. All analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC). and a two-sided *P* value of 0.05 was considered to be statistically significant.

Results

Patient Flow and Baseline Characteristics

We randomized 400 patients; 6 withdrew consent, leaving 196 in the PCT group and 198 patients in the STDC group who completed 90-day follow-up for inclusion in the primary analysis (Figure 1).

Baseline characteristics (Table 1) of the two groups were comparable in terms of APACHE II, total SOFA (27) score, and the proportion of patients with baseline PCT plasma concentration greater than 0.1 and greater than 0.25 ng/ml. The median (IQR) baseline PCT levels were comparable in the PCT versus STDC group: 5.65 (0.94–29.79) versus 8.84 (1.1–31.68), $P = 0.29$, respectively. Patients in the STDC group had a higher mean age and proportion of men (60 vs. 47%) than the PCT group, the importance of which is undetermined. In total, 242 (61.4%) patients had confirmed infections (subsequent positive isolates while in the ICU). The proportion of study days where the PCT algorithm was not followed was less than 3%, the majority of which was due to missed PCT sampling.

Main Outcomes

The median (IQR) time to antibiotic cessation (antibiotic treatment days) at Day 28 in the primary population and *a priori* defined subgroups were comparable (Table 2): unadjusted hazard ratio (95% CI) PCT versus STDC, 1.06 (0.85–1.33), $P = 0.59$ and 1.01 (0.80–1.26), $P = 0.97$ after adjustment for age, sex, and baseline PCT using Cox proportional hazard regression. Kaplan-Meier survival plot for time to antibiotic cessation at Day 28 showed a log-rank $P = 0.39$ (Figure 2). The number of DDD/100 occupied bed days and days alive and antibiotic-free at Day 28 was also comparable Table 2.

Main secondary outcomes, such as ventilation time, ICU and hospital stay, and ICU, hospital, and 90-day all-cause mortality were comparable in the two groups (Table 2). There was a trend to a higher number of isolates classified as multiresistant microorganisms throughout the study period in the PCT group and a trend to higher readmissions due to a secondary infection (12 vs. 3%, $P = 0.09$) in the STDC care group (Table 2).

Although baseline PCT was not predictive of mortality, the decline in PCT over the first 72 hours was significantly predictive of both hospital and 90-day all-cause mortality, with survivors displaying a greater decline in PCT. This result remained consistent after adjustment for significant confounders (OR [95% CI], 2.76 [1.10–6.96], $P = 0.03$ and 3.20 [1.30–7.89], $P = 0.01$, respectively) (Table 3).

Table 2. Main Clinical Outcomes

Population	All Cohort (*n = 394*)	PCT Guided (*n = 196*)	Standard Care (*n = 198*)	*P* Value
Primary outcome, primary population, d at 28 d, median (IQR)				
Time to antibiotic cessation, n = 394	10 (6–21)	9 (6–20)	11 (6–22)	0.58
Antibiotic free days at day 28, n = 94	19 (9–22)	20 (11–22)	17 (7–22)	0.18
Time to antibiotic cessation, a *priori* defined subgroup analysis, d, median (IQR)				
Suspected sepsis, n = 208	10 (6–18)	9 (6–17)	11 (6–18)	0.74
Suspected septic shock, n = 186	11 (6–22)	9 (6–22)	11 (6–24)	0.64
Confirmed positive culture, n = 242	13 (7–27)	13 (7–27)	13 (8–26)	0.77
Negative culture, n = 152	7 (4–13)	8 (4–12)	7 (4–15)	0.94
Positive blood culture, n = 79	14 (8–27)	14 (8–23)	15 (7–27)	0.39
Positive pulmonary culture, n = 129	13 (7–27)	11 (7–27)	15 (8–27)	0.33
DDD of prescribed antibiotics				
All antibiotics, total DDD, median (IQR)		1200 (500–3,000)	1500 (750–4,000)	0.001
WHO DDD per 100 OBD, mean (SD)		135 (93)	139 (98)	0.65
ICU, hospital, and 90-d clinical outcomes				
Ventilation time, d, median (IQR)	4 (2–9)	4 (2–9)	4 (2–11)	0.99
ICU length of stay, d, median (IQR)	6 (3–10)	6 (3–9.5)	6 (4–10)	0.87
Hospital length of stay, d, median (IQR)	17 (10–31)	15 (9–29)	17 (10–32)	0.19
Readmission ICU re infection,* n (%)	18 (5)	6/174 (3)	12/183 (12)	0.18
Multiresistant organisms,†	77 (11)	45/324 (14)	32/355 (9)	0.09
N (%) of total isolates through study				
Therapy withdrawn in hospital, n (%)	71 (18)	38 (19)	35 (18)	0.66
ICU mortality, n (%)	36 (9)	21 (11)	15 (8)	0.28
Hospital mortality, n (%)	56 (14)	30 (16)	26 (13)	0.50
Hospital mortality septic shock, n (%)	30 (16.2)	14 (15.2)	16 (17.2)	0.71
90-d all-cause mortality,‡ n (%)	66 (17)	35 (18)	31 (16)	0.60
90-d all-cause mortality septic shock, n (%)	33 (17.7)	17 (18.3)	16 (17.2)	0.85

Definition of abbreviations: DDD = daily defined dose; ICU = intensive care unit; IQR = interquartile range; OBD = occupied bed days; PCT = procalcitonin; WHO = World Health Organization.

*Clinically or microbiologically confirmed infection.

†Multiresistant organisms defined according to microbiological sensitivity and minimum inhibitory concentration to standard antibiotics.

‡After adjusting for age, sex, baseline procalcitonin, odds ratio, 1.44 (0.82–2.52); $P = 0.20$.

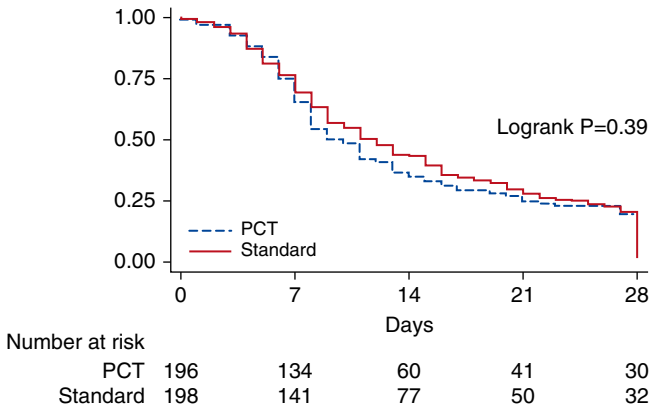

Figure 2. Time to antibiotic cessation. Kaplan-Meier survival analysis for time to antibiotic cessation until Day 28. PCT = procalcitonin.

Procalcitonin Plasma Concentrations, Sepsis Severity, Culture, and Mortality

Baseline and serial PCT plasma levels throughout the study were comparable in both the PCT and the STDC groups (Figure 3A). Baseline PCT plasma concentration was significantly higher in patients with positive versus negative culture (9.8 [1.7–41.3] vs. 3.3 [0.6–15.8], $P < 0.0001$); however, there was no difference in the PCT decline over time between patients with positive versus negative culture (Figure 3B). Similarly, in patients with septic shock, the median (IQR) baseline PCT was significantly higher than those with sepsis (13.6 [2.7–55.2] vs. 3.6 [0.5–15.6], $P < 0.0001$), with a faster decline in the serial PCT plasma concentration (Figure 3C).

Baseline PCT plasma levels were similar among survivors and nonsurvivors; however, there was a significantly faster decline over time in the serial PCT levels in survivors. A delayed rise in PCT was noticed in nonsurvivors, possibly due to recurrent infections (Figure 3D). Although all patients achieved greater than 30% decline in the PCT levels within 72 hours of enrollment, 95% of survivals at 90 days after randomization achieved 50% or greater decline in PCT over the first 72 hours (sensitivity, 95%; 95% CI, 90–100 for survival and NPV, 90%; 95% CI, 79–100) for death.

There were notable differences in the baseline plasma PCT levels between patients with positive blood versus pulmonary cultures (34.5 [16.4–90.3] vs. 5.2 [0.7–16.9], $P < 0.0001$ ng/l, respectively). Similarly, patients with positive urine culture had a significantly higher baseline PCT than those with positive pulmonary culture, who showed the lowest baseline PCT of all patients with positive cultures (*see* Figure E1 in the online supplement). A baseline cut-off of less than or equal to 3 ng/ml excluded a positive blood culture with a sensitivity of 90% (95% CI, 82–98) and an NPV of 96% (95% CI, 93–99%). A cut-off of less than or equal to 0.1 ng/ml excluded a positive culture in the first 72 hours, with a sensitivity of 100% and an NPV of 100%. In 152 (38.6%) patients, the presence of infection could not be confirmed with a positive culture throughout the study period; accordingly, in these patients the specificity of PCT was low.

Table 3. Multivariable Logistic Regression of PCT Decline versus Mortality

Variable	90-d Mortality*		Hospital Mortality†	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age, yr	1.06 (1.03–1.08)	<0.0001	1.06 (1.03–1.09)	<0.0001
Ventilation in first 72 h	3.63 (1.89–6.95)	0.0001	3.60 (1.79–7.23)	0.0003
Positive culture within 72 h	1.86 (1.01–3.40)	0.045	1.71 (0.90–3.26)	0.10
PCT decline rate first 72 h	3.20 (1.30–7.89)	0.01	2.76 (1.10–6.96)	0.03

Definition of abbreviations: CI = confidence interval; OR = odds ratio; PCT = procalcitonin.
OR generated from logistic regression adjusting for significant covariates where rate of PCT decline over first 72 hours (Log) was modeled as the primary exposure variable vs hospital and 90-day all-cause mortality for patients still alive after 72 hours.
*90-day mortality (n = 61/382), area under the receiver operating characteristics curve = 0.77, Hosmer-Lemeshow goodness of fit, $P = 0.67$.
†Hospital mortality (n = 51/382), area under the receiver operating characteristics curve = 0.77, Hosmer-Lemeshow goodness of fit, $P = 0.29$.

Discussion

This trial showed that in patients admitted to intensive care with presumed sepsis and/or undifferentiated infection, the use of an antibiotic prescription strategy based on a PCT algorithm with cut-off value of 0.1 ng/ml did not result in a significant reduction of time to antibiotic cessation, antibiotic-free days, or the overall antibiotic exposure when compared with standard care. It is possible, however, that a different PCT algorithm may have reduced antibiotic exposure.

In this group of patients, initial PCT plasma concentration differentiated sepsis severity and predicted patients who subsequently had a positive culture, in particular, blood culture. Although initial PCT levels did not predict mortality, a slow PCT decline over the first 72 hours was an independent predictor of hospital and 90-day all-cause mortality.

Our study population was representative of septic patients in general ICUs, with high severity of illness, proportion mechanically ventilated, and septic shock similar to other published reports (12, 16, 17). Numerous RCTs reported a reduction in antibiotic prescription with PCT-directed deescalation algorithms in non-ICU patients, in particular those with respiratory infections (11, 14, 29–31). In the intensive care setting, however, most trials were single center or unblinded. Importantly, contemporary strategies, shown to improve appropriateness and use of antimicrobial therapy, such as the antimicrobial stewardship (25, 32) programs, were not used.

In the Procalcitonin to Reduce Antibiotic Treatment Algorithm (PRORATA) trial, Bouadma and colleagues reported a significant 23% reduction in the antibiotic exposure and 2.7 more antibiotic-free

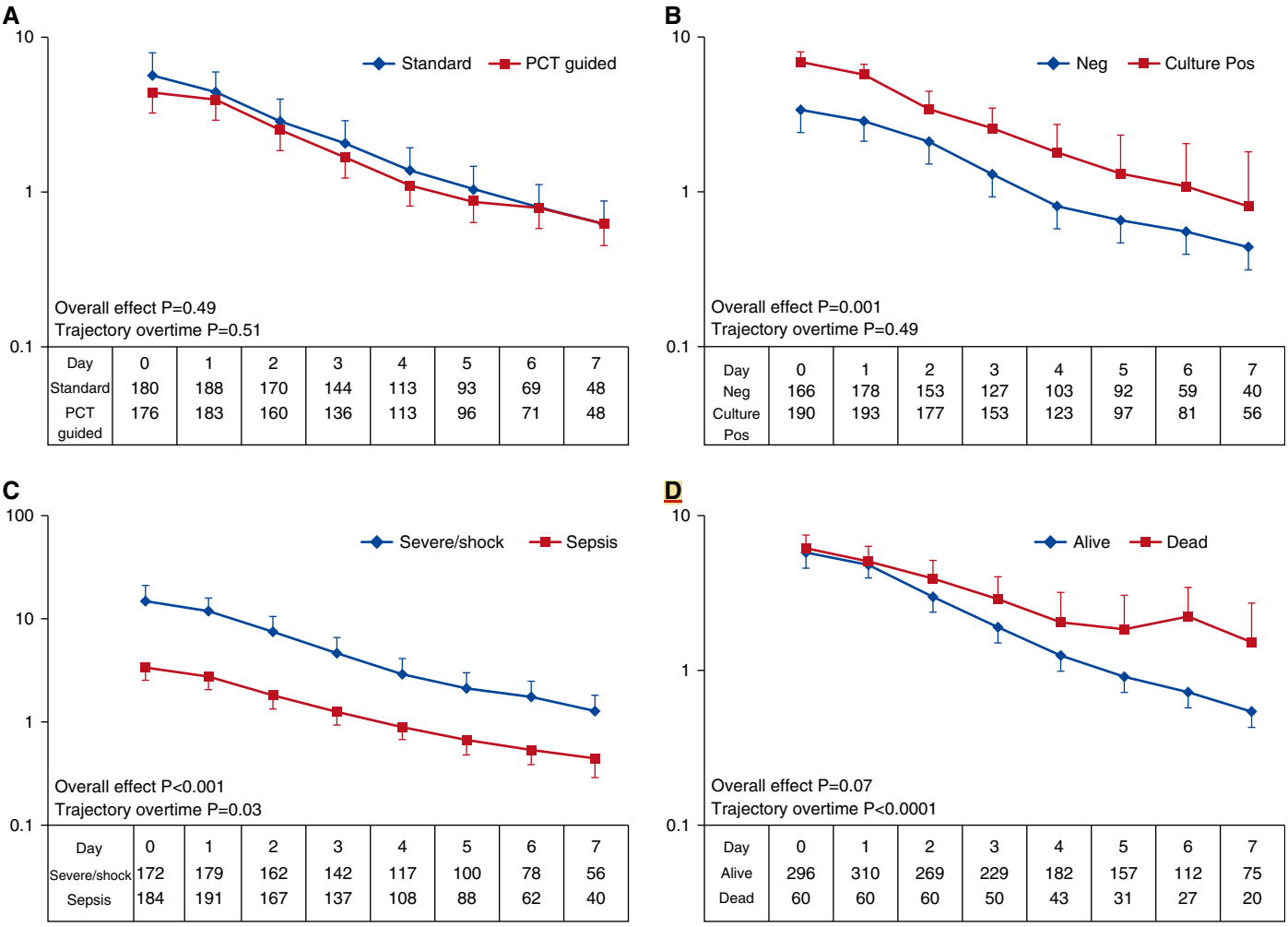

Figure 3. Serial daily procalcitonin (PCT) in primary populations and selected subgroups. The daily PCT plasma concentration expressed as geometric mean (95% confidence interval) is presented. (*A*) Serial PCT in the PCT-guided and the standard care group showing no difference in daily PCT or decline over time. (*B*) Positive versus negative culture with significantly higher PCTs on all study days ($P = 0.001$) in patients with positive culture. (*C*) Sepsis versus septic shock with significant difference in PCT on every study day ($P < 0.0001$) and faster decline in septic shock ($P = 0.03$). (*D*) Daily PCT versus 90-day all-cause mortality with significantly faster decline over time ($P < 0.0001$) in survivors with early separation after 24 hours and a late PCT rise in nonsurvivors.

days with a PCT deescalation algorithm; however, the mortality in this group was 3.8% higher than the control group (16). The PRORATA was a noninferiority open-label parallel group, in contrast to the single-blind design of our study. Furthermore, there are distinct differences between the two studies, which may explain our findings: First, we used a much lower PCT cut-off of 0.1 ng/ml versus 0.5 ng/ml in PRORATA. Second, we only included new admissions to ICU with a high clinical suspicion of presumed infection, the majority of whom had a baseline PCT level above the cut-off value. Third, the PCT algorithm was implemented only during ICU stay; this was, by comparison, significantly shorter in our study (mean ± SD, 8.57 ± 10.8 vs. 15.9 ± 16.1) days. Fourth, a smaller proportion of patients had pulmonary infection in our trial (43 vs. 72%); the use of PCT-guided algorithm in pulmonary infections has been most successful in reducing duration of antibiotic therapy in previous studies (14, 29–31). Fifth, our standard care explicitly included Antimicrobial Stewardship, a strategy not included in previous randomized trials, Finally, there was very high protocol compliance in our study, in contrast to 53% of patients managed outside the algorithm in the PRORATA study (16).

In the ICU setting, other previous trials focused on PCT algorithms to reduce antibiotic duration in specific groups of patients and were mostly single center and/or recruited small numbers. A study on ICU patients with proven bacterial infection showed no difference in duration of antibiotic therapy on an intention-to-treat analysis but reported reduction on by-protocol analysis (12). Similar results were also seen in a single-center study of 79 patients with mixed infection (13). Stolz and colleagues reported a 5-day (27%) reduction in the duration of antibiotic therapy in a multicenter trial of 101 patients with ventilator-associated pneumonia using 0.5 ng/ml cut-off; the subgroup with pulmonary infection in our study followed a similar trend (33).

However, despite reported association of early deescalation of antimicrobials with

lower morality in septic patients (34), a systematic review concluded that there is no evidence to support the safety of deescalation in patients with septic shock (35). A systematic review of the use of PCT in critically ill patients concluded that PCT could be used safely to reduce the duration of antibiotic therapy by 3.15 (95% CI, 1.95–4.36) days (36). Our data suggest that baseline and subsequent (within 48–72 h) PCT levels could be used to identify patients in whom bacterial infection is unlikely and for whom early deescalation of therapy is acceptable. Although the focus of previous trials and metaanalyses has been on the use of PCT algorithms to reduce the duration of antibiotic therapy (11, 12, 22, 23, 36, 37), our study supports the notion that in ICU patients with undifferentiated infections, the focus for PCT usefulness should be broader than just antibiotic deescalation.

After a decade of research on the use of PCT algorithms to reduce antibiotic exposure, there are still many unanswered questions. Although no universal cut-off value has been accepted, we recommend that the cut-off value for PCT algorithms, in undifferentiated infections, should be less than or equal to 0.1 ng/ml, especially in suspected pulmonary infections. It is still not known if PCT algorithms would lead to a reduction in the emergence of resistant microorganisms; our study showed no effect. This may be explained by institutional factors, such as ICU design and infection-control practices, which limit the ability of standard randomized trials to assess the impact of an antibiotic reduction strategy on the emergence of resistant organisms.

We used a low PCT cut-off value to test the usefulness of a possible universal cut-off for all infectious and septic presentations. Most participating ICUs did not have prior experience with PCT-guided algorithms; with the uncertainty about PCT-guided algorithms (20), a low cut-off was chosen to provide an additional safety margin. This was associated with high compliance with the algorithm and minimal protocol violations throughout the trial. In retrospect, the choice of 0.1 ng/ml cut-off seems well justified; with a number of positive pulmonary infections with a baseline PCT value between 0.1 and 0.25 ng/ml, a higher cut-off would have denied antibiotics to patients with positive pulmonary infections.

Besides the randomized multicenter study design, which controlled for known confounders, our study has many other strengths, as mentioned above; it was conducted in both academic and nonacademic ICUs with high level of protocol compliance, it incorporated best practice strategies, PCT was measured daily in all patients, data quality was monitored at all sites, and data management was conducted by a central body with a blinded statistician. Our study had some important limitations: our sample size calculation assumed 25% (2.3 d) reduction in antibiotic treatment from a baseline of 9 days; however, this translated into 25% (3.75 d), with 11 antibiotic treatment days being the baseline in the control arm. In hindsight, our study was underpowered to detect an ambitious reduction of 3.75 days, resulting in a nonsignificant 2-day reduction in antibiotic treatment days. The PCT algorithm was only followed during ICU stay; it was impractical to reliably follow the algorithm on the general words with multiple primary care teams involved. We included new ICU admissions with suspected sepsis and also excluded many patients for different reasons, including patients with high physiologic baseline PCT, infections where PCT does not reflect severity, patients needing prolonged antibiotics therapy, and those unlikely to survive to 90-day follow-up. This may limit the generalizability of our results.

Conclusions

An algorithm of PCT-guided antibiotic therapy with low cut-off value of 0.1 ng/ml did not reduce the duration of antibiotic treatment days by more than 25% in critically ill adults with undifferentiated infections. A different PCT algorithm, however, may still have reduced antibiotic exposure. The rate of decline in serial PCT in the first 72 hours was a significant predictor of hospital and 90-day all-cause mortality. The integration of PCT in clinical algorithms of antibiotic guidance and sepsis diagnosis in critically ill patients warrants further investigation. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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