Procalcitonin to Guide Duration of Antimicrobial Therapy in Intensive Care Units: A Systematic Review

Rajender Agarwal1 and David N. Schwartz2,3

1Department of Medicine, Stroger Hospital of Cook County, Chicago, Illinois; 2Division of Infectious Diseases, Department of Medicine, Stroger Hospital of Cook County, Chicago, Illinois; and 3Department of Medicine, Rush Medical College, Chicago, Illinois

Can the use of serum procalcitonin levels safely reduce antimicrobial use in intensive care unit (ICU) patients? We performed a systematic literature review that identified 6 published randomized controlled trials comparing PCT-guided antimicrobial therapy to usual care in ICU patients, extracting data on ICU and patient characteristics, PCT guideline content, intensity of antimicrobial exposure, ICU length of stay, infection relapse, and mortality. Procalcitonin guidance was associated with significantly reduced antimicrobial exposure (effect sizes, 19.5%–38%) in all 5 studies assessing its impact on treatment duration but did not significantly impact antimicrobial exposure in the study assessing treatment initiation only. Length of ICU stay was significantly decreased in 2 studies but was unchanged in the others. Neither infection relapse nor mortality varied significantly in any of the studies. Procalcitonin guidance of antimicrobial duration appears to decrease antimicrobial use in the ICU safely and significantly and may also decrease the length of stay in the ICU.

Emergence of multidrug-resistant organisms has led to guidelines by several national organizations to limit inappropriate antimicrobial use by optimizing the use of antimicrobials in hospitals [1, 2]. A recently developed approach is to measure proinflammatory biomarkers to guide the initiation and/or duration of antimicrobial therapy by helping physicians estimate the likelihood of invasive infection or to gauge the rapidity of the patient’s response to treatment, respectively.

Serum levels of procalcitonin (PCT), the 116-amino acid precursor to calcitonin, are elevated in calcitonin-secreting neoplasms and in a wide range of systemic inflammatory conditions, including clinically localized bacterial infection and sepsis; malaria; pancreatitis; inhalational, burn, and traumatic injury; and major surgery. PCT elevation occurs within 2–4 hours after onset of the inflammatory disorder, often peaks in the second day, and falls rapidly during clinical recovery. In all of these conditions, the magnitude and duration of PCT elevation correlate with injury severity and prognosis. PCT may also be elevated in viral and fungal infection (e.g., candidemia), though generally much less so than with bacterial infection [3].

Clinical trials involving patients in a variety of clinical settings have shown that the use of PCT levels successfully reduces antimicrobial initiation and associated toxicity among patients with acute respiratory infections without affecting other clinical outcomes [4–7]. PCT has performed less well in helping clinicians to distinguish bacterial infection from other causes among intensive care unit (ICU) patients with acutely deteriorating conditions [8, 9], largely owing to frequent comorbidities, including major surgery [9], that are also associated with elevated PCT [3]. However, a recent randomized controlled trial (RCT) involving ICU
patients with ventilator-associated pneumonia [10] and 2 others involving ICU patients with suspected bacterial infection at any body site [11, 12] used serial PCT measurement to facilitate the early discontinuation of antimicrobials rather than or in addition to assessing the need for their initiation; all trials demonstrated reduced antimicrobial use among patients randomized to PCT-based management compared with controls, without impacting survival. These promising findings prompted us to perform a systematic review to better assess the safety and effectiveness of PCT measurement to guide the duration of antimicrobial therapy in ICUs.

METHODS

Study Selection

We searched MEDLINE (1950 to January 2011) and EMBASE (1980 to January 2011) using keywords and Medical Subject Heading (MeSH) terms for PCT, critically ill patients, and antimicrobial therapy. The detailed search strategy can be found in Table 1. A screening of titles and abstracts was followed by full-text screening. We included in our review all RCTs that (1) were published in English, (2) focused on the ICU population, (3) examined the efficacy of PCT measurement to guide antimicrobial therapy, and (4) included the primary outcome, as described below.

Outcome Measures

The primary outcome was the duration or intensity of antimicrobial therapy. This could be defined as the number of days with antimicrobials, the number of days without antimicrobials, days of antimicrobial exposure per 1000 patient days, or number of antimicrobial days for the first infectious episode. This variation in outcome measures and heterogeneous reporting of measures of central tendency precluded formal meta-analysis. Secondary outcomes were length of ICU stay, length of hospital stay, days free of mechanical ventilation, relapse of infection, and mortality.

Data Extraction

We extracted data on the types of patients enrolled and excluded, details of the intervention used (eg, PCT assay used, whether PCT levels were used to guide the initiation and/or discontinuation of antimicrobials, frequency of PCT measurement), the frequency with which PCT algorithm recommendations were overruled by treating physician, size of the study samples, and our outcome measures. We evaluated the study quality of RCTs by examining the randomization and blinding procedures and the extent of attrition, using a modified version of the Jadad scale [13].

RESULTS

Study Selection

Our literature search initially yielded 1018 publications. Screening of titles and abstracts followed by full-text screening ultimately yielded 6 RCTs that met our inclusion criteria [10–12, 14–16] (Figure 1). Of these, 1 study was published only in abstract form [15].

Study Characteristics

Combined, the 6 studies included 1476 patients. The study characteristics are detailed in Table 2. All studies enrolled adult
ICU patients exclusively. In 4 studies, 11% [12], 30% [15], 47% [10], or 100% [16] of patients were postoperative; all patients were recruited from a surgical ICU in another study [14]; and the proportion of postoperative patients was not reported in one study [11]. Five studies included patients with community- or ICU-acquired suspected sepsis or septic shock [11, 12, 14–16], and the last study was limited to patients with ICU-acquired ventilator-associated pneumonia [10]. Immunosuppressed patients and patients requiring long-term antimicrobial therapy were excluded in 3 studies [10–12], and exclusion criteria were not specified in the remaining studies [14–16].

PCT levels were used to inform the need for initial antimicrobial therapy exclusively in 1 study [15], the duration of therapy exclusively in 4 studies [10, 11, 14, 16], and both the need for initial therapy and its duration in 1 study [12]. Except in the study in which PCT measurement was limited to the initial suspicion of infection [15], PCT levels were measured and reported to treating physicians daily for 7 days [11], 10 days [10], or until antimicrobial therapy was completed or the patient was discharged from the ICU [12, 14, 16]; PCT results were available within 1–3 hours after collection of blood samples where reported [10–12]. In most studies, use of antimicrobials was strongly discouraged for PCT levels of <0.25 µg/mL and discouraged for PCT levels of <0.50 µg/L. Antimicrobial use was encouraged for PCT levels >0.50 µg/L and strongly encouraged for PCT levels ≥1 µg/L. Where the PCT assay was reported [10–12, 14, 16], the Kryptor assay (Brahms) [17] was used.

Failure to follow PCT-guided recommendations was reported in 3 studies [10–12] and ranged between 16% and 53%. In 1 study [12], antimicrobial therapy was started despite low PCT levels because infection could not be ruled out, discontinued despite high PCT levels because infection was thought to be clinically cured or patients were discharged from the ICU, or continued because patients were considered clinically unstable. In other studies physicians refused to stop the antimicrobials [11] or prolonged treatment despite low PCT levels because of positive blood cultures or infection by Gram-negative bacilli [10].

The duration or intensity of antimicrobial therapy was measured as the total number of days with antimicrobials in 2 studies [10, 15], the number of days without antimicrobials in 3 studies [10–12], days of antimicrobial exposure per 1000 patient days in 3 studies [10–12], and the number of antimicrobial days for the first infectious episode in 4 studies [11, 12, 14, 16]. Rate of antimicrobial discontinuation and continuation of antimicrobials beyond 7 days were evaluated in 1 study [10]. Secondary outcomes included length of ICU stay or ICU-free days in all studies, length of hospital stay in 3 studies [10–12], days free of mechanical ventilation in 2 studies [10, 12], relapse of infection in 2 studies [11, 12], and mortality in 5 studies [10–12, 14, 16].

Study Quality
Appropriate performance of randomization was reported in 3 studies [10–12] and allocation concealment (investigator blinding) was reported in 2 studies [10, 11]; the nature of the study interventions made double blinding of clinicians and patients impossible, although outcome assessment was blinded in 1 study [12]. Attrition was reported in 3 studies [10–12] and was within acceptable limits (<15% of enrolled patients) in 2 [10, 12]. Intention-to-treat analysis was performed in 2 studies [11, 12]. Study quality is depicted graphically in Figure 2.

Outcomes
PCT guidance was relatively ineffective in limiting the initiation of antimicrobial therapy in the 2 studies in which this was assessed. Layios and colleagues found that initial PCT levels were <0.25 µg/mL in 28% of episodes of suspected infection that were subsequently classified as confirmed and that initial PCT levels were ≥1 µg/mL in 29% of episodes in which infection was judged to be absent [15]. The proportions of patients given antimicrobials (88% and 87%) and of the ICU days during which antimicrobials were given (64% and 60%) did not differ significantly between the PCT and control groups, respectively. Of the 307 patients randomized to PCT guidance reported by Bouadma and colleagues, 93 (30%) had initial PCT levels <0.5 µg/L, the cutoff point for discouraging antimicrobial initiation, but antimicrobials were initially withheld for only 28 (9%) [12].

Duration of antimicrobial therapy was significantly decreased in the PCT group in 5 of 6 included studies [10–12, 14, 16], as presented in Table 3. Patients in the PCT group had 23%–37%
<table>
<thead>
<tr>
<th>Study, year</th>
<th>Population</th>
<th>Sample size (intervention; comparison), no. of patients</th>
<th>Follow-up</th>
<th>Intervention</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouadma et al, 2010 [12]</td>
<td>Adult ICU patients with suspected bacterial infections or sepsis who had received antimicrobials for &lt;24 hours at the time of inclusion; 11% postoperative; patients with neutropenia (&lt;500 neutrophils/mL) induced by bone marrow transplantation or chemotherapy were excluded</td>
<td>630 (307; 314)</td>
<td>28–60 days</td>
<td>Starting antimicrobials: strongly discouraged if PCT &lt;0.25 μg/L, discouraged if PCT 0.25–0.50 μg/L, encouraged if PCT 0.50–1 μg/L, strongly encouraged if PCT ≥1 μg/L; stopping antimicrobials: strongly encouraged if PCT &lt;0.25 μg/L, encouraged if PCT 0.25–0.50 μg/L or decreased by ≥ 80% from peak concentration; changing antimicrobials: continuing antimicrobials encouraged for decreases ≥80% from peak concentration and PCT ≥0.5 μg/L; strongly encouraged for increases in concentration compared with peak concentration and PCT ≥0.5 μg/L; blood samples were obtained at each infectious episode and daily for patients on antimicrobials; PCT assay: Kryptor (Brahms); nonadherence to algorithm: 53% in PCT group, 45% in control group</td>
<td>Mortality; number of days without antimicrobials</td>
</tr>
<tr>
<td>Hochreiter et al, 2009 [14]</td>
<td>Adult surgical ICU patients requiring antimicrobial therapy based on confirmed or suspected bacterial infections and ≥2 concomitant Systemic Inflammatory Response Syndrome criteria</td>
<td>110 (57; 53)</td>
<td>Not reported</td>
<td>Antimicrobial therapy was discontinued if PCT &lt;1 μg/L or if PCT &gt;1 μg/L but had dropped to 25%–35% of the initial value over 3 days; PCT measured daily; PCT assay: Kryptor; adherence to PCT guidance not reported</td>
<td>Not specified</td>
</tr>
<tr>
<td>Layios et al, 2009 [15]</td>
<td>Adult ICU patients with suspected infection; 30% postoperative</td>
<td>529 (268; 261)</td>
<td>Not reported</td>
<td>Use of antimicrobials was discouraged if PCT &lt;0.50 μg/L and strongly discouraged if PCT &lt;0.25 μg/L; use of antimicrobials was recommended if PCT ≥0.50 μg/L and strongly recommended if PCT ≥1 μg/L; no information about frequency of PCT measurements; no information about PCT assay; adherence to PCT guidance not reported</td>
<td>Not specified</td>
</tr>
<tr>
<td>Nobre et al, 2008 [11]</td>
<td>Adult mixed surgical and medical ICU patients with suspected severe sepsis or septic shock; immunocompromised patients excluded</td>
<td>79 (37; 31)</td>
<td>28 days</td>
<td>In patients with baseline PCT ≥1 μg/L, antimicrobial discontinuation was recommended when PCT &lt;0.25 μg/L or when PCT dropped &gt;90% from the baseline peak; in patients with baseline PCT &lt;1 μg/L, antimicrobial discontinuation was recommended when PCT &lt;0.1 μg/L; PCT measured daily until 7 days or until antimicrobials were stopped, thereafter every 5 days even for patients transferred from ICU; PCT assay: Kryptor; nonadherence to algorithm: 19% in PCT group</td>
<td>Antimicrobial exposure</td>
</tr>
</tbody>
</table>
more days alive without antimicrobial therapy during the first 28 days, compared with the control group, and the PCT intervention was associated with relative reductions from 21% to 38% in the duration of the first antimicrobial course and from 20% to 23% in the days of antimicrobial therapy per 1000 ICU patient-days. PCT use led to a 33% reduction in the total duration of antimicrobials in 1 study [10].

Length of ICU stay was significantly decreased in the PCT group in 2 studies [11, 14], and no significant differences were found in the other studies. No significant differences were found in the PCT and control groups for any of the other secondary outcomes (Table 4).

**DISCUSSION**

Our systematic review evaluating the efficacy and safety of PCT-guided antimicrobial therapy among ICU patients shows that PCT guidance was associated with statistically and clinically significant reductions in antimicrobial therapy in 5 of the 6 studies published to date. The single negative study [15] assessed the impact of PCT guidance solely for the decision to initiate antimicrobial therapy, whereas the 4 studies that used PCT levels to guide antimicrobial duration alone [10, 11, 14, 16] or in addition to the decision to begin antimicrobials [12] demonstrated reduced antimicrobial use associated with PCT guidance. PCT-guided and control groups did not differ meaningfully in rates of mortality, infection relapse, or days free of mechanical ventilation in any of the studies, suggesting that the interventions were safe. Patients whose antimicrobial therapy was informed by PCT levels also had shorter ICU lengths of stay in 2 of the 5 studies, with no significant differences found in the others; there were no significant differences in hospital length of stay in any of the studies. These results suggest that our systematic review evaluating the efficacy and safety of PCT-guided antimicrobial therapy among ICU patients shows that PCT-guided therapy can substantially reduce antimicrobial use in the ICU setting without compromising clinical outcomes.

The failure of PCT guidance to meaningfully influence the decision to initiate antimicrobial use in ICU patients [12, 15] may be partly explained by noninfectious inflammatory conditions such as pancreatitis, trauma, or major surgery causing PCT elevation [3]. PCT elevation in patients with low levels of PCT levels is characteristic of critically ill patients with infections that are resistant to antimicrobial therapy. However, for ICU patients whose PCT levels are low to begin with or have fallen to low levels (assuming rapid decay of PCT levels), the subsequent receipt of negative culture results may provide corroboration sufficient to convince clinicians that antimicrobials may be stopped safely.

Boabdil et al had greater success in using PCT guidance to convince clinicians that antimicrobials may be stopped safely, but this success was considered in the context of the failure of PCT levels to predict infection in patients with low levels of PCT levels. In the absence of a clear signal from PCT levels, the failure of PCT guidance to meaningfully influence the decision to initiate antimicrobial therapy may be due to the complex interplay between the ICU setting and the patient’s clinical status.

**Note.** The intervention and comparison numbers do not always add up to the numbers of patients enrolled and assigned to groups, because some patients were excluded. ICU, intensive care unit; PCT, procalcitonin.
reduce the duration of antimicrobial therapy than in using it to reduce initiation of such therapy in their ICU patients with clinical sepsis [12]; this parallels the results of a recent multi-center RCT of PCT guidance for patients managed in hospital emergency departments for pneumonia and other lower respiratory tract infections. In the latter trial, absolute and relative reductions in rates of antimicrobial use associated with PCT guidance were much less pronounced on day 0, when antimicrobials were initiated, than on subsequent days of treatment [18].

PCT guidance consistently reduced the duration and intensity of antimicrobial use associated with PCT guidance were much less pronounced on day 0, when antimicrobials were initiated, than on subsequent days of treatment [18].

Figure 2. Assessment of methodologic quality of included studies. ICU, intensive care unit; RCT, randomized controlled trial.

As a biomarker for infection, PCT is more sensitive and specific than C-reactive protein [23]. The normal range of PCT in adult human serum is 0.033–0.003 ng/mL but, until recently, studies assessing the accuracy of PCT in predicting infection used assays with functional sensitivities that were much higher (eg, 0.5 ng/mL) [8, 23], so that the values obtained could (or should) have been interpreted only as abnormal (>0.5 ng/mL) or indeterminate [3]. This may have contributed to suboptimal test performance, as described in a recent meta-analysis [8]. More recent clinical trials and each of the studies examined in this review used the more sensitive Kryptor assay (Brahms) [17], with a functional sensitivity of 0.06 ng/mL.

A systematic review was published recently in which the data necessary to report formal quantitative meta-analysis of published RCTs of PCT-guided antimicrobial therapy in ICUs were clarified by contacting the study authors [24]. They found that use of PCT-guided algorithms significantly reduced the duration of antibiotic therapy, by 2 days for the first episode of infection and by 4 days for the total duration of antibiotic treatment. There were no significant differences in mortality or ICU length of stay [24]. This review included a study that we excluded because it reported neither the duration nor intensity of antimicrobial therapy [25], and it omitted a study published only in abstract form [15], which we included. Nonetheless, the quantitative findings reported by Kopterides et al are consistent with our semiquantitative review.
Table 3. Duration of Antimicrobial Therapy

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Duration of first antimicrobial course, days</th>
<th>Total duration of antimicrobial administration, days</th>
<th>Antimicrobial days/1000 patient-days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Days alive off antimicrobials in first 28 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PCT Control Absolute difference Relative difference</td>
<td>PCT Control Absolute difference Relative difference</td>
<td>PCT Control Absolute difference Relative difference</td>
</tr>
<tr>
<td>Bouadma, 2010 [12]</td>
<td>14.3a (9.1) 11.6 (8.2) 2.7b ( (P &lt; .001) )</td>
<td>6.1a (6.0) 9.9 (7.1) ( (P &lt; .001) )</td>
<td>−3.8b ( (P &lt; .001) )</td>
</tr>
<tr>
<td>Hochreiter et al, 2009 [14]</td>
<td>NR NR NR NR NR NR NR NR</td>
<td>5.9a (1.7) 7.9 (0.5) ( (P &lt; .001) )</td>
<td>−2.0b ( (P &lt; .001) )</td>
</tr>
<tr>
<td>Layios et al, 2009 [15]</td>
<td>NR NR NR NR NR NR NR NR</td>
<td>64% 60% 4% 0.03 NR NR NR NR NR NR</td>
<td>159</td>
</tr>
<tr>
<td>Nobre et al, 2008 [11]c</td>
<td>17.4a (7.6) 13.6 (7.6) 3.8b ( (P = .04) )</td>
<td>6d 10 ( (P = .001) )</td>
<td>−3.2b ( (P = .003) )</td>
</tr>
<tr>
<td>Schroeder et al, 2009 [16]</td>
<td>NR NR NR NR NR NR NR NR</td>
<td>6.6a (1.1) 8.3 (0.7) ( (P &lt; .001) )</td>
<td>−1.7b ( (P &lt; .001) )</td>
</tr>
<tr>
<td>Stolz et al, 2009 [10]</td>
<td>13a (2–21) (1.5–17) ( (P = .049) )</td>
<td>9.5 3.5 ( (P &lt; .001) )</td>
<td>10a (6–16) (10–23) ( (P = .038) )</td>
</tr>
</tbody>
</table>

**NOTE.** For the Layios study, duration is in percentage of the study duration (in days) that patients were on antibiotics. NR, not reported; PCT, procalcitonin.

*Mean (standard deviation).

*Mean difference in days.

*Per protocol analysis.

*Median.

*Median (interquartile range) in days.
### Table 4. Secondary Outcomes

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Mortality&lt;sup&gt;a&lt;/sup&gt; (PCT, no. of events/100 patients (%)</th>
<th>P</th>
<th>Control, no. of events/100 patients (%)</th>
<th>Infection relapse (PCT, no. of events/100 patients %)</th>
<th>P</th>
<th>Relative difference</th>
<th>Absolute difference</th>
<th>Duration of ICU stay, days (PCT)</th>
<th>Control, no. of days</th>
<th>Absolute difference</th>
<th>Relative difference</th>
<th>Duration of hospital stay (PCT)</th>
<th>Control, no. of days</th>
<th>Absolute difference</th>
<th>Relative difference</th>
<th>Days off mechanical ventilation (PCT)</th>
<th>Control, no. of days</th>
<th>Absolute difference</th>
<th>Relative difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouadma et al, 2010 [12]</td>
<td>65/307 (21)</td>
<td>.05</td>
<td>64/314 (20)</td>
<td>16/307 (7)</td>
<td>.45</td>
<td>15.9&lt;sup&gt;b&lt;/sup&gt; (16.1)</td>
<td>14.4 (14.1)</td>
<td>1.5&lt;sup&gt;c&lt;/sup&gt; (P &lt; .23)</td>
<td>0.10</td>
<td>26.1&lt;sup&gt;b&lt;/sup&gt; (19.3)</td>
<td>26.4 (18.3)</td>
<td>−0.3&lt;sup&gt;c&lt;/sup&gt; (P &lt; .87)</td>
<td>−0.01</td>
<td>16.2&lt;sup&gt;b&lt;/sup&gt; (11.1)</td>
<td>16.9 (10.9)</td>
<td>−0.7&lt;sup&gt;c&lt;/sup&gt; (P &lt; .47)</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hochreiter et al, 2009 [14]</td>
<td>15/57 (26)</td>
<td>.05</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>15.5&lt;sup&gt;b&lt;/sup&gt; (12.5)</td>
<td>17.7 (10.1)</td>
<td>−2.2&lt;sup&gt;c&lt;/sup&gt; (P &lt; .05)</td>
<td>−0.12</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Layios et al, 2009 [15]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>18&lt;sup&gt;c&lt;/sup&gt; (4–18)</td>
<td>7 (4–16)</td>
<td>1.0</td>
<td>0.14</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Nobre et al, 2008 [11]&lt;sup&gt;e&lt;/sup&gt;</td>
<td>5/31 (16)</td>
<td>.74</td>
<td>1/31 (3)</td>
<td>1/37 (3)</td>
<td>.70</td>
<td>3&lt;sup&gt;c&lt;/sup&gt; (1–18)</td>
<td>5 (1–30)</td>
<td>−2</td>
<td>−0.40</td>
<td>14&lt;sup&gt;d&lt;/sup&gt; (5–64)</td>
<td>21 (5–89)</td>
<td>−7</td>
<td>−0.33</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Schroeder et al, 2009 [16]</td>
<td>3/14 (21)</td>
<td>.05</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>16.4&lt;sup&gt;b&lt;/sup&gt; (8.3)</td>
<td>16.7 (5.6)</td>
<td>−0.3</td>
<td>−0.02</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Stolz et al, 2009 [10]</td>
<td>8/51 (16)</td>
<td>.33</td>
<td>12/50 (24)</td>
<td>8.5</td>
<td>1.5</td>
<td>10&lt;sup&gt;a&lt;/sup&gt; (0–18)</td>
<td>8.5 (0–18)</td>
<td>−0.3</td>
<td>−0.18</td>
<td>26&lt;sup&gt;d&lt;/sup&gt; (7–21)</td>
<td>26 (1722)</td>
<td>−0.0</td>
<td>−0.11</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

**NOTE.** ICU, intensive care unit; NR, not reported; PCT, procalcitonin. <sup>n</sup> = number of events; <sup>n</sup> = number of patients.

<sup>a</sup>At 28 days.

<sup>b</sup>Mean (standard deviation).

<sup>c</sup>Mean difference.

<sup>d</sup>Median (interquartile range).

<sup>e</sup>Per protocol analysis.

<sup>f</sup>Median (range).

<sup>g</sup>ICU-free days.
Our review has limitations apart from the absence of quantitative meta-analysis. Because only 6 studies met our selection criteria and all were conducted in Belgian, French, German, or Swiss hospitals (nearly all in teaching institutions), the generalizability of these results to other settings remains to be elucidated. Also, formal cost-effectiveness analysis was not performed in any of the studies under review and is not addressed here.

CONCLUSIONS

PCT-guided antimicrobial therapy significantly decreases exposure to antimicrobials in the ICU and may also decrease the ICU length of stay without apparent adverse effects. Although the consistency of benefit and safety of PCT guidance in this setting suggest that these results should be broadly generalizable, additional confirmatory research to confirm this would be useful. In addition, careful observational study will be important to confirm the effectiveness and assess the cost-effectiveness of PCT testing in real world, nonclinical trial settings.

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