Use of Procalcitonin in Patients With Various Degrees of Chronic Kidney Disease Including Renal Replacement Therapy

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Procalcitonin (PCT) has been shown to be a useful surrogate marker in identifying patients with various bacterial infections. PCT has been studied as a diagnostic marker in differentiating bacterial pneumonia from other respiratory conditions such as chronic obstructive pulmonary disease exacerbations or viral pneumonia. Differentiating bacterial from nonbacterial pneumonia using PCT has shown to reduce antibiotic usage, length of stay, and antibiotic-related adverse effects. PCT has also been studied in patients with sepsis in an effort to reduce unnecessary antibiotic usage and decrease the length of antibiotic therapy. This article focuses on the use of PCT in patients with various degrees of chronic kidney disease in addition to various forms of dialysis, as chronic kidney disease may alter baseline levels of PCT and thus result in inappropriate use of PCT in this population.

Keywords. procalcitonin; dialysis; chronic kidney disease; renal replacement therapy; serological marker.

In 1975, procalcitonin was identified as one of the precursors to calcitonin in animals prior to being discovered in humans [1, 2]. A similar precursor to calcitonin that was found in animals was subsequently identified in human thyroid medullary carcinoma tissue and was termed “serum immunoreactive calcitonin” (iCT) [3–7]. Levels of iCT increase in response to cellular injury, first noted in patients with inhalation injury secondary to burns [8]. An elevated level of the large molecular mass form of iCT was associated with early death and worsening outcomes in relation to other forms of iCT. The high molecular form of iCT was subsequently termed “procalcitonin” (PCT) [8]. The first study to investigate the usefulness of PCT in patients with infection was published in 1993 and showed that serum concentrations of PCT correlated with the severity of microbial infection [9, 10].

Limited information is available concerning the pharmacokinetics and associated PCT serum levels in patients with chronic disease states. This article will focus on patients with chronic kidney disease (CKD) including recipients of kidney transplant and renal replacement therapy (RRT), as these patient populations are at higher risk for severe infections [11].

PROCALCITONIN KINETICS

Procalcitonin levels have been shown to rise rapidly in response to infection or inflammation [12]. To the authors’ knowledge, there are no studies evaluating the pharmacokinetics of PCT in patients with true infections, especially those with CKD. In a study of healthy individuals, PCT levels peaked at 6 hours and remained detectable for >24 hours following an injection of Escherichia coli endotoxins [12]. Increases in PCT levels are secondary to leukocyte exposure from bacterial endotoxins within the spleen, kidneys, lung, and liver [13–16]. PCT levels have been shown to correlate with both interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) levels [17]. IL-6 and TNF-α are among the primary cytokines involved in the inflammatory cascade in response to infection [18]. Higher than normal baseline levels of PCT have been observed in patients with CKD.
ELEVATED PCT IN CKD PATIENTS WHO ARE DIALYSIS NAIVE

Elevated PCT levels have been observed in CKD patients including those not requiring dialysis, those requiring dialysis but not yet started (dialysis naive), and those on maintenance dialysis (CVVHD) [25, 33]. This suggests an indirect effect of renal disease on PCT levels, as it is postulated that decreases in renal function may result in increased serum concentrations of proinflammatory metabolites, which stimulate the immune system, resulting in increased inflammation and release of PCT into the circulation [21]. Serum PCT levels are significantly higher in CKD patients without a history of dialysis or infection compared with healthy individuals [21]. In one study, the mean PCT level in CKD patients without infections prior to starting RRT was 1.82 ± 0.39 ng/mL compared to the established threshold of <0.1 ng/mL in healthy individuals [21, 28]. On average, 36% of CKD patients without an infection have a PCT level of ≥0.5 ng/mL, whereas 36%–100% have a PCT level ≥0.5 ng/mL in the presence of an infection [21, 22]. Large variability in baseline PCT levels has been observed in patients with stage 5 CKD who are not on RRT, as PCT levels ranged from an average of 0.12 ng/mL to 1.82 ng/mL in related literature [21–24]. Studies have consistently found a statistical significance between PCT levels in patients with stage 5 CKD, those receiving RRT, and healthy controls [21–24].

ELEVATED PCT LEVELS IN DIALYSIS PATIENTS WITHOUT INFECTIONS

PCT levels drop significantly once a patient with CKD is started on RRT [21]. Patients with CKD started on RRT have displayed the most significant decrease in PCT levels following a 4-hour session of high-flux hemodialysis (HFHD) compared with all other forms of RRT [29, 30]. The magnitude of drop in PCT levels following HFHD has been attributed to the high permeability of PCT through the dialysis filter [19, 25]. Studies have failed to show a significant drop in PCT following low-flux hemodialysis (LFHD), resulting in a trend toward higher baseline PCT levels in patients on LFHD compared with those receiving HFHD [31, 32]. To date, studies have consistently shown a significant decrease in PCT levels following HFHD, peritoneal dialysis (PD), and continuous venovenous hemodialysis (CVVHD) [25, 33–36]. However, the magnitude of drop in PCT level varies depending on the method of RRT studied.

Adult patients on chronic hemodialysis (HD) without infections have an average baseline PCT level ranging from 0.26 ng/mL to 1.0 ng/mL prior to the start of dialysis sessions [19, 24–26, 29, 30, 35]. Several studies have shown that up to 100% of patients on HD have a predialysis PCT level of ≥0.5 ng/mL despite the absence of infection [11, 27, 36–38]. In contrast, healthy subjects without CKD or infection in the same studies had an average PCT level of 0.03–0.18 ng/mL [26, 29]. Following a 3- to 4-hour session of HFHD, PCT levels have been shown to decrease by 21%–83% [25, 34, 35, 38]. PCT levels recovered gradually over 48 hours, thus returning to baseline levels prior to the next dialysis session, supporting the hypothesis that elevated baseline PCT levels in patients with CKD are more likely due to the increased presence of inflammatory markers between dialysis sessions rather than a result of an immune/inflammatory reaction to the dialysate used during treatment [25, 35, 39]. These findings, in addition to an elevated baseline PCT level in patients on chronic HD, support the use of a higher baseline threshold level for patients with CKD regardless of RRT method used. Great importance must be rendered to obtaining PCT levels prior to HD session(s), to reflect the patient’s true PCT level and not an artificially low PCT level.

Patients on PD without any evidence of an infection have displayed an elevated baseline PCT level compared with healthy individuals [37, 40, 41]. Despite the small number of studies that strictly examined PCT in PD patients, average baseline PCT levels have ranged from 0.32 to 1.18 ng/mL compared to an average of 0.18 ng/mL in healthy patients in the same studies [40, 41]. Following PD, PCT levels have shown to decrease an average of 17%. This drop in PCT level emphasizes the need to check PCT levels prior to PD [21]. CVVHD is the least studied form of RRT in relationship to PCT levels; however, the small body of evidence supports a significant fall in PCT levels during dialysis in patients with sepsis or pneumonia [33].

ELEVATED PCT LEVELS IN DIALYSIS PATIENTS WITH INFECTIONS

Patients on RRT are at higher risk of infection compared with the rest of the population [42, 43]. The nature of these infections range from noninvasive infections of the dialysis port to the most severe of infections leading to sepsis. Patients on HD are...
at higher risk of developing bacteremia or sepsis compared to patients receiving PD who are at higher risk of developing peritonitis with or without secondary sepsis. Given the elevated baseline PCT levels in patients with CKD, it is crucial to distinguish elevated baseline PCT levels from PCT levels elevated due to infection. In one study that examined PCT levels in patients on HD with severe infections including sepsis, predialysis PCT levels were shown to be on average 5.9 ng/mL (range, 2.1–11.5), which was significantly higher than PCT levels in subjects without infections (mean, 0.8 ng/mL [range, 0.3–1.4]; P < .01) [25]. In another study of HD, patients with ongoing infection had baseline PCT levels that were significantly higher than those without an active infection (median, 2.5 ng/mL vs 0.3 ng/mL, respectively; P < .001) [26]. Patients receiving PD with an active infection have also shown to have a wide range of PCT levels similar to those receiving HD (median, 0.4–63 ng/mL) [37, 40]. In one study examining PCT levels in PD patients with an active infection, 62% of study participants had a PCT level of ≥0.5 ng/mL, 38% had a level of ≥1.5 ng/mL, and 24% had a level of ≥10 ng/mL [37]. Of note, however, 38% of patients on PD with an active infection had PCT levels of <0.5 ng/mL [37]. Based on such findings, it is essential to determine the best PCT baseline cutoff value for patients receiving RRT in the absence of an infection to accurately differentiate those with CKD with an infection from those without.

Patients with infections who started on CVVHD have baseline PCT levels similar to those of patients with stage 5 CKD who have not initiated RRT. PCT levels obtained at CVVHD initiation from afferent dialysis ports in septic patients had shown levels ranging from 10 ng/mL to >100 ng/mL [44–46]. Various studies have evaluated the clearance of PCT via CVVHD over a defined amount of time such as 24 or 48 hours. Most CVVHD studies concerning PCT included only subjects with sepsis, pneumonia, or other systemic severe infections on CVVHD with a blood flow rate of 100–150 mL/minute. PCT clearance from plasma varied widely based on the type of filter used in each study. Significant decrease in plasma PCT levels have been observed within 15 minutes of starting CVVHD, and this precipitous drop continues for up to 12–24 hours after ongoing CVVHD, resulting in an overall decrease of >85% in plasma PCT levels [44–47]. Only 1 study to date has observed a minimal decrease (<20%) in PCT levels after 24 hours of CVVHD in septic patients [48]. Based on these findings, it is recommended that PCT levels be checked prior to the initiation of CVVHD in patients with suspected sepsis, pneumonia, or any other severe systemic infection.

**PCT THRESHOLDS IN PATIENTS ON RRT**

Because patients on RRT are more likely to develop severe infections, it is critical that PCT cutoff values be selected for various types of RRT that are highly sensitive and thus capable of detecting all patients with severe infections. Unfortunately, any threshold that will increase sensitivity will inversely decrease specificity and result in unnecessary use of antibiotics. For this reason, it is essential that healthcare providers use serology test results, clinical signs and symptoms of infection, and sound judgment to determine if antibiotic therapy is warranted in a given patient.

Based on findings in non-CKD patients with pneumonia or sepsis, several studies have determined the appropriateness of using a PCT cutoff value of ≥0.2–0.5 ng/mL as an indication for infection [10]. As previously discussed, a large proportion of patients without infections receiving chronic RRT may have predialysis PCT levels ≥0.5 ng/mL. In studies that used a heterogeneous population of patients, a cutoff value of ≥0.5 ng/mL had a sensitivity of 73%–100% and a specificity of 48%–88% [22, 26, 49]. When the cutoff value was increased from ≥0.5 ng/mL to ≥1.5 ng/mL, the sensitivity decreased as the specificity increased to 59% and 96%, respectively [26]. On closer examination of studies that included patients on RRT, a significant difference between HD and PD was observed with regard to sensitivity and specificity (Table 1) [26, 49].

Using a cutoff value of ≥0.5 ng/mL in HD patients yields a sensitivity of 87%–98% and a specificity of 70%–96% [22, 30]. Raising the cutoff value to ≥1.5 ng/mL in HD patients resulted in little change to specificity while significantly decreasing sensitivity [25, 26]. In one study, a cutoff value of ≥0.5 ng/mL yielded a sensitivity of 98% and a specificity of 70% with a receiver operating curve (ROC) of 0.87 [26]. Using a cutoff value of ≥0.85 ng/mL yielded a sensitivity of 100% and a specificity of 67%, with an ROC of 0.83 [22]. If a PCT threshold value of ≥0.85 ng/mL yielded a sensitivity of 100%, then using a PCT cutoff value of ≥0.5 ng/mL will maintain the same sensitivity. Based on these statistical findings and evidence showing that a significant amount of PCT is cleared through HD, using a cutoff value of ≥0.5 ng/mL can be used as a serological marker in detecting infections in HD patients; however, this may result in unwarranted treatment as some patients will inherently have an elevated PCT level due to inflammation from CKD. Using a PCT cutoff value of ≥1.5 ng/mL would result in a 40% chance of not identifying patients on HD with infection compared to <5% if a cutoff value of ≥0.5 ng/mL is used. Due to the high sensitivity and specificity of PCT levels in HD patients prior to dialysis, PCT levels of ≥0.5 ng/mL can be used as a rule-in test for severe infections whereas a level of ≤0.5 ng/mL can be used as a rule-out test for severe infections (Figure 1).

When examining patients on PD with suspected peritonitis, a PCT level of ≥0.5 ng/mL resulted in a sensitivity of 42%–70% and a corresponding specificity of 40%–100% [37, 49–51]. Increasing the threshold value to ≥1.5 ng/mL resulted in a decrease in sensitivity to 38% and an insignificant change in specificity (approximately 100%) [37]. In an effort to increase
the sensitivity of PCT, cutoff values of $\geq 0.38 \text{ ng/mL}$ and $\geq 0.75 \text{ ng/mL}$ have been suggested; however, the corresponding sensitivities were significantly lower when with using a cutoff value of $\geq 0.5 \text{ ng/mL}$ [37, 50]. Sensitivity can be maximized in PD patients by using a PCT cutoff of $\geq 0.5 \text{ ng/mL}$, which in turn will result in a corresponding sensitivity of 70% at best and a specificity of 100% [51]. Given the low sensitivity and high specificity of PCT levels to detect infection among patients receiving PD, PCT levels are more useful as a rule-out rather than a rule-in test for severe infections (Figure 1).

### SPECIAL POPULATIONS IN RRT

Recipients of kidney transplant are at higher risk of infection compared to healthy individuals due to immunosuppressive medications. Limited data have been published regarding renal transplant patients and the use of PCT as a serological marker for infection. Two studies to date have addressed this population with regard to the optimal cutoff value for PCT in detecting severe infections [26, 27, 52, 54]. A PCT cutoff value of $\geq 0.5 \text{ ng/mL}$ has been associated with a sensitivity of 87%–93% and specificity of 70%–79% [26, 54]. Increasing the threshold value to $\geq 1.5 \text{ ng/mL}$ resulted in a 31% decrease in sensitivity [26]. Due to the high mortality rate in transplant patients with infection, one study showed a cutoff value of $\geq 0.22 \text{ ng/mL}$ would result in 100% sensitivity and $>90\%$ specificity (Table 1) [26]. Of note, administration of OKT-3 and/or antithymocyte globulin treatment has been shown to result in a $>10$-fold increase in PCT levels despite the absence of infection; therefore, PCT levels should not be used as a serological marker in patients receiving these agents [54, 55].

### LIMITATIONS OF USING PCT IN PATIENTS WITH CKD AND RECEIVING RRT

Several limitations and precautions should be taken when using PCT levels to decide if a patient requires antibiotic therapy. First, studies have shown that up to 20% of patients with/without renal disease may not exhibit significant increases in PCT levels within the expected 4–6 hours of infection but thereafter [56]. Thus, it is the opinion of the authors that clinicians should recheck PCT levels at 6–8 hours to prevent overlooking a late PCT peak in an individual who does require antibiotic therapy. Second, the clinician should be aware of the lapse in time since the last RRT session as to avoid misinterpreting artificially low PCT levels. Last, current use of PCT in CKD and RRT populations has no evidence of certain benefits such as decreased antibiotic use, adverse effects, and length of hospital stay due to the lack of studies examining this aspect of PCT in this population. More studies are needed to examine if the benefits of using PCT as mentioned carry over to the CKD and RRT populations.

### CONCLUSIONS

Figure 1 summarizes the recommended thresholds for PCT when using various forms of RRT. Table 1 outlines the trials on which the recommendations are based, including sensitivities, specificity, and ROC. Most evidence supports the use of higher PCT cutoff values to either rule out or rule in infection. Based on the discussed evidence, recommendations for specific populations with CKD can be deduced in regard to the use of PCT levels as a marker for severe infections such as sepsis or...
pneumonia. First, in patients with stage 1–4 CKD not receiving RRT, a PCT level cutoff value of ≥0.25 ng/mL can be used to rule in infections, similar to healthy patients [23]. Second, patients with stage 5 CKD, HD, or PD should use a PCT level of ≥0.5 ng/mL to differentiate infected from noninfected patients. Third, levels <0.5 ng/mL can be used to rule out infections in these aforementioned patients as the baseline level is strongly dependent on the presence or absence of other comorbidities [23]. Fourth, a PCT level of <0.5 ng/mL can be used to rule out severe infections in patients receiving PD, but it should not be used as a rule-in test if the PCT level is ≥0.5 ng/mL, as the sensitivity of PCT levels is lacking in this specific population. Fifth, PCT levels in HD patients should be obtained just prior to the HD session. In addition, a cutoff PCT level of ≥0.5 ng/mL can be used to rule in infection, whereas a level of <0.5 ng/mL can be used to rule out infection for HD patients. Last, PCT levels should be obtained in patients with a suspected systemic infection prior to the initiation of CVVHD due to the rapid and significant drop in PCT levels once CVVHD is initiated [57]. Regardless of all the data on PCT use, it is essential that clinicians use clinical judgment in addition to PCT levels and other biomarkers to determine if a patient has an infection. If PCT is used as a tool, clinicians should be aware that PCT levels can be used as a rule-in or rule-out test for specific CKD stages in addition to the type of RRT and presence of comorbidities.

Notes

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