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Review Article

The use and value of procalcitonin in solid organ transplantation

Sandkovsky U, Kalil AC, Florescu DF. The use and value of procalcitonin in solid organ transplantation.

Abstract: Procalcitonin (PCT) has been increasingly used as a biomarker of bacterial infection and as a tool to guide antimicrobial therapy, especially in lower respiratory tract and bloodstream infections. Despite its increased use, data in patients with solid organ transplants are limited. Even without the presence of infection, PCT increases as a result of surgical procedures during transplantation, implantation of devices, and use of induction immunosuppressive therapy. The risk of infection is also higher in solid organ transplant recipients when compared to the general population. Monitoring PCT in the early post-transplant period seems to be a promising method for early detection of infectious complications. It has been shown that elevated PCT levels after one wk of transplantation are correlated with infectious complications. PCT may be a useful adjunctive biomarker that may improve early identification and guide appropriate treatment of infection or rejection, with the potential to further improve clinical outcomes. The use of serial PCT measurements may be more reliable than single values. It is important to recognize which factors may lead to PCT increases in the post-transplantation period, which in turn will help understand the kinetics and utility of this biomarker in this important patient population.

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Procalcitonin (PCT), the pro-peptide precursor of calcitonin, is mainly produced by the thyroid gland, but the levels are usually very low as it is quickly converted to calcitonin (1). It is believed that in the setting of bacterial infection, peripheral blood monocytes, the liver, and other tissues release PCT in response to cytokines (such as tumor necrosis factor [TNF], interleukin-6, and granulocyte colony-stimulating factor) and endotoxin from bacterial cell wall (1, 2). Cytokines and endotoxin are also believed to halt the conversion from PCT to calcitonin, thus increasing the concentrations of PCT (3).

Laboratory measurement of PCT has been increasingly used as a biomarker of bacterial infection. Its main use has been as adjunctive tool in the diagnosis of lower respiratory and intra-abdominal infections, bacteremia, and sepsis. PCT is not usually elevated in the setting of viral infections; this is because interferon γ, which is released in response to viral particles, blocks the production of PCT (2, 4). In many instances, elevations of PCT can reliably indicate the host's response to an infectious process, as well as the degree of disease severity (4). However, in other situations, PCT may be elevated in the absence of bacterial infection, for

example, in cirrhosis, pancreatitis, cardiogenic shock, trauma, and ischemic bowel. In these cases, PCT elevation may constitute an early sign of bacterial translocation through the intestinal wall, although more data are needed to fully understand this process (2).

In solid organ transplantation (SOT) recipients, the kinetics of PCT may be affected by several factors including recent surgical procedures, presence of underlying end-organ disease, maintenance immunosuppression and type of immunosuppressive agents, making its use and interpretation more complex than in non-transplant patients (3, 5–21). In this article, we review the published evidence regarding the use of PCT in SOT with the aim to differentiate infectious vs. non-infectious syndromes post-transplantation, rejection from infection, and colonization from infection. In addition, we look at the impact of induction therapy and maintenance immunosuppression therapy on PCT levels, and the prognostic value associated to this biomarker.

Several PCT assays have been developed with different lower detection limits: Kryptor (BRAHMS Diagnostica, Berlin, Germany), LUMItest (BRAHMS Diagnostica), PCT-Q (BRAHMS Diagnostica), LIAISON BRAHMS PCT (DiaSorin, Saluggia, Italy), PCT-ELISA (USCN Life Science, Wuhan, Hubei), and VIDAS (bioMerieux, France).

Use of PCT to differentiate infectious vs. non-infectious syndromes in transplantation

Many SOT recipients are critically ill after receiving their allografts; thus, differentiating infectious vs. non-infectious etiologies is essential to guide the management of the patients.

Serum PCT levels rise in response to surgical procedures (5, 6, 18, 21–26). Major surgery causes a systemic inflammatory response that translates in elevated PCT levels in the first 24–48 after the procedure (6, 16, 18). In heart and lung transplant recipients, PCT levels were high during first day after transplantation (17, 22, 27, 28) and remained elevated during the subsequent days in the subgroup who developed infectious complications (17, 22, 28); in the same population, CRP levels and leukocyte counts could not differentiate between patients with and without infection at any time point (17, 22). PCT dynamic can be clinically useful as shown in one study where PCT increased in the second post-operative day to 54.6 ± 8.8 ng/mL in patients with complications, compared to 9.1 ± 9.3 ng/mL in patients without complications; on post-operative day 7, 75% of the patients without a complicated course had normal PCT value, while only 4% of the patients with infectious and non-infectious complications had below threshold detection levels (17). Kinetics of PCT were also shown to have significantly different interpatient variability in a recent study of patients who underwent lung transplantation; in 23 of 26 patients, PCT peaked at 24 h post-procedure, but the peak was delayed to 72 h in three patients. More importantly, median PCT concentrations were significantly higher among those who developed pulmonary infection (8.56 vs. 4.61 ng/mL) vs. those who did not (29). It was also reported that after lung transplantation, in patients who did not receive induction therapy, PCT plasma concentrations reached their peak in the first 48 h and normalized within the first week post-transplantation (22). In another study of heart and kidney transplant recipients, PCT raised in response to heart surgery but did not significantly increase after kidney transplant, possibly correlating with the extent of the surgery; in those who developed bacterial complications, PCT peaked to high levels (46–297 ng/mL) and decreased as a response to successful antimicrobial therapy; in contrast, PCT concentrations remained low in one patient who suffered from CMV infection (27). In a study among 104 liver transplant recipients, Kaido et al. measured perioperative PCT and PCT levels at days 2, 3, 5, 7, 14, 21 and 28 post-transplant. The authors found that PCT levels increased post-operatively and gradually decreased thereafter (30). PCT concentrations were higher among those who received the organ from deceased donors, but this difference was not evident at 14 d post-procedure. While patients who developed bacteremia had a serum PCT of 5.71 ± 1.27 ng/mL), levels remained low (0.53 ± 0.08 ng/dL) in patients who had CMV antigenemia (30). On the other hand, one should be vigilant in the setting of CMV reactivation or infection as the virus has indirect immunomodulatory effects that might trigger superimposed bacterial and/or fungal infections. In this case, serial PCT measurements would be useful to detect early bacterial infections (31).

PCT levels may also indicate the severity and progression of the infection process; this could guide the length of the anti-infective therapy and help to assess the response to treatment. One study demonstrated that in heart transplant recipients with local infections, PCT values minimally increased above the cutoff (0.6 ng/mL), while in multiple infections and sepsis, the levels were substantially raised (7.3 and 22.4 ng/mL) (32). In contrast, in the same study, the CRP values displayed similar increase with any type of infection

(6.8 mg/dL local infection, 6.4 mg/dL multiple infections, and 8.3 mg/dL during sepsis) compared to smaller increase with rejection (1.9 mg/dL) (32).

Although the literature is not as extensive, in the setting of liver or kidney transplantation, PCT levels seem to follow a similar course, with peaks in the first or second day after procedure, and subsequent reduction over the week following transplantation when the course is uncomplicated (21, 23–26, 33, 34). Peak PCT levels do not correlate with a complicated course, rather PCT levels that remain high or fail to decrease over the first post-operative week correlate better with complications (26). Eyraud et al. showed that PCT levels were not affected by the presence of post-transplant organ dysfunction at day 0, subsequently peaked between days 1 and 2 after transplantation and decreased by day 7. In this study, significantly higher PCT concentrations were seen among those who received their organs from donors who suffered cardiac arrest or infection (24). In children, the PCT dynamic seems to be similar. Coelho et al. (23) showed that in children who underwent liver transplantation and had no infectious complications, PCT peaked to a median value of 1.6 ng/mL (range 0.69–18.3 ng/mL) between the first and second post-operative days and decreased to a median value of 0.21 ng/mL (range 0.05–2 ng/mL) by post-operative day 4. A recent systematic review and meta-analysis attempted to clarify the role of PCT as potential biomarker to use in identifying infectious complication after transplantation; this meta-analysis included seven different studies (four with liver grafts, one with lung grafts, one with kidney grafts, and one with various allografts) (22, 33–38) and found a pooled sensitivity of 85% and specificity of 81% for PCT for the identification of bacterial infection after transplantation. When only studies that included liver transplant recipients were considered, the sensitivity and specificity of PCT were 90% and 85%, respectively (20). However, we have to consider that the number of studies included in this meta-analysis was small and definite conclusion cannot be drawn at this time. Considering the sensitivity and specificity results from the meta-analysis, PCT should not be used alone for clinical decision, rather it should be used in combination with clinical presentation, other biomarkers, and microbiological results.

PCT may also be used to predict catheter-related bloodstream infections as shown by Chen et al. (35), where PCT values above 3.1 ng/mL had a sensitivity of 72% and specificity of 87% to predict catheter-related bacteremia among a group of liver transplant recipients, although this sensitivity and specificity were lower than expected.

A cutoff of serum PCT level early after transplant surgery that would be associated with infection has not been defined. The complexity of the transplant procedure that would trigger an inflammatory response depends on the type of allograft and extent of the surgery; PCT levels may increase or remain stable after transplantation (27). Perrakis et al. (26) found that PCT values >5 ng/mL increased 11.7 times the odds of developing complications (including renal failure, bleeding, respiratory failure, and infection) after liver transplantation. Prieto et al. (38) reported a peak PCT cutoff of 1.92 ng/mL as a predictor for infectious and non-infectious complications with a sensitivity of 95.6% and specificity of 89.5%, although those who suffered complications had worse baseline characteristics and higher Child–Pugh scores. In a cohort of 82 patients with renal transplant and end-stage renal disease, PCT > 0.5 ng/mL had a sensitivity of 78.6% and specificity of 85.7% in renal transplant recipients vs. 97.7% and 70%, respectively, in hemodialysis; this likely reflects a PCT release effect from the membranes used for dialysis (39). The amount of allograft-associated lymphoid tissue that upregulates the inflammatory response or requires induction with lytic therapy might impact PCT levels; however, this does not limit the utility of PCT as diagnostic tool as PCT should be followed dynamically with serial measurements.

In sum, when plasma concentrations of PCT remain elevated or increase in serial measurements after transplantation, an infectious etiology should be suspected and actively sought. It is possible that the length of the procedure and extent of surgery could have an impact on the PCT levels. As liver and kidney transplantation are less extensive procedures when compared to lung or heart transplants, it might be expected to have higher initial PCT levels post-procedure. PCT might help identify those patients in whom unnecessary antimicrobial therapy can be discontinued and those who may need to be worked up for occult infections and broad-spectrum antimicrobial therapy continued.

Rejection vs. infection

Acute allograft rejection may sometimes be difficult to clinically differentiate from infectious episodes, especially when patients present with fever and non-specific signs or symptoms. Several authors have evaluated the utility of PCT in differentiating acute rejection from bacterial infections. PCT should not be elevated in the setting of rejection, unless a concomitant bacterial infection is

present (33). In a retrospective study of 127 heart, lung, and liver transplant recipients, Hammer et al. (13) showed that PCT levels were not different among those who had allograft rejection compared to those without rejection or infection. In the cohort analyzed by Hammer et al. (13, 14, 32, 40), PCT levels did not increase above the cutoff of 0.5 ng/mL during rejection; using the cutoff value of 0.5 ng/mL, PCT had a sensitivity of 89% and specificity of 89% to detect infectious episodes. Although mild PCT elevations were seen in a cohort of 110 adult heart, lung, and liver transplant recipients during rejection episodes or viral infections, levels >0.14 ng/mL correlated with bacterial infection and increasing concentrations could be seen one wk before microbiological diagnosis was attained (36). A study from Spain showed that PCT increased as a response to infection but remained low among patients with rejection only (38). In observations of renal transplant recipients where PCT and CRP were used to differentiate infectious syndromes from acute rejection, CRP increased after episodes of acute rejection and infection (although the levels were significantly lower for those with rejection only); PCT on the other hand was not elevated in patients with acute allograft rejection (27, 34), making PCT a potentially more reliable marker. Kaido et al. (30) found that PCT remained low (mean 0.42 ± 0.18 ng/mL) among patients who developed acute cellular rejection very early post-liver transplant. The data remained consistent in the pediatric population. In children who underwent liver transplantation, PCT rose as a response to infections, but it was not elevated among those who underwent episodes of acute rejection (23, 33). Despite the available data, PCT monitoring may not be as valuable when patients with acute rejection present with fever or leukocytosis or when certain immunosuppressive regimens such as thymoglobulin (which can significantly elevate PCT levels) are used to treat acute rejection.

Colonization vs. Infection

There is limited and inconclusive data regarding the role of PCT in differentiating infection from airway colonization after lung transplantation. Zeglen et al. has evaluated this in two different studies. The first study suggests that colonization of the bronchial airways with *Pneumocystis jirovecii* and *Pseudomonas aeruginosa* might trigger a mild inflammatory response that would increase PCT levels. However, this conclusion should be interpreted with caution as the authors describe an aggressive antibiotic intervention in patients diagnosed with *Pneumocystis* and *Pseudomonas* colonization (41). In the second study of lung transplant patients, PCT levels were mildly elevated with mold infections or colonization, but levels were below 2 ng/mL in more than 80% of the patients (49.2% of patients had PCT < 0.5 ng/mL and 32% patients had PCT levels >0.5 and <2 ng/mL) (42). Both studies enrolled a relatively low number of patients, collected few PCT samples, and did not make a clear correlation with timing of transplantation, clinical evolution, microbiology results, and imaging (41, 42).

Differentiating airway colonization from serious infections remains sometimes a great challenge to the clinicians. Missed diagnosis of infection would cause delayed antibiotic administration with potentially long-term effects on morbidity and mortality, while using antimicrobials to treat colonization might promote antibiotic resistance, expose patients to side effects, and increase costs. More studies regarding the role of PCT in differentiating airway colonization from infection are needed.

Effect of induction therapy on the dynamic of procalcitonin

In the last decade, there has been growing evidence that treatment with monoclonal and polyclonal antibodies can upregulate plasma PCT concentrations (15, 19, 21, 43). Similarly, high PCT levels were found in allogeneic stem cell transplant recipients after antilymphocyte antibody administration (9). In heart transplant recipients treated with ATG, peak PCT levels (11.7 ± 19.7 ng/mL) were observed in the first 24 h after the first dose administration; however, independent of further ATG doses administration, PCT values continued to decrease during subsequent days (6.7 ± 10.5 ng/mL third day, 3.2 ± 7.4 ng/mL on fifth day and 1.2 ± 3.0 ng/mL on seventh day) (43). Sabat et al. found similar alterations to PCT kinetics after ATG administration; in 11 renal transplant recipients who received ATG as part of induction therapy, PCT levels peaked to a mean 154.6 ± 46.97 (baseline 0.4 ± 0.07) after 24 h of administration and subsequently decreased regardless of repeated ATG administration. On the other hand, those who received interleukin-2 receptor antagonists or steroids did not show PCT elevations (19). In a group of liver transplant recipients, ATG administration was associated with high peak PCT concentrations on post-operative day 1 (median 53 ng/mL, range 7.9–249.1 ng/mL) when compared to those who did not receive ATG; subsequent ATG doses did not elicit further PCT elevations and levels decreased (21). In a study of liver transplant

recipients treated with OKT3 for steroid-refractory rejection, plasma PCT levels increased from 1.05 ± 0.45 ng/mL (prior to antibody administration) to 12.1 ± 6.4 ng/mL (24 h after antibody administration) (15). Treatment with OKT3 for acute rejection has also resulted in elevations of PCT in renal transplant recipients (19, 34).

Why would lytic therapy affect PCT levels? PCT synthesis is induced by pro-inflammatory cytokines such us TNF-alpha, IL-1beta, IL-2, and IL-6; their levels always peak before PCT level (9, 19, 44). It is known that antilymphocyte antibodies bind to lymphocyte surface antigens, modulating $CD4^+$ cells activity and also causing lymphocyte depletion. Recent studies demonstrated that on $CD4^+$ and $CD8^+$ cells, the antibodies cause upregulation of transcripts of immune regulatory cytokines (IL-2, IL-6, IL-10, and IFN-gamma) accompanied by the release of these cytokines (45–47). Similarly, OKT3 administration leads to a transient TNF-alpha release (19), and a significant and persistent release of IL-10 (48). It has also been speculated that the cytokine release induced by OKT3 and ATG could potentially result in transient increase in gut permeability with endotoxin translocation and subsequent PCT release (19).

Effects of chronic immunosuppression on PCT levels

Whether PCT levels are affected by chronic immunosuppression has not been deeply investigated. Most published studies support the notion that chronic immunosuppression should not affect baseline PCT levels in the absence of infection (14, 22–24, 27, 36, 39–42, 49–51). In a human model of endotoxemia, administration of oral prednisolone in doses up to 30 mg, two h before lipopolysaccharide infusion, did not affect PCT kinetics (12). On the other hand, another human model of endotoxemia subjects exposed to ibuprofen had increased levels of calcitonin precursors, those exposed to the TNF receptor antagonist etanercept had decreased levels of calcitonin precursors, whereas those exposed to the soluble human type I IL-1 receptor antagonist had no change in concentrations (52). It is our current practice to use PCT for the evaluation of solid organ transplant patients who have suspected infectious syndromes is similar to that used for other patients who present in the acute care setting. If the degree of immunosuppression and the type of immunosuppression are not acutely changed, the dynamic of PCT should not be substantially affected; thus, PCT may probably be used as an adjunctive diagnostic biomarker in SOT, but more evidence is needed.

Prognostic value of procalcitonin for graft outcome and survival

Several studies have evaluated PCT as a marker of graft outcome and survival. In a small study of heart transplant recipients, an increase of PCT to more than 10 ng/mL was associated with poor outcomes (28). In the study by Madershahian et al. (17), PCT levels predicted poor outcomes and death in heart transplant recipients; peak PCT values and PCT values on the seventh post-operative day were significantly higher in the group of non-survivors compared to survivors (81.6 ± 58.5 vs. 44.7 ± 19.8 ng/mL and, respectively, 12.8 ± 12.2 vs. 4.7 ± 3.5 ng/mL). Kunz et al. measured PCT immediately before and daily after liver transplantation in 22 patients and found that all patients had increased PCT levels without clinical signs of infection. PCT levels also predicted clinical outcomes; while a two-fold reduction in PCT was seen daily in patients who had uncomplicated courses, persistently elevated or increasing concentrations were seen in those who had systemic inflammatory complications (25). A prospective study of more than 500 kidney transplant recipients showed that doubling PCT levels from baseline was associated with three-fold increased risk for graft failure and 1.6-fold increase risk of mortality. The risk of graft failure remained near two-fold higher after adjusting for age, sex, creatinine clearance, proteinuria, BMI, smoking, hsCRP, but the hazard ratio for mortality was reduced to only borderline significant 1.4 (95% CI 1.0–1.9) (53). It should be noted that PCT levels in this study (where the median level was 0.023 ng/mL) were well below what is usually reported by clinical laboratories; as an example, our laboratory's cutoff value is 0.05 ng/mL, whereas the test used in this study was BRAHMS PCT sensitive LIA (BRAHMS Aktiengesellschaft, Hennigsdorf, Germany) (53, 54). Thus, measuring PCT at such low levels is neither practical nor feasible in everyday practice.

A small study was conducted among 26 lung transplant recipients where PCT values were monitored daily post-transplantation until discharge from ICU or death. The authors found moderate but significant correlations between Simplified Acute Physiology II scores and peak PCT values and also with time to reach a cutoff PCT value of 0.5 ng/mL; on the other hand, no correlation was seen between PCT values and cold-ischemia time, primary graft dysfunction, and death. The small number of patients precludes further conclusions in this study (29). In a retrospective study among kidney transplant recipients, there was increased mortality among those who developed pneumonia

and had a CRP level >10 mg/dL or a PCT level >8.8 ng/mL; however, after a multivariate analysis was conducted, only CRP remained associated with increased mortality (OR 1.1; 95% CI 1.0–1.2) although the association was not as strong (55).

The predictive discrimination between survival and death by an absolute PCT value is actually impractical for individual patients in clinical settings. The cutoff values for prediction of outcomes were different among several studies, and the selected populations were heterogeneous in terms of allograft type, induction, and maintenance therapy administered. On the other hand, it is probably more relevant to use dynamic changes of PCT levels as those have been shown to better predict outcome in patients with severe sepsis and septic shock (10, 11).

In conclusion, PCT is a promising biomarker to detect early infectious complications among transplant recipients. PCT also seems to provide better discrimination over C-reactive protein and leukocyte count in patients with and without infections, as well as between patients with rejection or non-viral infections. PCT is an adjunctive biomarker that may improve early identification and guide appropriate treatment of infection or rejection, both of which could further improve clinical outcomes in transplant recipients. PCT test should not be used as a stand-alone test and clinical decisions should not be based on a single PCT value; the use of sequential PCT measurements may lead to more reliable diagnostics in the post-transplantation period. We should use caution when interpreting published data as different assays from different manufacturers might not be interchangeable.

An increased PCT indicates a systemic inflammatory host response, but the magnitude of the response seems to be different in infection and allograft rejection. Considering this is a rapid assay, it might be suitable as a "screening" test for clinical decision making, and it might help decide which patients are more likely to be infected or have rejection. Monitoring PCT in the early post-transplant period seems to be promising method for early detection of infectious complications. However, it remains unclear how often and for how long PCT should be monitored in the post-operative period to maximize the benefits without unnecessary costs. Also it remains undefined which PCT cutoff points would clearly differentiate a normal post-operative course from rejection or infection. The PCT sequential measurements rather than absolute values might be more useful and reliable tool to incorporate in diagnostic algorithms.

Due to the small number of patients included in most of the studies, different designs, most of them being retrospective in nature, firm conclusions cannot be drawn. PCT seems to have similar dynamic in transplant recipients as in the non-immunocompromised patients. PCT also seems to have higher diagnostic value than CRP for differentiating between infection and colonization and also between non-viral infections and rejection. Different cutoff values might be needed to optimize the discriminative power of PCT for patients who receive lytic induction therapy. Further research is necessary to develop a PCT-based algorithm to guide procedures for the diagnosis of rejection and for the reduction of unnecessary antibiotic exposure.

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