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Review

Role of Procalcitonin in Management of Infection in Solid Organ Transplantation Recipients: Review

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Abstract

Infections are a common cause of morbidity and mortality in solid organ transplantation (SOT) recipients. Procalcitonin (PCT) has garnered attention as an inflammatory marker that has been shown to be a valuable marker for early identification of systemic bacterial infection. However, interpretation of PCTs value in the different types of infections, transplanted organs, and post-operative courses can be challenging. We review the role of PCT in the management of infections in SOT recipients. First, the PCT level can be elevated immediately after transplant surgery, but those levels decline over one week and do not rise significantly unless an individual develops a systemic bacterial infection. Second, PCT is elevated in systemic bacterial infection, but not in localized bacterial infections or viral infection. Third, procalcitonin does not rise significantly during episodes of acute rejection, but it can be elevated with the use of antithymoglobulin for induction or rejection treatment. While issues remain with the use of PCT as a predictive, it may provide an important piece of information that guides clinical decision-making.

Keywords
Procalcitonin; solid organ transplantation; infection

1. Introduction

Infections, as defined by positive culture or biopsy, are a common cause of morbidity and mortality in solid organ transplantation (SOT) recipients [1]. Poor nutritional status, exposure to the health care environment before transplantation and the use of immunosuppressive therapy after the transplantation increase the risk of infections in this population. As is recognized with non-immunosuppressed hosts, early identification of sepsis, with the subsequent administration of empiric antimicrobials and adjustment of immunosuppressant therapy leads to improved patient survival [2-4]. However, patients with suspected sepsis must be distinguished from those with multiple organ dysfunction syndrome of non-infectious etiologies.

A positive fluid or tissue culture remains the gold standard for the diagnosis of bacterial infection. However, cultures are problematic in regard to both sensitivity and specificity. Their lack of sensitivity can lead to missed and delayed diagnoses [5]. From a specificity standpoint, positive cultures can be misleading as the results may represent colonization as opposed to true infection. These diagnostic issues may lead to unnecessary or unnecessarily broad antibiotics that, in turn, may result in complications such as increased antibiotic resistance or *Clostridium difficile* colitis.

Other than cultures, there are a variety of surrogate markers whose elevation may suggest the presence of infection. These include white blood cell count with differential, temperature, neopterin, interleukin-2 receptor, interleukin-6, interleukin-8, tumor necrosis factor-alpha and C-reactive protein (CRP). While an elevated white blood cell count (WBC) is commonly used to predict infection in a normal host, it is not a sensitive marker in the SOT population as the immune system of SOT recipients is blunted from chronic immunosuppression [6, 7]. Beyond WBC, CRP is a well-studied inflammatory marker that can be elevated in the setting of surgery, infection, chronic inflammation, viral illnesses, and even malignancy; however, due to its lack of specificity, it cannot distinguish infection from other potential causes of elevation in SOT recipients [8, 9]. In particular, differentiating acute rejection from infection is a challenge as both present with similar physiologies and similarly elevated CRPs [10].

In recent years, procalcitonin (PCT) has garnered attention as an inflammatory marker that may aid in the diagnosis of infection and the use of antibiotics [11-13]. In SOT recipients, specifically, procalcitonin has been shown to be a valuable marker for early identification of systemic bacterial infection [14, 15]. As in non-immunosuppressed patients, PCT increases in SOT recipients within three hours of the onset of systemic bacterial infections [16]. Its level is not confounded by graft rejection or concomitant viral infection [14, 16]. However, in SOT recipients, there is a lack of consensus regarding PCT cutoff values for the identification of infection. Variables such as the type of transplanted organ, immunosuppression use, and the timing of transplant have all shown an effect on PCT levels [17]. Interpretation of PCTs value in the different types of infections, transplanted organs, and post-operative courses can be challenging. In this article, we review the role of PCT in the management of infections in SOT recipients.

2. PCT as A Marker for Bacterial Infection

PCT, a 116 amino acids pro-peptide of calcitonin, is produced under normal conditions in the C cells of the thyroid gland and K cells of the lung. It does not normally circulate in the bloodstream of healthy individuals [18]. Its clinical relevance was first identified in 1993, when noted to be elevated in children with severe bacterial infections [19], though the mechanism of its production and role in the inflammatory cascade was not well known. In the presence of a systemic bacterial infection, cytokines such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and granulocyte colony-stimulating factor trigger non-neuroendocrine tissues to express the CALC-1 gene, which in turn produces procalcitonin [20-22]. Cytokines associated with infection and bacterial endotoxins slow the conversion of PCT to calcitonin and therefore, thus raising serum PCT concentrations. The lag time for PCT induction is approximately 2 to 4 hours after the onset of systemic bacterial infection, peaking at 24 to 48 hours [23]. After reaching its peak levels, the circulating PCT declines. Its serum half-life is approximately one day, though this may be prolonged by decreased renal clearance. Because PCT elevation is triggered by systemic inflammation, local infections such as abscesses and slowly-evolving infections such as chronic osteomyelitis and tuberculosis may not raise PCT levels [24]. Additionally, PCT is not elevated in viral infections as interferon gamma blocks PCT production. It is not affected by anti-inflammatory agents such as steroids or non-steroidal anti-inflammatory drugs [17] (Figure 1).

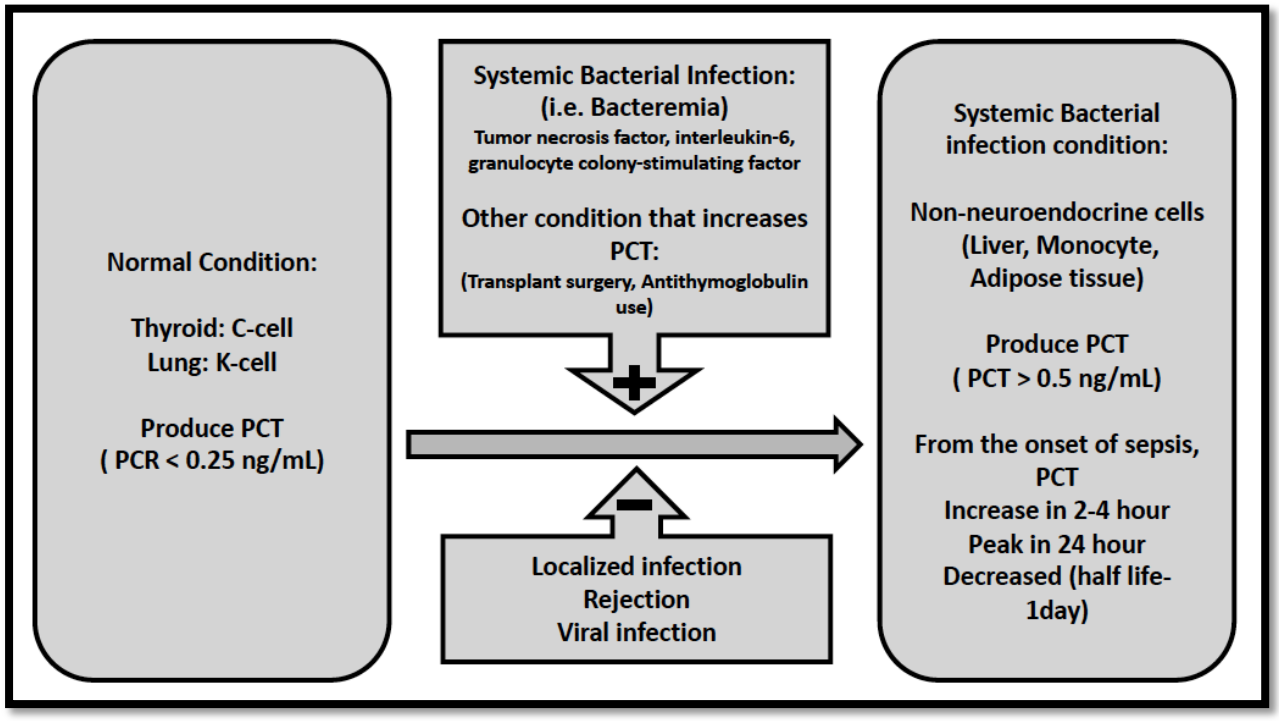

Figure 1 Procalcitonin in response to systemic bacterial infection.

3. How PCT is Used

PCT levels can be used in two ways—as individual values with predictive qualities in and of themselves and as a series kinetic values whose predictive nature lies in their change over time. A PCT level higher than 0.5ng/mL has a high positive predictive value to rule in systemic bacterial

infection. A level less than 0.25ng/mL has a high negative predictive value to rule out a systemic bacterial infection [25-27]. In the outpatient setting, low cut-off values (e.g. <0.25 ng/mL) have been used to minimize unnecessary antimicrobial therapy [25-27]. In its predictive role as a kinetic value, a decreasing PCT level provides a means to monitor the success of antibacterial therapy. In the intensive care unit (ICU), changes in PCT after the initiation of antibiotics have been used to optimize the duration of antimicrobial therapy. In studies of both general sepsis as well as pneumonia, it has been shown that antibiotics may be safely stopped once PCT levels decrease by more than 80% from the peak value after antibiotic initiation [28, 29]. In a systematic review, the use of algorithms based on the change in PCT values, did not increased mortality but did reduce antibiotic exposure [30]. While PCT does not identify the organism to adjust antibiotics, it can be a useful biomarker in deciding to initiate empiric antimicrobial therapy. Combined with the newer rapid organism-identifying technologies such as matrix-assisted laser desorption/ionization time of flight and polymerase chain reaction-based methods, PCT may have an important role in directing antimicrobial use.

4. PCT Levels in SOT

PCT is commonly elevated to levels of 10-1000ng/mL in severe systemic bacterial infections [9]. In healthy individuals, PCT values are normally below 0.5 ng/mL [27, 31]. With its stable biochemical properties, PCT has been used to differentiate systemic bacterial infections in the many clinical settings including the transplant population. In a meta-analysis of seven PCT studies, Yu et al. calculated the predictive value of PCT for infection [32]. PCT demonstrated a sensitivity of 85% and specificity of 81% in identifying bacterial infection after transplantation. These parameters were similar to the performance of PCT in evaluating bacteremia in the normal host [8]. When including only liver recipients, the sensitivity and specificity were higher, and, in all patients, the diagnostic value of PCT was not compromised by long-term immunosuppression.

Despite these promising results, there are unique challenges in the interpretation of the PCT levels in SOT recipients, especially at the early transplant course. PCT can be elevated after the major surgery or trauma [33]. Consequently, in heart, lung and liver transplant recipients, PCT is increased in the first post-operative week. However, after that first week, persistently elevated or increasing PCT levels can be used to predict infection [34]. This predictive value has been shown to be superior to CRP for identifying infection [31].

Liver SOT**:** In liver transplant recipients, PCT levels, in the absence of infection, can be elevated in the first seven days following transplant, with a peak at day two, before declining to a normal level. It is postulated that the influx of bacterial endotoxin from the small bowel during the transplantation and the transiently impaired endotoxin clearance from the graft raises the post-operative PCT level [35, 36]. Kaido et al. observed that deceased-liver transplant recipients had higher PCT levels than living-liver transplant recipients. This may be explained by an increase in endotoxin production with longer ischemic times.

Beyond the immediate post-operative stage, an elevated PCT has significant associations with infection. Among liver transplant patients with bacteremia, PCT levels are significantly increased compared to patients without bacterial infection, even those with cytomegalovirus (CMV) antigenemia or with acute rejection. Using low and high cut-off values of 0.5 ng/mL and 2.0 ng/mL, respectively, PCT demonstrated a high negative predictive value of 96% and a positive predictive

value of 83% in the diagnosis of bacteremia [14]. PCT has also been studied to predict catheter-related bloodstream infections in liver transplant recipients. Chen et al. found 25 patients out of 55 patients who developed catheter-related bloodstream infection had higher PCT levels [37]. Perrakis et al. measured post-operative PCT levels in thirty-two liver transplant recipients. Two patients who had a rapid increase in procalcitonin died. Lower peak procalcitonin levels (< 5 ng/mL) were observed in ten patients, nine of which suffered no complications. Procalcitonin levels greater than 5 ng/mL were noted to have an eleven-fold higher risk of complications [38]. They concluded that a higher initial PCT might be correlated with post-operative complications and worse outcomes. In another large study of liver transplant recipients, 233 patients were evaluated [39]. PCT was elevated in patients with significant infections, though was not a statistically significant marker for infection. However, it was felt that post-surgical elevation of PCT may have confounded the association as most infections occurred within one week of surgery. Furthermore, localized infections were included in the study and may have confounded the results [39].

Lung SOT**:** In lung transplant recipients, PCT is elevated in the early transplant period, peaking in the first 24 hours before declining over the next seven days [40]. Elevated PCT levels in the setting of infection have been reported in lung transplant recipients [15, 40, 41]. In 233 patients, Suberviola et al. found that PCT levels above 0.5 ng/mL on admission and 1.17ng/mL on day one after transplantation were significantly associated with an increased risk of infection [15]. Besides infection, PCT has been used to assess pulmonary graft dysfunction, a form of acute lung injury associated with early post-transplantation morality [42, 43]. Mazo et al. measured PCT in the early period after lung transplantation and found a PCT level measured to be less than 2 ng/mL with 24 hours of transplant has a highly negative predictive value for grade 3 pulmonary graft dysfunction [44].

Renal SOT**:** Unlike liver and lung recipients, renal transplant recipients did not see a significant post-operative rise in PCT, possibly due to the comparatively less extensive nature of renal transplant surgery [16]. In a cohort of fifty-seven renal transplant recipients, Eberhard et al. monitored the PCT level during the first six weeks after the transplantation. Seventeen (31%) of the patients developed an invasive bacterial infection all of whom had a significantly elevated PCT level when compared to ones without infection [45]. Similar findings were seen in a study that evaluated the PCT level in 56 dialysis and 28 renal transplant patients. PCT was significantly associated with infection. Using the cut off value of 0.5 ng/mL, PCT had a sensitivity of 78.6% and specificity of 85.7% in predicting infection in renal transplant recipients [46]. In renal recipients, PCT was also associated with graft outcomes. Van Ree et al. performed a prospective study evaluating the value of PCT in predicting graft outcome in 575 renal transplant recipients. They measured a PCT level during outpatient visits when the patients had no evidence of infection. Doubling of PCT level from baseline correlated with a three-fold risk of graft failure [47].

Heart SOT: In heart transplant recipients, Madershashian et al. evaluated the association of PCT levels with complications after the heart transplant surgery. Evaluated complications included not only the infection, but also bleeding, the need for repeat surgery, the development of rejection, and the occurrence of acute kidney injury. Among the patients who had a complication, PCT level was elevated on day two (54.6 ng/mL vs. 9.1 ng/mL) and day seven (7.8 ng/mL vs. 0.6 ng/mL). Similar to the liver and lung transplant recipients, significant elevation of PCT was observed immediately after the surgery in both group [48] (Table 1).

Table 1 Summary of procalcitonin studies in SOT (Single allograft).

Transplanted Organ (N)	Article (Author, country, published year)	Procalcitonin Comparison Group	Result and Comment
Liver Transplantation			
Liver (22)	Kuse, Germany, 2000 [49]	Microbiologically documented infection	Procalcitonin level >5.9 ng/mL had more likely to have the infection
Liver (61)	Fazakas, Hungary, 2003 [50]	Post-operative complication	Post-operative day two PCT level was higher in groups that developed complication than other groups (30.6 ng/mL vs. 4.8 ng/mL)
Liver (67)	Eyraud, France, 2008 [35]	Infection	High peak PCT level was associated with infection and cardiac arrest of donor
Liver (64)	Prieto, Spain, 2008 [51]	Infection	23 who developed infection had higher PCT level than ones did not have an infection (cut off 1.92 ng/mL)
Liver (135)	Van den Broek, Germany 2010 [39]	Clinically significant infection (N=30, 8 pulmonary infection, 9 intraabdominal infection, 13 bacteremia)	Patient with clinically significant infection had higher peak PCT than non-infected, but it was not an independent marker.
Liver (32)	Perrakis, Germany, 2010 [38]	Noncomplicated vs. complicated group	Peak PCT level >5ng/mL had increased odds ratio of a complication 11.2.
Liver (55)	Chen, China, 2011 [37]	Catheter-related bloodstream infection	25 (45%) who developed catheter-related bloodstream infection had higher PCT level than those who did not. (cut off value 3.1 ng/mL)
Liver (34)	Grammatikopoulos, United Kingdom, 2012 [52]	Fever, 22 (66%) developed the infection	PCT levels were significantly higher in bacterial and fungal infection in comparison to other inflammatory markers (CRP, IL-6).
Liver (104)	Kaido, Japan 2014 [14]	Post-operative Bacteremia CMV antigenemia Acute cellular rejection	Increased (Deceased-donor had higher level increase than living donor) in the first 7 days, peak in day 2 to 3. 45 (43%) out of 104 patients with bacteremia had higher PCT level. PCT level did not increased in CMV antigenemia compared to bacteremia (0.53 ng/mL vs 5.71 ng/mL) PCT level did not increased in acute

			rejection compared to bacteremia (0.42 ng/mL vs 5.71 ng/mL)
Liver (65)	Gur, Turkey 2017 [53]	Infection by culture positive versus control	Higher PCT level (20.5 ng/ml vs. 2 ng/ml) in the infection group than the control group
Lung Transplantation			
Lung (25)	Suberviola, Spain, 2012 [41]	Infection versus non-infection	Six developed infections (3 pneumonia, 2 bacteremia, 1 peritonitis) had higher PCT than control (cut off 8.18 ng/mL)
Lung (26)	Desmard, French, 2015 [40]	Respiratory infection	Doubling PCT level was associated with respiratory infection (RR 4.2, 95% CI (1.95 to 9.03)
Lung (233)	Suberviola, Spain 2017 [15]	Infection	PCT levels above the median (0.5ng/mL on admission or 1.17 ng/mL on day 1) were associated with an increased risk of infection
Lung (100)	Mazo, Spain 2018 [44]	ICU survival, pulmonary graft dysfunction	PCT <2ng/mL within 24 hours of transplant has a high predictive value to exclude grade 3 pulmonary graft dysfunction (97%) and for ICU mortality (100%)
Heart transplantation			
Heart (52)	Madershahian , Germany, 2008 [54]	Event (complication including bleeding, acute kidney injury, infection, rejection)	28 pts eventful group had lower PCT than 24 pts with an event on the second day and day seven
Kidney Transplantation			
Kidney (57)	Eberhard, Germany,1998 [45]	17 patients with invasive bacterial infection compared with 30 non-infected	PCT was elevated with invasive bacterial infection
Kidney (575)	Van Ree, Netherland, 2009 [47]	Graft failure (Procalcitonin level obtained at outpatient at the time of no active infection)	Doubling PCT level from baseline was associated with a three-fold increase of graft failure.
Kidney (406)	Dizdar, Turkey, 2014 [55]	82(20%) patients developed pneumonia	PCT level >8.8 ng/mL increased the risk of death from pneumonia

5. Non-Infectious Causes of PCT Elevation in SOT Recipients

There are a variety of non-infectious conditions that can lead to an elevation of serum PCT in SOT recipients. These includes cirrhosis, inhalational injury, obstructive pancreatitis, autoimmune disorders, trauma, ischemia, malignancy, rhabdomyolysis and the use of immunosuppressive drugs [17, 34, 45, 56-58]. As with transplant itself, other major surgeries result in an elevation of PCT levels, especially in the first 24-48 hours after surgery [59]. Transient gut translocation of

bacterial products into the systemic circulation may also lead to a rise in PCT, even if the translocation does not lead to other sequelae suggestive of infection [34, 57]. While the above may confound the clinical utility of PCT as a predictor of bacterial infection, acute rejection typically demonstrates only a modest increase in PCT [9, 60].

6. The Effect of Antithymocyte Globulin (ATG) on PCT Levels

Antithymocyte globulin (ATG) used during induction or rejection treatment can raise PCT levels [54, 61, 62]. In heart transplant recipients, PCT levels have been shown to increase after ATG induction, though trend down on further dosing [54]. Similar PCT kinetics have been observed in renal transplant recipients receiving ATG, though those who received interleukin-2 receptor blockade did not demonstrate an elevation in PCT levels [61]. For those receiving ATG, the early elevation in PCT may have been confounded by post-surgical elevation of procalcitonin. However, SOT recipients treated for acute rejection, distant from the time of transplantation, had similar PCT elevation after ATG administration [45, 61, 63]. The mechanism behind this elevation is thought to be twofold. First, ATG leads to transient elevation of cytokines such as TNF alpha and interleukin-10, which can in turn trigger PCT production. Also, cytokines produced in the setting of ATG can transiently increase gut permeability with associated endotoxin translocation. Endotoxin, as had been noted, leads to a rise in PCT levels [61]. Beyond ATG, other common chronic immunosuppression like cyclosporine, tacrolimus, azathioprine, and steroids do not affect the baseline PCT level [16, 26, 44, 60, 64]. If the degree of immunosuppression and the type of immunosuppression are not changed, the dynamics of the PCT level should remain stable and can be used as a biomarker to differentiate systemic bacterial infection.

7. Remaining Challenges

There are areas not well described regarding PCT use in SOT recipients. PCT is not well studied in specific types of infection in different allograft SOT recipients. Most of the studies described above were retrospective and had different definitions of infection. Therefore, it is hard to generalize regarding the value of PCT to identify risk for infection in individual patients. Further, the degree of PCT elevation in different pathogens, by organism or organism type, was not defined. While it is generally elevated in systemic bacterial infections, it remains an insensitive test for predicting or identifying localized infection. Also, if PCT is to be used post-operatively for screening or monitoring, a patient's baseline, pre-operative PCT level, history of other recent surgeries, and the presence of rejection may all confound the utility of PCT monitoring. Furthermore, the length and most appropriate time window for screening is unknown, which may further affect the clinical usefulness of the test. While all of the above questions relate to PCT levels in recipients, another area of interest yet to be explored is the association of donor PCT levels on recipient outcomes. An exploration of the above issues may help establish the value of measuring PCT levels in transplant patients.

8. Summary

The use of PCT holds potential as a modality for assessing the presence of systemic bacterial infection in SOT recipients. At this stage, there are a few facts to consider if using PCT to predict

the presence of infections in SOT recipients. First, the PCT level can be elevated immediately after transplant surgery, especially in heart, lung, and liver transplant recipients. However, those levels decline over one week and do not rise significantly unless an individual develops a systemic bacterial infection. Second, PCT is elevated in systemic bacterial infection, but not in localized bacterial infections or viral infection. Therefore, clinicians should still take care to rule out localized bacterial infections or viral infections in patients with low PCT levels. Third, procalcitonin does not rise significantly during episodes of acute rejection, but it can be elevated with the use of ATG for induction or rejection treatment. However, PCT is not affected by other immunomodulators. While issues remain with the use of PCT as a predictive, it may provide an important piece of information that guides clinical decision-making.

Author Contributions

All authors contributed in critical review of the literature, writing of the manuscript and approval of final version.

Competing Interests

The authors have declared that no competing interests exist.

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