Clinical Policy Bulletin: Procalcitonin (PCT)

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Policy

Aetna considers the measurement of procalcitonin (PCT) medically necessary for initiating and discontinuing antibiotic therapy in persons in the intensive care unit and for persons with respiratory tract infections in the hospital setting to reduce antibiotic prescription rates and duration of use.

Aetna considers the measurement of procalcitonin (PCT) experimental and investigational for the following indications because of insufficient evidence of its effectiveness (not an all-inclusive list):

- Diagnosis and monitoring of surgical infections
- Diagnosis and prognosis of bacterial infections in persons with severe acute malnutrition
- Diagnosis of appendicitis
- Diagnosis of chronic renal insufficiency
- Diagnosis of infective endocarditis
- Diagnosis of non-alcoholic fatty liver disease
- Diagnosis of parapneumonic pleural effusions
- Diagnosis of spontaneous bacterial peritonitis
- Differentiation of infection from other inflammatory complications following hematopoietic stem cell transplant
- Evaluation of fever of uncertain source in infants
- Evaluation of individuals with suspected lower respiratory tract infection or sepsis in the ambulatory care/emergency department setting
- Prediction of neurological deficits following carotid endarterectomy
- Prediction of pneumonia in persons with acute cough
- Prognostication in persons with acute coronary syndrome.

Background

Sepsis and septic shock are the leading causes of death in intensive care units (ICUs) despite advances in critical medicine. Sepsis is the systemic inflammatory response to infection frequently associated with hypo-perfusion followed by tissue injury and organ failure. The activation of neutrophils and monocytes/macrophages, with the consecutive release of pro-inflammatory mediators and activation of the coagulation cascade, seems to play a key role in the
pathogenesis of sepsis. Removal of the septic source, anti-microbial therapy and supportive treatment are the basic treatment for sepsis.

Procalcitonin (PCT), a propeptide synthesized in the C cells of the thyroid, is a precursor of calcitonin. Procalcitonin is not found in the serum of healthy individuals; however, in response to bacterial infections, a rapid rise in serum PC levels occurs. Procalcitonin has been identified as a promising biomarker that may assist in distinguishing bacterial infection from other causes of fever or sepsis (e.g., viral infections) that do not lead to an increase in serum PCT levels. The level of PCT in the serum is reportedly a reflection of the severity of bacterial infection, ranging from slightly elevated in infections with minor systemic inflammatory response to very high values in cases of severe sepsis and septic shock. Once an infection is under control, PCT levels decrease.

The U.S. Food and Drug Administration (FDA) has cleared for marketing through the 510(k) process the BRAHMS sensitive KRYPTOR (Brahms USA, Inc., Annapolis, MD), the VIDAS BRAHMS PCT (bioMerieux, Inc., Hazelwood MO), and the BRAHMS PCT LIA (BRAHMS Diagnostica, LLC, Tracys Landing, MD) quantitative assays to determine the concentration of PCT in serum and plasma. These devices utilize different technologies and instruments to obtain results but have a similar indication for use, which is to aid in the assessment of risk progression to severe sepsis and septic shock in critically ill patients on the first day of admission to ICU. The devices are intended to be used in conjunction with other laboratory findings and clinical assessments to determine whether an infection is bacterial or viral, thus, potentially avoiding unnecessary use of antibiotics. According to the BRAHMS website, PCT levels greater than 2.0 ng/ml on the first day of ICU admission represent a high risk for progression to severe sepsis and/or septic shock while levels less than 0.5 ng/ml represent a low risk, and levels less than 0.3 ng/ml are below the detection limit of test and represent a healthy condition. BRAHMS website states that, "PCT levels below 0.5 ng/ml do not exclude infection, because localized infections (without systemic signs) may also be associated with such low levels. As various non-infectious conditions are known to induce PCT as well; PCT levels between 0.5 ng/ml and 2.0 ng/ml should be reviewed carefully to take into account the specific clinical background and conditions(s) of the individual patient. PCT should always be interpreted in the clinical context of the patient. Therefore, clinicians should use the PCT results in conjunction with other laboratory findings and clinical signs of the patient." The first hours of sepsis can not be detected with the BRAHMS PCT LIA assay; however, the BRAHMS PCT Kryptor test is more sensitive and can provide information in less than an hour after a blood sample is drawn. The FDA has determined through the 510(k) process that the BRAHMS PCT KRYPTOR test system is substantially equivalent to other inflammatory response markers; the manufacturer was not required to provide the evidence of effectiveness that is necessary to support a premarket approval application.

An assessment of procalcitonin prepared for the Agency for Healthcare Research and Quality (AHRQ) (Soni et al., 2011) concluded that PCT guidance reduces antibiotic use when used to discontinue antibiotics in adult intensive care unit patients and to initiate or discontinue antibiotics in patients with respiratory tract infections. The authors of the AHRQ assessment identified 18 randomized, controlled trials that addressed 5 patient populations. The report found high quality evidence that PCT guidance reduced antibiotic use when used to discontinue antibiotics in adult intensive care unit patients and to initiate or discontinue antibiotics in patients with respiratory tract infections, moderate evidence that this can be accomplished without increasing morbidity and low quality evidence that this can be accomplished without increasing mortality. The report found, by contrast, moderate evidence that PCT-guided intensification of antibiotics in adult intensive care unit patients increases morbidity. The report also found moderate evidence from single good quality study that PCT guidance reduces antibiotic use for suspected early neonatal sepsis, but found insufficient evidence on morbidity and mortality outcomes. The report found insufficient evidence to draw conclusion on outcomes of PCT guidance for: (i) fever of unknown source in children 1 to 36 months of age; and (ii) preemptive antibiotics after surgery. The authors noted that immunocompromised hosts and other special populations were generally excluded from PCT guidance studies. The authors stated, therefore, that findings from this review should be extrapolated to patients with the following conditions: pregnancy; absolute neutropenia; immunocompromised status; chronic infections, and infections for which prolonged antibiotic therapy is standard of care (e.g., infective endocarditis). The authors stated that populations for future research should include immunocompromised patients, patients with infections and conditions (e.g., pregnancy, cystic fibrosis), and pediatric patients. The report stated that future research should...
compare PCT guidance with antibiotic stewardship programs and to implementation of guidelines. The report noted outcomes of high interest for future research are the consequences of reduction in antibiotic use for antibiotic resistance and for adverse events of antibiotic therapy.

In preterm infants, PCT appears to be reasonably specific, but lacks sensitivity as a marker of sepsis. Turner et al. (2006) evaluated the role of PCT in detecting nosocomial sepsis in preterm infants, after the onset of clinical symptoms in 100 preterm infants. Procalcitonin and C-reactive protein (CRP) levels were measured within 3 days of sepsis work-up events. Blood samples were drawn from 36 infants during 85 episodes of sepsis performed between 4 and 66 days of life. Of these episodes, 51 (60 %) were not a result of documented sepsis and thereby served as the negative comparison group. Median PCT levels were higher in the septic group compared with the non-septic group at the time of the sepsis work-up (2.7 versus 0.5 ng/ml, p = 0.003), at 1 to 24 hours after the sepsis work-up (4.6 versus 0.6 ng/ml, p = 0.003), and at 25 to 48 hours (6.9 versus 2.0 ng/ml, p = 0.016). Using high cut-off levels, both PCT (2.3 ng/ml) and CRP (30 mg/l) had high specificity and positive-predictive value (97 %, 91 % and 96 %, 87 %, respectively) but low sensitivity (48 % and 41 %, respectively) for detection of sepsis.

Studies and systematic reviews are in disagreement over the utility of PCT in distinguishing infection from other causes of systemic inflammatory response syndrome in older individuals (Suprin et al, 2000; Gattas et al, 2003; Uzzan et al, 2006; Tang et al, 2007).

Nobre et al (2008) reported on a study suggesting that monitoring plasma PCT levels could allow discontinuation of antibiotic therapy safely earlier than is currently done using clinical criteria alone. In this study, 79 patients were enrolled among 282 patients who were assessed. A total of 40 patients were randomized to a control group, consisting of treatment according to standard practice, and 39 patients were randomized to the PCT group, in which a recommendation was given to continue or stop antibiotic therapy based on a 90 % or greater reduction in PCT level 3 days (for patients with baseline PCT levels less than 1 µg/L) or 5 days (for patients with baseline levels 1 µg/L or of antibiotic therapy. Only 37 control-group and 31 PCT-group patients reached the 3- or 5-day mark and were evaluable per protocol. Excluding 6 patients for whom the algorithm was over-ruled (i.e., the treating physician referred to stop the antibiotics, despite the investigators’ encouragement to do so), PCT-group participants had a shorter median duration of antibiotic therapy than did controls (6.0 versus 12.5 days; p = 0.0002). Clinical cure and 28-day mortality rates were similar between groups, but the median ICU stay was shorter for PCT-group patients (3.0 versus 5.0 days; p = 0.03). Ampel (2008) noted that this study was plagued by the initial exclusion of many patients, the need to analyze data per protocol rather than by intent-to-treat, and algorithm over-ruling.

In a systematic review to assess the diagnostic accuracy of PCT in sepsis diagnosis in critically ill patients, Tang et al (2007) examined 18 studies. The authors reported that the diagnostic performance of PCT is poor, with mean values of sensitivity and specificity being 71 % (95 % confidence interval [CI]: 67 to 76). The authors concluded that PCT cannot reliably differentiate sepsis from other non-infectious causes of systemic inflammatory response syndrome in critically ill adult patients and that these findings do not support the widespread use of PCT testing in critical care settings.

Measurement of PCT is a promising biomarker for the assessment of risk progression to severe sepsis and septic shock in critically ill individuals on their first day of ICU admission. However, there is insufficient evidence of its clinical utility.

Jensen et al (2008) noted that for the first time ever, a mortality-endpoint, large scale randomized, controlled trial with biomarker-guided strategy compared to the best standard of care, is conducted in an ICU setting. Results will, with high statistical power answer the question: Can the survival of critically ill patients be improved by actively using biomarker PCT in the treatment of infections?

Manzano and associates (2009) compared PCT measurements between semi-quantitative and quantitative assay. Procalcitonin was measured with the PCT-Q and the Kryptor assays in a pediatric emergency department. Among 359 pairs of results, 103 had discordant results. The linear weighted kappa was 0.44 (95 % CI: 0.36 to 0.51). The concordant/discordant results distribution varied depending on the laboratory technician (p = 0.018). The authors
concluded that agreement between PCT measured semi-quantitatively and quantitatively was moderate. This is probably due to a subjective interpretation of the assay result.

Rowther and colleagues (2009) compared the results of polymerase chain reaction (PCR) and PCT with blood culture in ICU patients suspected of having septicemia. A total of 90 patients (60 patients meeting the criteria for sepsis and patients not meeting the criteria for sepsis) were evaluated. Compared with blood culture as the gold standard, the sensitivity, specificity, and positive- and negative-predictive values for PCR were 100 %, 43.33 %, 46.87 %, and 10 respectively, and for PCT were 100 %, 61.66 %, 56.6 %, and 100 %, respectively. The average times required to produce a final result were as follows: PCR, 10 hrs; blood culture, 33 hrs; PCT, 45 mins. Both PCR and PCT may be useful as rapid tests for detecting septicemia but compared with blood cultures lacked specificity.

Mommertz and co-workers (2009) stated that outcome of carotid endarterectomy (CEA) is defined by mortality rate due to cerebral ischemia. These investigators assessed the role of the acute phase protein PCT as a predictor for neurological deficits following carotid endarterectomy. A total of 55 patients with high grade stenosis of the internal carotid artery and inter-disciplinary consensus for endarterectomy were followed. Neurological examination was performed before and after the procedure to analyze peri-operative neurological deficits. Blood samples were obtained before and after CEA and PCT was analyzed in 55 consecutive patients (65.5 % symptomatic/34.5 % asymptomatic). No peri-operative or in-hospital death was observed. Major complications did occur, 2 patients suffered from bleeding requiring surgical intervention and 1 patient had a temporary peripheral face nerve lesion. Post-operative neurological examination revealed no new deficit, there was no significant change of (level pre- and post-CEA (the mean pre-operative PCT was 0.25 ng/ml [SD 0.78, min = 0.1, max = 4.3]; the mean operative PCT was 0.11 ng/ml [SD 0.06, min = 0.1, max = 0.5]). There was no association found between peri-operative neurological deficit and PCT. The authors concluded that these findings demonstrates that there is still insufficient evidence to recommend PCT measurement as a predictor for peri-operative neurological deficit during CEA.

In a review on the use of PCT in the diagnosis and monitoring of surgical infections, Zielińska-Borkowska et al (2009) stated that further research is needed to ascertain the accurate diagnostic value and the clinical application of the PCT level as a marker of surgical infections.

Sand et al (2009) examined if PCT levels in the serum of patients with acute appendicitis have any diagnostic value. This prospective study included 103 patients who received an appendectomy, based on the clinical diagnosis of acute appendicitis. White blood cell count (WBC), CRP and PCT values were determined pre-operatively. All appendectomy specimens were sent for routine histopathological evaluation. Based on this information, the patients were assigned to 5 groups that reflected the severity of the appendicitis. Of the 103 patients who were included in the study, 98 had appendicitis. Fourteen (14.3 %) showed an increase in PCT values. Of those, 4 had a serum PCT greater than 200 ng/ml, 9 had a PCT value greater than 2 to 10 ng/ml and 1 had a PCT value greater than 10 ng/ml. The sensitivity of PCT was calculated to be 0.14. The mean WBC value was 13.0/nl (+/- 5.2, range of 3.4 to 31), and for CRP it was 0.5 mg/dl (+/- 13, range of 0 to 60.2). The values of CRP, WBC and PCT increased with the severity of the appendicitis. The authors concluded that PCT is potentially increased in rare cases of severe inflammation and, in particular, after appendiceal perforation or gangrenous appendicitis. However, its remarkably low sensitivity prohibits its routine use in the diagnosis of appendicitis.

In a case-control study, Oruc and co-workers (2009) examined the diagnostic and discriminative role of serum PCT levels in non-alcoholic fatty liver disease (NAFLD). A total of 50 NAFLD cases and 50 healthy controls were included in the study. Liver function tests were measured, body mass index was calculated, and insulin resistance was determined by using a homeostasis model assessment (HOMA-IR). Ultrasound evaluation was performed for each subject. Serum CRP was measured with nephelometric method; and serum PCT was measured with Kryptor based system. Serum PCT levels were similar in steatohepatitis (n = 20) and simple steatosis (n = 27) patients, and were not different than the control group (0.06 +/- 0.01, 0.04 +/- 0.01 versus 0.06 +/- 0.01 ng/ml, respectively). Serum CRP levels were significantly higher in simple steatosis, and steatohepatitis groups compared to healthy controls (7.5 +/- 1.6 and 5.2 +/- 2.5 versus 1.4 +/- 0.5 mg/dl, respectively p < 0.01). C-reactive protein could not differentiate steatohepatitis from simple steatosis. Beside, 3 patients with focal fatty liver disease had normal serum CRP levels. The authors concluded that serum PCT
was within normal ranges in patients with simple steatosis or steatohepatitis and has no diagnostic value. Serum C level was increased in NAFLD compared to controls; CRP can be used as an additional marker for diagnosis of NA but it has no value in discrimination of steatohepatitis from simple steatosis.

Ataoglu and colleagues (2010) stated that PCT is implicated as an inflammatory marker in early atherosclerosis. In order to investigate the clinical consequences of increased PCT levels in acute coronary syndrome, 77 patients (2 non-ST-elevation myocardial infarction [MI], 34 with ST-elevation MI, and 14 with unstable angina pectoris) were included and followed-up for 6 months. The PCT levels were determined at initial presentation and within 48 hrs of admission. Five patients died during hospitalization and their PCT levels within 48 hrs of admission were significantly higher than survivors (n = 72) (0.588 +/- 0.56 versus 0.399 +/- 1.33 ng/ml, respectively). The PCT levels within 48 post-admission in the 9 patients who died within 6 months were also significantly higher compared with the survivors (0.451 +/- 0.44 versus 0.406 +/- 1.37 ng/ml, respectively). The authors concluded that higher PCT levels within 48 post-admission may reflect an inflammatory state that is associated with increased early and 6-month mortality.

Knudsen et al (2010) noted that diagnostic delay contributes to high morbidity and mortality in infective endocarditis; a readily available diagnostic marker of infective endocarditis is desirable. Serum PCT (S-PCT) has been proposed as a candidate, but data on its yield are conflicting. These investigators tested its diagnostic value in a large population of patients seen in a tertiary center. This prospective study included 759 consecutive patients referred for echocardiographic examination on clinical suspicion of infective endocarditis. Transthoracic echocardiography was followed by immediate trans-esophageal examination, and a blood sample was obtained for PCT analysis. Infective endocarditis was diagnosed by an inter-disciplinary team and confirmed according to the Duke criteria. The team was unaware of the results of PCT analyses. Infective endocarditis was present in 147 patients (19 %). Procalcitonin was higher in these patients than in those in whom infective endocarditis was rejected (median of 0.21 ng/ml versus 0.1 ng/ml; p < 0.0005). Multi-variate analysis identified significant independent determinants of high PCT: blood culture endocarditis-typical microorganisms (odds ratio [OR], 2.81), temperature greater than or equal to 38°C (OR, 2.61), symptoms less than or equal to 5 days (OR, 2.39), immunocompromised status (OR, 1.74), and male gender (OR, 1.61). Tests at various PCT thresholds yielded an acceptable sensitivity of 95 % at 0.04 ng/ml, but specificity was 14 %. Only 12 % had PCT below this threshold, which might justify postponement of further examinations for infective endocarditis. The authors concluded that PCT was significantly higher in patients with infective endocarditis than in patients without infective endocarditis and bacteremia with endocarditis-typical organisms was the strongest independent determinant of high procalcitonin. The clinical importance of this is questionable, because a suitable PCT threshold diagnosing or excluding infective endocarditis was not established.

Cincinnati Children's Hospital Medical Center's evidence-based care guideline for fever of uncertain source in infants less than 90 days of age or less (2010) noted that CRP and PCT have been studied in infants less than 90 days presenting with fever of uncertain source. Inclusion in a diagnostic evaluation of fever of uncertain source does not improve the confidence of ruling out serious bacterial infections at this time.

The Pediatric Infectious Diseases Society and the Infectious Diseases Society of America's clinical practice guideline "The management of community acquired pneumonia in infants and children older than 3 months of age" (Bradley et al 2011) stated that acute-phase reactants (e.g., the erythrocyte sedimentation rate, CRP concentration, or serum PC concentration) can not be used as the sole determinant to differentiate viral and bacterial causes of community acquired pneumonia.

In a pilot study, Shomali and colleagues (2012) examined the role of PCT in non-neutropenic febrile cancer patient (NNCPs). Between July 2009 and July 2010, a total of 248 NNCPs with fever were studied. Procalcitonin was measured in plasma within 24 hours of fever onset and 4 to 7 days thereafter, using a Kryptor system with a lower of quantitation of 0.075 ng/ml. Patients' clinical, microbiological, and radiological data were reviewed to make the diagnosis and were correlated with PCT levels. This study included 30 patients with blood-stream infection (BSI), 6 with localized bacterial infection, 141 with no documented infection, and 8 with tumor-related fever. Most patients were inpatients or admitted to the hospital during the study. Patients with BSI had significantly higher PCT levels than those with documented localized infections (p = 0.048) and no documented infection (p = 0.011). Procalcitonin
were significantly higher in septic patients than in those without sepsis \((p = 0.012)\). Patients with stage IV disease metastasis had significantly higher baseline PCT levels than did those with early stages of cancer \((p < 0.05)\). Procalcitonin levels dropped significantly in patients with bacterial infections in response to antibiotics \((p < 0.0001)\) authors concluded that baseline PCT levels are predictive of BSI and sepsis in NNCPs. They may be predictors of metastasis and advanced cancer. Subsequent decrease in PCT levels in response to antibiotics is suggestive of bacterial infection. They stated that larger trials are needed to confirm the results of this study.

Su and associates (2012) stated that spontaneous bacterial peritonitis (SBP) is a life-threatening disease that pose great diagnostic challenge to clinicians. These investigators systemically and quantitatively summarized the current evidence on the diagnostic value of the PCT test in identifying SBP. They searched Embase, Medline, the Cochrane database and reference lists of relevant articles with no language restrictions through May 2012. They selected or research that reported the diagnostic performance of PCT alone or compared with other biomarkers to diagnose S. These researchers summarized test performance characteristics using forest plots, summary receiver operating characteristic curves and bivariate random effects models. They found only 3 qualifying studies examining 181 ep of suspected infection with 50 (27.6 %) confirmed SBP episodes from 3 countries. Bivariate pooled sensitivity, specificity, positive likelihood ratios and negative likelihood ratios were 86 % \((95 \text{ CI}: 73 \text{ to } 94 \%)\), 80 % \((95 \text{ CI} \% \text{ to } 87 \%)\), 7.73 \((95 \text{ CI}: 0.91 \text{ to } 65.64)\) and 0.14 \((95 \text{ CI}: 0.01 \text{ to } 1.89)\), respectively. The global measures of accuracy, area under the receiver operating curve \((\text{AUC})\) and diagnostic odds ratio \((\text{DOR})\), showed PCT has excel discriminate capability and individual study showed serum PCT testing has better accuracy than ascitic PCT, serum CRP or IL-6 testing. There was evidence of significant heterogeneity but no evidence of publication bias. The authors conclude that the existing literature suggested moderate-to-high accuracy for PCT as a diagnostic aid for SBP. However, they stated that larger, appropriately designed prospective studies are needed to conclusively address the value of serum PCT testing in SBP diagnosis.

Zou and colleagues (2012) performed a systematic review and meta-analysis of the diagnostic performance of ple fluid PCT or CRP in differentiating parapneumonic effusion in patients with pleural effusion. These investigators searched the Embase, Medline, and Cochrane database December 2011. Original studies that reported the diagnostic performance of PCT alone or compared with that of other biomarkers for differentiating the characteristic pleural effusion were included. These researchers found 6 qualifying studies including 780 patients with suspected parapneumonic effusion and 306 confirmed cases of parapneumonic effusion. Six studies examined the diagnostic performance of pleural fluid PCT, 3 also tested for serum PCT, and another 3 tested for serum CRP. The bivariate pooled sensitivity and specificity were as follows 0.67 \((95 \text{ CI}: 0.54 \text{ to } 0.78)\) and 0.70 \((95 \text{ CI}: 0.63 \text{ to } 0.76)\), respectively, for pleural fluid PCT; 0.65 \((95 \text{ CI}: 0.55 \text{ to } 0.74)\) and 0.68 \((95 \text{ CI}: 0.62 \text{ to } 0.74)\), respectively, for se PCT; and 0.54 \((95 \text{ CI}: 0.47 \text{ to } 0.61)\) and 0.77 \((95 \text{ CI}: 0.72 \text{ to } 0.81)\), respectively, for serum CRP. There was evidence of significant heterogeneity \((I(2) = 55.0 \%)\) for pleural fluid or serum PCT but not for CRP \((I(2) = 0.0 \%)\). Authors concluded that the existing literature suggested that both pleural fluid and serum PCT tests have low sensi and specificity for differentiating parapneumonic effusion from other etiologies of pleural effusion. Compared with serum CRP has higher specificity and a higher positive likelihood ratio, and thus, it has a higher rule-in value than P

Lu and co-workers (2013) noted that the diagnostic value of PCT for patients with renal impairment is unclear. Th investigators searched multiple databases for studies published through December 2011 that evaluated the diagno performance of PCT among patients with renal impairment and suspected systemic bacterial infection. They summarized test performance characteristics with the use of forest plots, hierarchical summary receiver operating characteristic \((\text{HSROC})\) curves, and bivariate random effects models. These researchers identified 201 citations, which 7 diagnostic studies evaluated 803 patients and 255 bacterial infection episodes. Hierarchical summary rece operating characteristic-bivariate pooled sensitivity estimates were 73 % \([95 \text{ CI}: 54 \% \text{ to } 86 \%]\) for PCT tests an \((95 \text{ CI}: 52 \% \text{ to } 92 \%)]\) for CRP tests. Pooled specificity estimates were higher for both PCT and CRP tests \([\text{PCT} \% \text{ CI}: 79.5 \text{ to } 93 \%; \text{CRP}, 84 \% \text{ CI}: 52.5 \text{ to } 96 \%]\). The positive likelihood ratio for PCT \([\text{likelihood (L}} 6.02, 95 \text{ CI}: 3.16 \text{ to } 11.47]\) was sufficiently high to be qualified as a rule-in diagnostic tool, while the negative like ratio was not low enough to be used as a rule-out diagnostic tool \((LR-0.31, 95 \text{ CI}: 0.17 \text{ to } 0.57)\). There was no consistent evidence that PCT was more accurate than CRP test for the diagnosis of systemic infection among pati
with renal impairment. The authors concluded that both PCT and CRP tests have poor sensitivity but acceptable specificity in diagnosing bacterial infection among patients with renal impairment. Moreover, they stated that given poor negative likelihood ratio, its role as a rule-out test is questionable.

Lyu and associates (2013) conducted a systematic review and meta-analysis of the performance of the PCT diagnostic test for identifying infectious complications after hematopoietic stem cell transplantation (HSCT). These investigators searched Embase, Medline, the Cochrane database, and reference lists of relevant articles, with no language restrictions, through December 2011. They selected original articles that reported diagnostic performance of PCT or compared with other biomarkers for identifying serious infections in HSCT recipients. They quantitatively evaluated test accuracy parameters with the use of forest plots, hierarchical summary receiver operating characteristic curve bivariate random effect models. These researchers found 6 qualifying studies (studying 1,344 episodes of suspected infection with confirmed infectious episodes) from 3 countries. These 6 studies examined both PCT and CRP test performance. Bivariate pooled sensitivity, specificity, positive likelihood ratios, and negative likelihood ratios were 0.60 to 0.72, 0.72 to 0.79, 2.39 to 3.09, and 0.47 to 0.57 for PCT, and 0.54 to 0.93, 0.56 to 0.86, 1.86 to 4.84, and 0.27 to 0.65 for CRP. In terms of AUC, CRP was superior to PCT in detecting infectious complications, with an AUC of 0.82 for CRP versus an AUC of 0.69 for PCT. The authors concluded that the pooled accuracy estimates of 6 different studies indicated only a moderate rule-out diagnostic value of both PCT and CRP in discriminating infection from other inflammatory complications following allogeneic HSCT.

Yu and colleagues (2013) systematically summarized the current evidence on the diagnostic value of PCT in identifying infective endocarditis (IE). These investigators searched Embase, Medline, Cochrane database, and reference lists of relevant articles with no language restrictions through September 2012 and selected studies that reported the diagnostic performance of PCT alone or compared with other biomarkers to diagnose IE. They summarized test performance characteristics with the use of forest plots, hierarchical summary receiver operating characteristic curves, and bivariate random effects models. These researchers found 6 qualifying studies that included 1,006 episodes of suspected infection with 216 (21.5 %) confirmed IE episodes from 5 countries. Bivariate pooled sensitivity, specificity, positive likelihood ratios, and negative likelihood ratios were 64 % (95 % CI: 52 % to 74 %), 73 % (95 % CI: 58 % to 84 %), 50 % (95 % CI: 35 % to 70 %), and 34 % (95 % CI: 19 % to 60 %), respectively. Of the 5 studies examining CRP, the pooled sensitivity, specificity, positive likelihood ratios, and negative likelihood ratios were 75 % (95 % CI: 62 % to 85 %), 72 % (95 % CI: 61 % to 82 %), 2.81 (95 % CI: 1.70 to 4.65), and 0.34 (95 % CI: 0.19 to 0.60), respectively. The global measures of accuracy, area under the receiver operating characteristic curve (AUC) and DOR, showed CRP (AUC = 0.82, DOR = 8.55) may have higher accuracy than PCT (AUC = 0.71, DOR = 4.67) in diagnosing IE. The authors concluded that the current evidence does not support the routine use of serum PCT or CRP to rule in or rule out IE in patients suspect of having IE.

van Vugt and colleagues (2013) quantified the diagnostic accuracy of selected inflammatory markers in addition to symptoms and signs for predicting pneumonia and derived a diagnostic tool. Diagnostic study performed between 2006 and 2010. Participants had their history taken, underwent physical examination and measurement of CRP and PC venous blood on the day they first consulted, and underwent chest radiography within 7 days. Main outcome measure was pneumonia as determined by radiologists, who were blind to all other information when they judged chest radiographs. Of 3,106 eligible patients, 286 were excluded because of missing or inadequate chest radiographs, leaving 2,820 patients (mean age of 50, 40 % men) of whom 140 (5 %) had pneumonia. Re-assessment of a subset of 1,694 chest radiographs showed agreement in 94 % (κ = 0.45, 95 % CI: 0.36 to 0.54). Six published "symptoms and signs models" varied in their discrimination (ROC ranged from 0.55 to 0.71). The combination of clinical prediction items derived from the patients included absence of runny nose and presence of breathlessness, crackles and diminished breath sounds on auscultation, tachycardia, and fever, with an ROC area of 0.70 (0.65 to 0.75). Addition of CRP at the optimal cut-off of greater than 30 mg/L increased the ROC area to 0.77 to 0.81) and improved the diagnostic classification (net re-classification improvement 28 %). In the 1,556 patients classified according to symptoms, signs, and CRP greater than 30 mg/L as "low risk" (less than 2.5 %) for pneumonia the prevalence of pneumonia was 2 %. In the 132 patients classified as "high risk" (greater than 20 %), the prevalence
of pneumonia was 31%. The positive likelihood ratio of low, intermediate, and high risk for pneumonia was 0.4, 1, 8.6, respectively. Measurement of PCT added no relevant additional diagnostic information. A simplified diagnostic score based on symptoms, signs, and CRP greater than 30 mg/L resulted in proportions of pneumonia of 0.7%, 3%, and 18.2% in the low, intermediate, and high risk group, respectively. The authors concluded that the clinical rule on symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough performed better in patients with mild or severe clinical presentation. Moreover, they stated that addition of CRP concentration at the optimal cut-off of greater than 30 mg/L improved diagnostic information, but measurement of PCT concentration did not add clinically relevant information in this group.

Smith et al (2013) noted that although prior randomized trials have demonstrated that PCT-guided antibiotic therapy effectively reduces antibiotic use in patients with community-acquired pneumonia (CAP), uncertainties remain regarding the cost-effectiveness of PCT protocols in practice. These investigators estimated the cost-effectiveness of PCT protocols in CAP. Measures were costs and cost per quality adjusted life year gained. When no differences in clinical outcomes were assumed, consistent with clinical trials and observational data, PCT protocols cost $10 to $54 more per patient than usual care in CAP patients. Under these assumptions, results were most sensitive to variations in: antibiotic cost, likelihood that antibiotic therapy was initiated less frequently or over shorter durations, and the likelihood that physicians were non-adherent to PCT protocols. Probabilistic sensitivity analyses, incorporating PCT protocol-related change in quality of life, found that protocol use was unlikely to be economically reasonable if physician protocol non-adherence was high, as observational study data suggested. However, PCT protocols were favored if they decreased hospital length of stay. The authors concluded that PCT protocol use in hospitalized CAP patients, although promising, lack physician non-adherence and resource use data in routine care settings, which are needed to evaluate its potential in patient care.

Page and colleagues (2014) stated that early recognition of bacterial infections is crucial for their proper management but is particularly difficult in children with severe acute malnutrition (SAM). These researchers evaluated the accuracy of CRP and PCT for diagnosing bacterial infections and assessing the prognosis of hospitalized children with SAM, and determined the reliability of CRP and PCT rapid tests suitable for remote settings. From November 2007 to July 2011 these investigators prospectively recruited 311 children aged 6 to 59 months hospitalized with SAM plus a medical complication in Maradi, Niger. Blood, urine, and stool cultures and chest radiography were performed systematically on admission. C-reactive protein and PCT were measured by rapid tests and by reference quantitative methods using frozen serum sent to a reference laboratory. Median CRP and PCT levels were higher in children with bacteremia pneumonia than in those with no proven bacterial infection (p < 0.002). However, both markers performed poorly in identifying invasive bacterial infection, with AUC of 0.64 and 0.67 before and after excluding children with malaria, respectively. At a threshold of 40 mg/L, CRP was the best predictor of death (81% sensitivity, 58% specificity). Rapid test results were consistent with those from reference methods. The authors concluded that CRP and PCT are not sufficiently accurate for diagnosing invasive bacterial infections in this population of hospitalized children with complicated SAM. However, a rapid CRP test could be useful in these settings to identify children most at risk for death.

The AHRQ’s assessment of “Future research needs on procalcitonin-guided antibiotic therapy” (Noorani et al. 2013) identified 3 priority populations that were most in need of rigorous research:

- The critically ill patient (all ages) with suspected lower respiratory tract infection (LRTI) or general infection
- The patient (all ages) with suspected LRTI in the ambulatory care/emergency department setting in the United States
- The immunocompromised patient (all ages)

An UpToDate review on “Evaluation and management of severe sepsis and septic shock in adults” (Schmid and Mandel, 2014) states that “There is no single test that immediately confirms the diagnosis of severe sepsis or septic shock. However, several laboratory tests, all of which are still investigational, have been studied for their diagnostic markers of active bacterial infection:

Elevated serum procalcitonin levels are associated with bacterial infection and sepsis. Despite this, meta-analysis of 18 studies found that procalcitonin distinguished sepsis from non-septic systemic inflammation poorly (sensitivity of 71 percent and specificity of 71 percent) and another meta-analysis of six trials (four in patients with sepsis and two in patients with other infections) found that using clinical algorithms based upon procalcitonin levels did not affect mortality.

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes not covered for indications listed in the CPB:

84145

Other CPT codes related to the CPB:

35301  Thromboendarterectomy, including patch graft, if performed; carotid, vertebral, subclavian neck incision

ICD-9 codes covered if selection criteria are met:

460 - 466.19  Acute respiratory infections

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

038.0 - 038.9  Septicemia
411.1  Intermediate coronary syndrome [acute coronary syndrome]
421.0 - 421.1  Acute and subacute endocarditis
511.1  Pleurisy with effusion, with mention of a bacterial cause other than tuberculosis [parapneumonic]
540.0 - 542  Appendicitis
567.23  Spontaneous bacterial peritonitis
571.8  Other chronic nonalcoholic liver disease [fatty liver]
585.9  Chronic kidney disease, unspecified [chronic renal insufficiency]
778.4  Other disturbances of temperature regulation of newborn [fever of uncertain source]
998.59  Other postoperative infection
996.88  Complications of transplanted organ, stem cell [differentiation of infection from other inflammatory complications following hematopoietic stem cell transplantation]
V45.89  Other postprocedural status

Other ICD-9 codes related to the CPB:

V42.81 - V42.82  Organ or tissue replaced by transplant, bone marrow or peripheral stem cells [hematopoietic stem cells]

The above policy is based on the following references:

35. Cincinnati Children's Hospital Medical Center. Evidence-based care guideline for fever of uncertain source in infants 60 days of age or less. Cincinnati, OH: Cincinnati Children's Hospital Medical Center; October 27, 2010.