Assessment of Procalcitonin as a Diagnostic and Prognostic Marker in Patients with Solid Tumors and Febrile Neutropenia

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BACKGROUND. Cancer patients with fever and neutropenia currently are assessed on clinical grounds only. The current study prospectively evaluated the efficacy of baseline procalcitonin (PCT) in the detection of bacteremia and in the prediction of outcome in patients with solid tumors and febrile neutropenia.

METHODS. PCT levels were determined at baseline and every 48 hours in 104 patients undergoing chemotherapy who developed fever (axillary temperature > 38 °C on 2 occasions or > 38.3 °C in a single record) and neutropenia (absolute neutrophil count < 500 cells/μL).

RESULTS. The median baseline PCT values were significantly higher in patients who had microbiologically documented infections (1.24 ng/mL) compared with patients who had clinically documented infections (0.27 ng/mL) or fever of unknown origin (0.21 ng/mL; $P < 0.01$). Accordingly, a PCT cut-off value of 0.5 ng/mL was reached more frequently in patients who had microbiologically documented infections compared with patients who had clinically documented infections or fever of unknown origin (66.7% vs. 13.4%, respectively; $P < 0.001$). Furthermore, this threshold also was associated with an increased likelihood of treatment failure (70.0% vs. 14.9%; $P < 0.001$). All 4 septic patients and all 5 patients who ultimately died presented PCT values 5-fold to 10-fold greater than the median values. Clinical evaluation in combination with baseline PCT assessment appeared to improve clinical risk evaluation alone.

CONCLUSIONS. Baseline PCT levels were higher in patients who had febrile neutropenia with bacteremia compared with patients who had clinical infections or fever of unknown origin. PCT helped to identify patients who had microbiologic infections and patients who were at high risk of treatment failure, and PCT may constitute a complementary tool in the initial assessment of such patients. ***Cancer* 2004;100:2462–9.** © *2004 American Cancer Society.*

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Procalcitonin (PCT) is a protein that consists of 116 amino acids with a molecular weight of 13 kilodaltons (kD). The structure of PCT detected in plasma during inflammation is identical to that produced by thyroid C-cells as precursor of calcitonin. All PCT formed in C-cells is converted into calcitonin, so that no PCT enters the circulation, and its levels in healthy individuals are below the level of detection.[1] After the administration of endotoxin, PCT levels react after 2–3 hours, peak at 6–8 hours, and then plateau for up to 24 hours.[2,3] It is degraded by specific proteases and has a half-life of between 25 hours and 30 hours.[4]

It is known that the production of PCT is linked to bacterial

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endotoxin; however, cytokines secreted during sepsis and other unknown mediators may be implicated in PCT release, considering the similarity in the concentration of PCT in gram-negative and (endotoxin-lacking) gram-positive bacteremias.[5] In contrast to cytokines such as tumor necrosis factor (TNF) and interleukin-6 (IL-6), PCT rises specifically in bacterial processes[1] and not in response to other types of inflammation (e.g., viral infection, organ transplant rejection, or autoimmune diseases).[6] Its behavior in systemic fungal infections is controversial; whereas some reports found a correlation with the severity infection,[7] other reports found poor PCT sensitivity in this setting.[8] Currently, the origin of the considerable secretion of PCT in sepsis is unclear, but monocytes and an acute-phase origin from the neuroendocrine cells in the liver, lungs, or intestine are candidates.[9–12]

A role for PCT in sepsis is supported by the sequence homologies between PCT and cytokines, such as TNF, IL-6, and granulocyte–colony-stimulation factor.[12] PCT may act as a mediator that sustains and augments the inflammatory response in a manner similar to that of IL-6 and IL-8 as part of the integral host response to sepsis. The homology between PCT and apoptosis-regulating intracellular pathway proteins, such as the bcl-2 family and the caspases, suggests a potential intracellular function of PCT in modulating the apoptotic response to inflammation.[12]

A number of clinical studies have shown that PCT is a sensitive and specific marker of sepsis in critically ill pediatric and adult patients[13–20] and in patients with hematologic malignancies and febrile neutropenia.[21–26] To our knowledge, the majority of those studies focused on a population with a high-risk profile, such as hematologic patients, but there have been no reports of adequate size that address this issue in patients with solid tumors and febrile neutropenia. These patients have a lower proportion of complicated neutropenic episodes and many may benefit from outpatient management, provided that a sensitive and specific risk assessment could be made. We prospectively assessed the efficacy of baseline PCT levels in the detection of bacteremia and in the prediction of outcome in a group of patients with solid tumors and febrile neutropenia.

MATERIALS AND METHODS

Eligibility

Adult patients with histologically proven solid malignancies undergoing chemotherapy were eligible for this study if they met all of the following inclusion criteria: NCI-CTC (v2.0) Grade 4 neutropenia (absolute neutrophil count [ANC] < 500 cells/μL) and fever, defined as axillary temperature > 38.0 °C on 2 occasions 4 hours apart in 1 day or > 38.3 °C in a single record. The study was evaluated and approved by our Institutional Review Board, and patients were required to provide written informed consent.

Initial Assessment and PCT Determination

Evaluation included a detailed medical history and physical examination; a complete blood count; serum creatinine, electrolyte, and liver function tests; urinalysis; arterial blood gas; coagulation tests; and a chest X-ray. Two blood cultures and a urine culture were taken, as well as cultures from exudates or other body sites if clinically indicated. Patients were scored prospectively according to both the Talcott risk assessment scale and the Multinational Association for Supportive Care in Cancer (MASCC) risk-assessment scale, which have been described elsewhere.[27,28]

PCT levels were determined at baseline and every 2 days until the episode resolved (i.e., until the ANC was > 500 cells/μL and the patient was afebrile for 2 consecutive days). Blood samples were centrifuged within 30 minutes after collection at 4000 revolutions per minute for 10 minutes at 4 °C. Serum samples were stored at -80 °C until PCT concentrations were assayed. PCT levels were determined by use of an assay on the basis of inmunochemiluminiscence (LUMItest®; B.R.A.H.M.S. Diagnostica, Berlin, Germany). Each sample was analyzed twice, and mean values were considered.

Diagnostic Criteria

The febrile neutropenic episodes were classified as fever of unknown origin (FUO) when there were no signs or symptoms of a focal infection and microbiologic cultures were negative; clinically documented infection (CDI) when there were signs or symptoms of a focal infection and microbiologic cultures were negative; or microbiologically documented infection (MDI) when a causative pathogen was isolated in blood cultures (in association or not associated with a clinical infection). Bacteremia was considered present when one positive culture was obtained, except for coagulase-negative staphylococci, for which at least two positive blood cultures were required. Regarding outcome, the episodes were classified as a success without modification when the episode resolved with the initial treatment; a success with modification when the febrile episode resolved within 72 hours but required the addition of another antibiotic, antifungal, or antiviral agent; or treatment failure when fever persisted for 72 hours or reappeared, bacteremia persisted or reappeared, or the infection progressed, as evidenced by worsening of the source of infection, the

appearance of signs or symptoms of septic shock, or death.

Statistical Analysis

The data were evaluated using descriptive methods (mean and standard deviation, median, range, frequency, and percentage). The independent variables were compared with the Mann–Whitney *U* test, the dependent variables were compared with the Wilcoxon test, and comparisons of proportions were summarized with the Pearson chi-square test. The correlation analyses were summarized with Spearman correlation coefficients as a two-tailed analysis.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the PCT assessment also were evaluated. Calculations were performed with the SPSS software package (Statistical Program for Social Science, version 10.0; SPSS, Inc., Chicago, IL).

RESULTS

Characteristics of Study Population and Febrile Neutropenic Episodes

Between April 2002 and May 2003, 104 patients were enrolled in the study. Patient characteristics are listed in Table 1. All patients had solid tumors and were undergoing chemotherapy. Depending on the risk-assessment scale used, between 56% (Talcott scale) and 72% (MASCC scale) of patients were classified as having a low risk of complication. Episode characteristics are depicted in Table 2. Globally, 39 clinical infections were documented and included pneumonia (9 episodes), mucositis (9 episodes), urinary tract infection (5 episodes), diarrhea (5 episodes), sepsis (4 episodes), skin infections (4 episodes), and upper respiratory tract infections (3 episodes). There were 15 episodes of bacteremia. Thirteen of those 15 patients had an associated clinical infection (sepsis in 4 patient, mucositis in 4 patients, pneumonia in 2 patients, skin infection in 2 patients, and urinary tract infection in 1 patient). Overall success was documented in 90.4% of patients. The causes for treatment failure were persistent fever (two patients), persistent infection (three patients), and death (five patients). Two of 5 deaths were considered to be unrelated to the febrile neutropenic episode and were caused by disease progression (bowel obstruction and respiratory failure) 15 days and 22 days, respectively, after the neutropenic episode had resolved.

Baseline PCT Values Related to the Classification and Outcome of the Episode

The median and mean baseline PCT values are shown in Table 3. There was a statistically significant difference between patients who had MDI compared with patients who had FUO and CDI episodes ($P < 0.01$) (Fig. 1). The median baseline PCT level was similar between patients with FUO and patients with CDI. There also were differences in baseline PCT values regarding outcome, but they were not found to be statistically significant. All 4 septic patients presented baseline PCT values that were 10-fold greater than the median values (10.86 ng/mL, 6.20 ng/mL, 5.25 ng/mL, and 3.70 ng/mL, respectively).

When baseline PCT values were categorized according to a cut-off point of 0.5 ng/mL, significant differences were observed between the described

TABLE 1
Patient Characteristics

Characteristic	No. of patients (%)
Total no. of episodes	104 (100.0)
Age (yrs)	
Median	58
Range	24–79
Gender	
Male	40
Female	64
Tumor type	
Breast carcinoma, adjuvant	27 (26.0)
Breast carcinoma, metastatic	15 (14.4)
Small cell lung carcinoma	17 (16.3)
Nonsmall cell lung carcinoma	8 (7.7)
Germ cell tumor	8 (7.7)
Ovarian carcinoma	7 (6.7)
Gastric carcinoma	5 (4.8)
Colorectal carcinoma	5 (4.8)
Cervical carcinoma	4 (3.8)
Sarcoma	4 (3.8)
Prostate carcinoma	2 (1.9)
Bladder carcinoma	1 (1.0)
Head and neck squamous cell carcinoma	1 (1.0)
Days from last cycle	
Median	12
Range	4–26
Prior antibiotics	18 (17.3)
Karnofsky performance status	
Median	80
Range	20–100
Risk assessment	
Low-risk (Talcott scale)	58 (55.8)
Low-risk (MASCC scale)	75 (72.1)
Management (%)	
Outpatient oral antibiotics	24 (23.0)
Inpatient parenteral antibiotics	80 (77.0)
Antibiotic therapy	
Monotherapy	69 (66.3)
Combined therapy	35 (33.7)
Granulocyte-stimulating factors	
Yes	73 (70.2)
No	31 (29.8)

MASCC: Multinational Association for Supportive Care in Cancer.

TABLE 2
Characteristics of the Episodes

Characteristic	No. of episodes (%)
Total no. of episodes	104 (100.0)
Baseline blood count	
Median ALC cells/μL (range)	865 (10–3500)
Median ANC cells/μL (range)	110 (0–480)
Median APC cells/μL (range)	133,000 (9000–441,000)
Median Hb g/dL (range)	10.7 (6.9–15.6)
Duration of fever	
Median	1
Range	1–7
Duration of Grade 4 neutropenia (days)	
Median	2
Range	1–7
Duration of hospital stay (days)	
Median	4
Range	1–26
Classification	
Fever of unknown origin	63 (60.6)
Clinically documented infection	26 (25.0)
Microbiologically documented infection	15 (14.4)
Clinical infections	
Pneumonia	9 (23.0)
Mucositis	9 (23.0)
Urinary tract	5 (12.8)
Gastrointestinal tract (diarrhea)	5 (12.8)
Sepsis	4 (10.3)
Skin infection	4 (10.3)
ENT infection	3 (7.7)
Microbiologic infections (bacteremias)	
Staphylococcus aureus, oxacillin susceptible	4 (26.7)
Staphylococcus epidermidis, oxacillin susceptible	1 (6.7)
Staphylococcus epidermidis, oxacillin resistant	2 (13.3)
Streptococcus viridans	2 (13.3)
Listeria spp.	1 (6.7)
Escherichia coli	2 (13.3)
Klebsiella pneumoniae	2 (13.3)
Pseudomona aeruginosa	1 (6.7)
Outcome	
Success without modifications	83 (79.8)
Success with modifications	11 (10.6)
Failure	10 (9.6)

ALC: absolute lymphocyte count; ANC: absolute neutrophil count; APC: absolute platelet count; Hb: hemoglobin; ENT: ear-nose-throat.

groups. Patients who had MDI presented with a greater proportion of positive values compared with patients who had CDI or FUO (66.7% vs. 13.4%, respectively; $P < 0.001$). In addition, patients who experienced treatment failure demonstrated a greater proportion of positive values compared with patients who had documented treatment success (70.0% vs. 14.9%, respectively; $P < 0.001$). A PCT cut-off value of 1.0 ng/mL demonstrated similar differences between groups (data not shown). It is interesting to note that all five patients who ultimately died presented baseline PCT values five-fold greater than the median value. There was a statistically significant, negative correlation between MASCC scores and baseline PCT values ($P = 0.003$, Spearman correlation).

TABLE 3
Baseline Procalcitonin Values Related to the Classification and Outcome of the Episode

Classification	No. of patients	Median (range) (ng/mL)	95% CI (ng/mL)
Fever of unknown origin	63	0.21 (0.09–1.43)	0.29–0.32
Clinically documented infection	26	0.27 (0.10–10.6)	0.23–2.61
Microbiologically documented infection	15	1.24 (0.09–10.9)	0.72–3.8
Outcome			
Success without modifications	83	0.20 (0.09–10.60)	0.28–0.91
Success with modifications	11	0.32 (0.11–8.30)	−0.63–2.63
Failure	10	1.67 (0.21–10.86)	0.33–5.37

95% CI: 95% confidence interval.

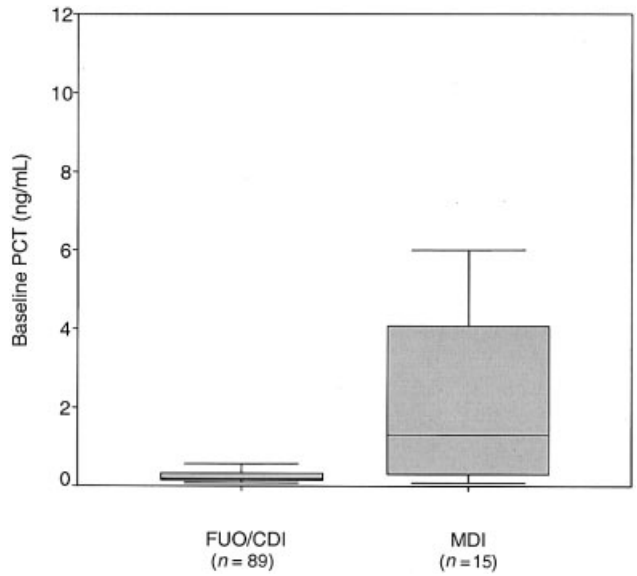

FIGURE 1. Procalcitonin (PCT) values in patients with fever of unknown origin (FUO) and clinically documented infection (CDI) versus patients with microbiologically documented infection (MDI).

Sensitivity and Specificity of Baseline PCT

In an attempt to establish the optimal PCT cut-off value to differentiate between the distinct types of episodes and outcomes, the sensitivity, specificity, PPV, and NPV of baseline PCT values were explored. The optimal combination of values was achieved with 0.5 ng/mL. The results are shown in Table 4. Sensitivity fell dramatically with a PCT cut-off value of 1.0 ng/mL without a significant gain noted in specificity, PPV, or NPV (data not shown).

TABLE 4
Definitions of Sensitivity, Specificity, PPV, and NPV of a Procalcitonin Cutoff Point of 0.5 ng/mL for the Diagnosis of Bacteremia, Clinical Infection plus Bacteremia, Failure, and Death

No. of TP results		No. of FN results	No. of FP results		No. of TN results	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	MDI			FUO + CDI					
10		5	12		77	66.7	86.5	45.5	93.9
	CDI + MDI			FUO					
17		24	5		58	41.5	92.0	77.3	70.7
	Failure			Success					
7		3	14		80	70.0	85.1	33.3	96.4
	Death			No death					
5		0	16		83	100.0	83.8	23.8	100.0

PPV: positive predictive value; NPV: negative predictive value; TP: true-positive; FN: false-negative: FP: false-positive; TN: true-negative; Dx: diagnosis; MDI: microbiologically documented infection; FUO: fever of unknown origin; CDI: clinically documented infection.

Evolution of PCT Values

Two or more PCT determinations were available from 82 patients. An increment of at least 50% from baseline PCT values was observed in 50.0%, 18.2%, and 12.0% of patients with MDI, CDI, and FUO, respectively ($P = 0.032$). In addition, an increment of at least 50% from baseline PCT values was observed in 71.4%, 18.2%, and 12.5% of patients who experienced treatment failure, success with modification, and success without modification, respectively ($P = 0.001$).

Combined Clinical and PCT Assessment

The sensitivity, specificity, PPV, and NPV of the Talcott and MASCC risk-assessment scales alone and in combination with PCT evaluation are shown in Table 5. With regard to the detection of bacteremic episodes, according to the Talcott risk-assessment scale, 4 of 15 patients with MDI were classified with low-risk febrile neutropenia. Three of those patients had baseline PCT values $>$ 0.5 ng/mL. Therefore, the combined risk assessment increased sensitivity for the detection of bacteremia from 73.3% to 93.3% ($P = 0.31$) and increased the NPV from 93.1% to 98.0% ($P = 0.37$). Using the MASCC risk assessment scale, 6 of 15 patients with MDI were categorized with low-risk episodes; 4 of those patients had PCT values $>$ 0.5 ng/mL. The combined approach increased the sensitivity for bacteremia detection from 60.0% to 86.7% ($P = 0.19$) and increased the NPV from 92.0% to 96.8% ($P = 0.29$).

Addressing outcome prediction, the Talcott risk-assessment scale had 100% sensitivity for detecting treatment failures or severe complications. Conversely, according to the MASCC risk-assessment scale, 3 of 10 treatment failures initially were considered low-risk episodes; 2 of those patients had PCT values $>$ 0.5 ng/mL; thus, the combined assessment increased sensitivity for the detection of treatment failure from 70% to 90% ($P = 0.58$) and increased the NPV from 96.0% to 98.4% ($P = 0.6$).

PCT in Outpatients

Twenty-four low-risk patients were treated with oral antibiotics as outpatients. Two of 24 patients were admitted to the hospital 24 hours and 36 hours, respectively, after initial assessment because of persistent fever; both episodes resolved with intravenous therapy. No further complications were reported, and the treatment was deemed successful with modifications (all episodes in this outpatient group ultimately were classified as FUO). Two patients (8.3%) in this group had baseline PCT values $>$ 0.5 ng/mL, 1 of which corresponded to a patient who was admitted later due to persistent fever.

DISCUSSION

PCT, which is a propeptide of calcitonin, usually is produced in the C-cells of the thyroid. In healthy individuals, PCT levels are very low ($<$ 0.1 ng/mL). In patients with sepsis, however, a dramatic increase in PCT levels is observed. The rapid detection of sepsis in an ill patient is of paramount importance to institute the prompt administration of appropriate antimicrobial agents. This is of special relevance in the setting of the neutropenic host, in which the rapid-acting, nonspecific immune response is hampered by the immunologic deficit.

A first observation by Assicot et al. revealed that serum concentrations of PCT increase during septic episodes in pediatric and severely burned patients and that serum PCT concentrations are correlated with the severity of microbial infection.[13] Several reports have confirmed these results in the setting of critically ill

TABLE 5
Definitions of Sensitivity, Specificity, PPV and NPV of the Talcott Risk Assessment Scale and Multinational Association for Supportive Care in Cancer Risk Assessment Scales Alone and in Combination with Procalcitonin (Cutoff point, 0.5 ng/mL) for the Diagnosis of Bacteremia and Treatment Failure

Scale	No. of TP results	No. of FN results	No. of FP results	No. of TN results	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	MDI		FUO + CDI					
Talcott	11	4	35	54	73.3	60.6	23.9	93.1
Talcott + PCT	14	1	40	49	93.3	55.1	25.9	98.0
	MDI		FUO + CDI					
MASCC	9	6	20	69	60.0	77.5	31.0	92.0
MASCC + PCT	13	2	28	61	86.7	68.5	31.7	96.8
	Failure		Success					
Talcott	10	0	36	58	100.0	61.7	21.7	100.0
Talcott + PCT	10	0	44	50	100.0	53.2	18.5	100.0
	Failure		Success					
MASCC	7	3	22	72	70.0	76.6	24.1	96.0
MASCC + PCT	9	1	32	62	90.0	66.0	22.0	98.4

PPV: positive predictive value; NPV: negative predictive value; TP: true-positive; FN: false-negative: FP: false-positive; TN: true-negative; MDI: microbiologically documented infection; FUO: fever of unknown origin; CDI: clinically documented infection; PCT: procalcitonin; MASCC: Multinational Association for Supportive Care in Cancer.

patients with sepsis.[14–20] PCT provides better sensitivity and specificity than C-reactive protein (CRP) for the diagnosis of infection and for monitoring response to antibiotics, and it is a better prognostic indicator than CRP in this population, most likely because of a faster rise in PCT serum levels compared with CRP levels after bacterial challenge and a shorter half-life.[11] One study in 101 critically ill patients reported that PCT levels were correlated negatively with survival.[19]

Ruokonen et al. reported that in a study of 27 hematologic patients, PCT was a specific marker, but not a sensitive marker of infection in febrile neutropenic episodes.[21] Another study compared PCT with CRP, IL-6, IL-8, soluble IL-2 receptor and soluble TNF receptor II in 122 episodes of neutropenic fever in pediatric patients and found that PCT was superior in terms of sensitivity and specificity, with an optimal PCT cut-off level of 0.5 ng/mL.[25] However, a smaller study ($n = 66$ patients) in a similar patient population did not confirm these results.[26] Studies in adult hematologic patients have shown significantly increased levels of PCT in individuals who had microbiologically documented infections compared with patients who had unexplained fever,[22–24] and a correlation between PCT levels and response to antibiotic therapy.[24] This study was designed as a prospective assessment of the efficacy of baseline PCT in the detection of bacteremia and in the prediction of outcome in a group of patients with solid tumors and febrile neutropenia.

In the current series, patients who had MDI demonstrated significantly higher median values of PCT at the time they presented with febrile neutropenia (1.24 ng/mL) compared with patients who had CDI (0.27 ng/mL) or FUO (0.21 ng/mL). This finding is consistent with prior reports concerning patients with hematologic malignancies.[24,25] A PCT cut-off value of 0.5 ng/mL was associated with optimal values of sensitivity (67%) and NPV (94%) to detect MDI while maintaining an acceptable specificity (87%). This threshold level has been suggested previously as the most discriminant and appropriate level for clinical use.[21,25,26] In addition, baseline PCT levels were significantly higher in patients who failed to respond to treatment (7 of 10 patients had PCT $>$ 0.5 ng/mL) or who died (5 of 5 patients) compared with patients who had successful outcomes with or without treatment modifications (14 of 94 patients). The documented findings that not only are baseline PCT levels higher in patients with bacteremias and complicated infections, but also that they keep rising in patients who have a poor response to treatment and outcome, confirm the findings of other author[24] and add to the biologic plausibility of our hypothesis.

Nonetheless, the current results show a weaker consistency compared with the results obtained in critically ill and hematologic patients, in which infections generally are more severe and PCT values range between 10-fold and 100-fold greater than normal levels. However, acute-phase reactants may have a greater practical utility in management strategies for patients with solid tumors compared with the populations described earlier, because critically ill and hematologic patients are hospitalized universally, and these measurements have a limited impact on cost-effectiveness issues. In contrast, a large proportion of patients with solid tumors and febrile neutropenia can

benefit from outpatient management, given the fact that < 20% of these individuals have complicated infections.[29–31]

Fever with neutropenia is a very heterogeneous clinical entity that includes patients who have widely variable risks of developing serious medical complications and of dying during the infectious episode. The degree and duration of neutropenia soon were identified as key factors related to the risk and outcome of infection.[32] However, this finding was of little use to the treating physician, because these factors can be determined only retrospectively. The critical task, therefore, is to devise objective criteria that prospectively can identify early in the course of the febrile neutropenic episode the level of risk of each particular patient, so that therapy can be tailored accordingly. Talcott et al. developed a risk assessment model based on the retrospective review of 261 episodes of neutropenia and fever that was validated prospectively in 444 episodes from 2 different institutions in the U.S.[27,33] Their patients were stratified into four groups: Group 1 included neutropenic patients who already were hospitalized at the onset of fever; Group 2 included outpatients who had concurrent comorbidities; Group 3 was comprised of outpatients who had progressive or uncontrolled disease; and Group 4 included all nonhospitalized febrile neutropenic patients without any significant comorbidities or progressive disease. Serious medical complications occurred in 34% of patients with risk factors (Groups 1–3), whereas there were serious medical complications observed in only 5% of patients in the low-risk group (Group 4). Multiple complications (17%) and death (10%) were common among patients in the high-risk groups but were not reported to occur in the low-risk population. More recently, the MASCC has developed an international validated scoring system to identify low-risk febrile neutropenic cancer patients based on a prospective study that included 1351 patients from 20 institutions in 15 countries.[28]

A relevant issue behind this prospective evaluation of PCT in the context of febrile neutropenia was to challenge its ability to early discriminate between patients at low risk and high risk for developing complications and how it compared and combined with the Talcott and MASCC criteria. The strength of particular interest would be to identify low-risk patients efficaciously, without falsely including high-risk patients, to offer outpatient management confidently to this patient population. The addition of PCT to clinical risk assessment scales in the current study cohort appeared to augment sensitivity but, more important, incremented the NPV for the detection of bacteremia or treatment failure up to 98%, a determinant factor when the decision to be made is whether a patient can be discharged safely and treated on an outpatient basis. Although none of the individual increments of sensitivity and NPV were found to be statistically significant (possibly related to the relatively low number of outpatients and the low rate of complications observed), altogether, there was a trend toward the improvement of these parameters.

Baseline PCT levels were found to be higher in neutropenic patients who had bacteremia compared with patients who had a clinical infections or FUO. PCT may constitute a complementary tool in the initial assessment of these patients. However, these results have to be interpreted with caution because of the low rate of complicated infection in the current series and the single-center nature of this study; confirmatory studies are warranted.

REFERENCES

1. Maruna P, Nedelnikova K, Gurlich R. Physiology and genetics of procalcitonin. *Physiol Res.* 2000;49(Suppl 1):S57–S61.
2. Dandona P, Nix D, Wilson MF, et al. Procalcitonin increase after endotoxin injection in normal subjects. *J Clin Endocrinol Metab.* 1994;79:1605–1608.
3. Brunkhorst FM, Heinz U, Forycki ZF. Kinetics of procalcitonin in iatrogenic sepsis. *Intensive Care Med.* 1998;24:888–889.
4. Le Moullec JM, Jullienne A, Chenais J, et al. The complete sequence of human preprocalcitonin. *FEBS Lett.* 1984;167:93–97.
5. Feezor RJ, Oberholzer C, Baker HV, et al. Molecular characterization of the acute inflammatory response to infections with gram-negative versus gram-positive bacteria. *Infect Immun.* 2003;71:5803–5813.
6. Meisner M. Pathobiochemistry and clinical use of procalcitonin. *Clin Chim Acta.* 2002;323:17–29.
7. Christofilopoulou S, Charvalos E, Petrikkos G. Could procalcitonin be a predictive biological marker in systemic fungal infections? Study of 14 cases. *Eur J Intern Med.* 2002;13:493–495.
8. Delevaux I, Andre M, Colombier M, et al. Can procalcitonin measurement help in differentiating between bacterial infection and other kinds of inflammatory processes? *Ann Rheum Dis.* 2003;62:337–340.
9. Nijsten MW, Olinga P, The TH, et al. Procalcitonin behaves as a fast responding acute phase protein in vivo and in vitro. *Crit Care Med.* 2000;28:458–461.
10. Meisner M, Muller V, Khakpour Z, Toegel E, Redl H. Induction of procalcitonin and proinflammatory cytokines in an anhepatic baboon endotoxin shock model. *Shock.* 2003;19:187–190.
11. Whicher J, Bienvenu J, Monneret G. Procalcitonin as an acute phase marker. *Ann Clin Biochem.* 2001;38:483–493.
12. Russwurm S, Wiederhold M, Oberhoffer M, Stonans I, Zipfel PF, Reinhart K. Molecular aspects and natural source of procalcitonin. *Clin Chem Lab Med.* 1999;37:789–797.
13. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet.* 1993;341:515–518.
14. Al-Nawas B, Krammer I, Shah PM. Procalcitonin in diagnosis of severe infections. *Eur J Med Res.* 1996;1:331–333.

15. Benoist JF, Mimoz O, Assicot M, Edouard A. Serum procalcitonin, but not C-reactive protein, identifies sepsis in trauma patients. *Clin Chem.* 1998;44:1778–1779.
16. Oberhoffer M, Vogelsang H, Russwurm S, Hartung T, Reinhart K. Outcome prediction by traditional and new markers of inflammation in patients with sepsis. *Clin Chem Lab Med.* 1999;37:363–368.
17. Schroder J, Staubach KH, Zabel P, Stuber F, Kremer B. Procalcitonin as a marker of severity in septic shock. *Langenbecks Arch Surg.* 1999;384:33–38.
18. Ugarte H, Silva E, Mercan D, De Mendonca A, Vincent JL. Procalcitonin used as a marker of infection in the intensive care unit. *Crit Care Med.* 1999;27:498–504.
19. Muller B, Becker KL, Schachinger H, et al. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. *Crit Care Med.* 2000;28:977–983.
20. Tugrul S, Esen F, Celebi S, et al. Reliability of procalcitonin as a severity marker in critically ill patients with inflammatory response. *Anaesth Intensive Care.* 2002;30:747–754.
21. Ruokonen E, Nousiainen T, Pulkki K, Takala J. Procalcitonin concentrations in patients with neutropenic fever. *Eur J Clin Microbiol Infect Dis.* 1999;18:283–285.
22. Bernard L, Ferriere F, Casassus P, et al. Procalcitonin as an early marker of bacterial infection in severely neutropenic febrile adults. *Clin Infect Dis.* 1998;27:914–915.
23. Engel A, Steinbach G, Kern P, Kern WV. Diagnostic value of procalcitonin serum levels in neutropenic patients with fever: comparison with interleukin-8. *Scand J Infect Dis.* 1999; 31:185–189.
24. Giamarellos-Bourboulis EJ, Grecka P, Poulakou G, Anargyrou K, Katsilambros N, Giamarellou H. Assessment of procalcitonin as a diagnostic marker of underlying infection in patients with febrile neutropenia. *Clin Infect Dis.* 2001;32: 1718–1725.
25. Fleischhack G, Kambeck I, Cipic D, Hasan C, Bode U. Procalcitonin in paediatric cancer patients: its diagnostic relevance is superior to that of C-reactive protein, interleukin 6, interleukin 8, soluble interleukin 2 receptor and soluble tumour necrosis factor receptor II. *Br J Haematol.* 2000;111: 1093–1102.
26. de Bont ES, Vellenga E, Swaanenburg J, Kamps W. Procalcitonin: a diagnostic marker of bacterial infection in neutropenic cancer patients with fever? *Infection.* 2000;28:398–400.
27. Talcott JA, Siegel RD, Finberg R, Goldman L. Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. *J Clin Oncol.* 1992;10:316–322.
28. Klastersky J, Paesmans M, Rubenstein EB, et al. The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol.* 2000;18: 3038–3051.
29. Rolston KV. New trends in patient management: risk-based therapy for febrile patients with neutropenia. *Clin Infect Dis.* 1999;29:515–521.
30. Hidalgo M, Hornedo J, Lumbreras C, et al. Outpatient therapy with oral ofloxacin for patients with low risk neutropenia and fever: a prospective, randomized clinical trial. *Cancer.* 1999;85:213–219.
31. Garcia-Carbonero R, Mayordomo JI, Tornamira MV, et al. Granulocyte colony-stimulating factor in the treatment of high-risk febrile neutropenia: a multicenter randomized trial. *J Natl Cancer Inst.* 2001;93:31–38.
32. Pizzo PA, Robichaud KJ, Gill FA, et al. Duration of empiric antibiotic therapy in granulocytopenic patients with cancer. *Am J Med.* 1979;67:194–200.
33. Talcott JA, Finberg R, Mayer RJ, Goldman L. The medical course of cancer patients with fever and neutropenia. Clinical identification of a low-risk subgroup at presentation. *Arch Intern Med.* 1988;148:2561–2568.