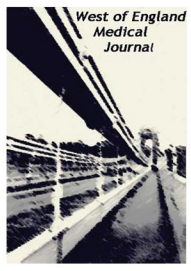

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Fever and Malignancy:

Can procalcitonin differentiate between neoplastic and infective causes of fever in the neutropenic patient?

INTRODUCTION

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Neutropenia is a common and anticipated side effect of antineoplastic chemotherapy used in the management of both solid and haematological malignancy[1]. Modern treatment regimens have significantly improved survival, with some haematological malignancies now having cure rates in excess of 80%[2, 3]. Due to the intensive nature of such therapies, increasing numbers of patients are experiencing profound and prolonged periods of neutropenia, leaving them susceptible to opportunist infection[3-6].

Neutropenic sepsis is defined by the National Institute for Health and Care Excellence (NICE) as a neutrophil count of less than 0.5 x 109 per litre and having either a temperature of ≥ 38C or other signs and symptoms suggestive of sepsis[6].

The mortality rate of neutropenic sepsis ranges from 2%-21%[1], therefore prompt recognition and treatment of this potentially fatal condition is necessary. Current NICE guidelines recommend that intravenous broad spectrum antibiotics commence within 1 hour of patient presentation and continue until resolution of fever[6].

Upwards of 70% of haematological patients will experience febrile neutropenia[1] secondary to the myelo-suppressive effects of chemotherapy. It is well recognised in literature and clinical practice that haematological malignancies can also cause both neutropenia and fever independent of chemotherapy[5]. Most notably due to bone marrow failure or the release of rogue inflammatory cytokines[7], resulting in patients presenting with a non-infective aetiology of febrile neutropenia.

This combination of possible aetiologies can pose a potential diagnostic challenge for clinicians[7]. This is further complicated as many neutropenic patients will not mount a sufficient inflammatory response[1], making it difficult to isolate the foci of infection. Often extensive investigation is required.

The 'gold standard' for diagnosing bacteraemia is blood culture[6]. Although recommended by NICE[6], blood culture has a low sensitivity in this population and the causative organism is isolated in fewer than 20% of cases[4]. C-reactive protein (CRP) is also routinely measured in patients presenting with febrile neutropenia[6]. CRP is not specific to infection though, and can be elevated in a wide range of inflammatory processes including malignancy[8].

It is essential that all patients presenting with febrile neutropenia are managed according to current guidelines due to the high mortality rate associated with neutropenic sepsis. Despite the advent of scoring systems such as the Multinational Association for Supportive Care in Cancer (MASCC) index[1], (which are designed to identify patients who are at low risk of serious complications from sepsis). Patients who have a non-infective cause of fever may still be admitted in line with the neutropenic sepsis protocol, due to their profound neutropenia[1]. Repeat cycles of febrile neutropenic episodes can cause significant morbidity, due to prolonged hospital admissions, side-effects from antimicrobial therapy and the distress of extensive investigations[2, 5, 9].

There is a need to identify a biomarker that can discriminate between infective and other causes of fever in patients presenting with suspected neutropenic sepsis. Procalcitonin, a prohormone of calcitonin, has been suggested as a promising candidate[2, 8, 10]. It is released in response to bacterial endotoxins by many tissues throughout the body[8, 9], suggesting it maybe more specific than CRP.

Previous reviews have been highly heterogeneous and have pooled data from patients with both solid and haematological malignancy as well as adult and paediatric populations[11-13], therefore making it difficult to draw conclusions regarding haematological patients specifically. The aim of this review is to assess whether procalcitonin is able to differentiate between infective and other causes of fever, specifically in adult patients who have presented with neutropenic sepsis and have a confirmed diagnosis of haematological malignancy.

METHODS

Literature Search Term and Strategy

A search of the Medline OVIP SP database was performed. The search included all literature published between 1946 and July 2016. The search terms and strategy used are as follows; Procalcitonin AND febrile neutropenia OR neoplastic OR haematological disease OR neutropenic sepsis OR leukopenia. The search term haematological disease was limited to human studies only and the search allowed for language variations in the spelling of haematological. Additional literature was identified by searching the bibliographies of literature returned in the search.

Study Selection Criteria

Study inclusion criteria:

Studies that only include adult participants

- with a confirmed haematological malignancy who are presenting with febrile neutropenia.
- Studies that include patients who have undergone antineoplastic chemotherapy or other antineoplastic therapy such as haematopoietic stem cell transplant which is thought to be the cause of the neutropenic episode.
- Studies that report the sensitivity and specificity of procalcitonin.

Study exclusion criteria:

- Studies that include paediatric participants.
- Studies that include participants with a diagnosis of a solid malignancy, with the exception of lymphomas.

Quality of Studies

The quality of included studies were assessed using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool[14]. The QUADAS-2 tool has four categories; patient selection, index test, reference test and, flow and timing. As recommended by the QUADAS-2 guide, the signalling questions in each category have been adjusted to ensure they are applicable to this review. If each signalling question is answered 'yes', then the study is considered to be a low risk of bias. If any of the signalling questions are answered 'no' then the study has a risk of bias[14].

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Data Extraction

For each study that was included the following data was extracted; name of lead author and country of study, date of publication, number of participants and febrile episodes assessed, age category of participants, intervals of when procalcitonin was measured, sensitivity and specificity, positive predictive values and negative predictive values where available and the optimum cut off value reported for each category.

RESULTS

Results of the Literature Search

A search of the literature returned ninety-six records. An additional nine records were identified by reading the bibliographies of the found literature. Once duplicates had been accounted for the titles and abstracts were screened, sixty-two records were excluded at this stage. Full text review was undertaken of the remaining thirty-nine articles and twenty-eight articles were excluded due to the reasons identified in Figure 1. The resulting eleven studies have been included in this review. The main reasons for exclusion were; six were review articles, five studies contained mixed results for both haematological and solid malignancy and five studies reported insufficient data regarding procalcitonin.

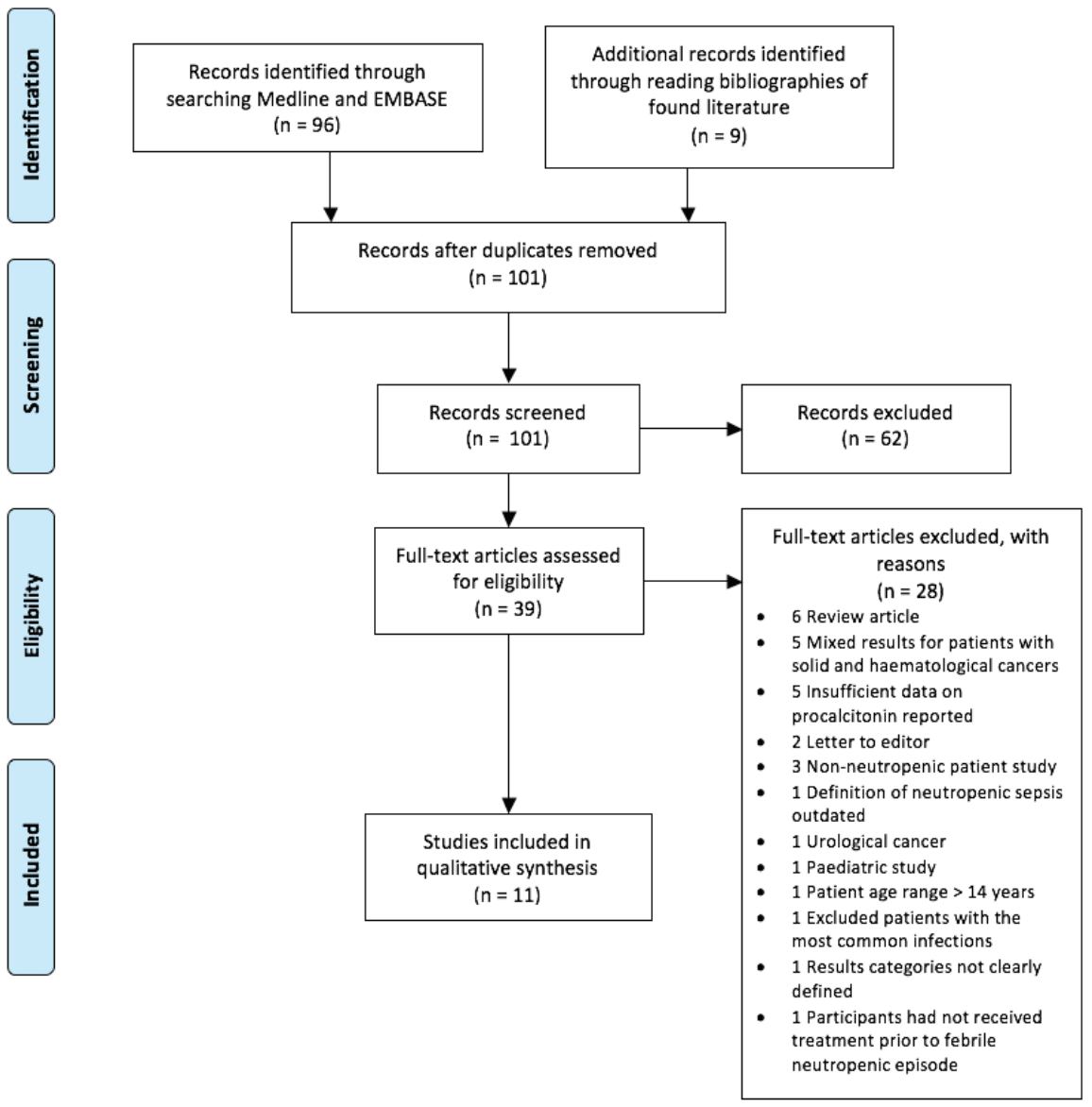

Figure 1.
Flow diagram of studies excluded and included (Adapted from PRISMA Flow Chart)(15)

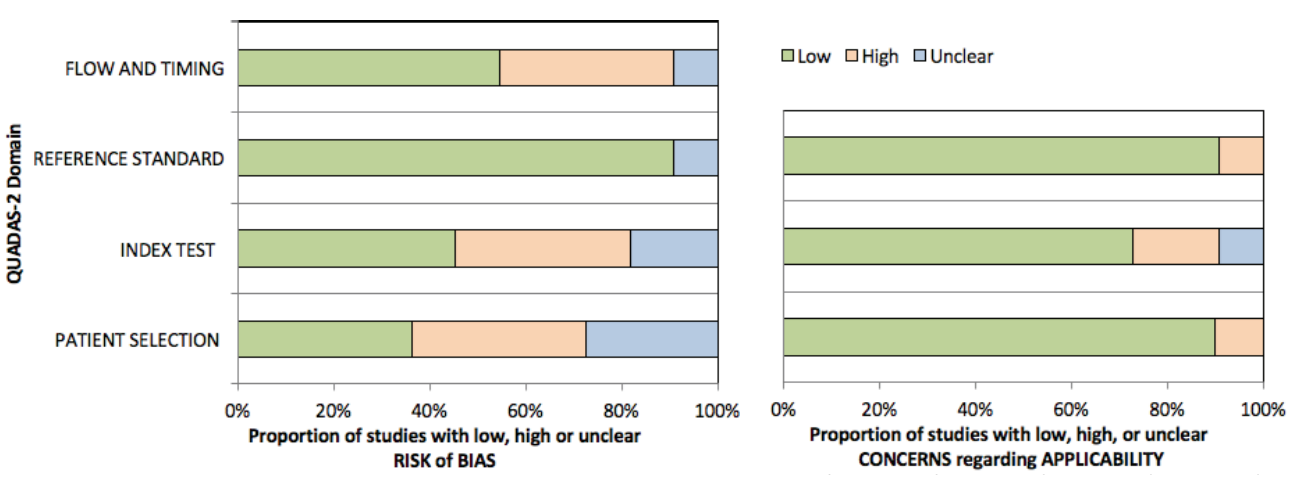

Figure 2.
Graphs representing the results of the QUADAS-2 Quality Assessment of Included Studies (Adapted from the QUADAS-2 Tool Kit)(14)

Quality of Included Studies

Results of the quality assessment using the modified QUADAS-2 tool are presented in Figure 2. Patient selection has the highest area of suspected bias amongst the studies included, this was due to many studies enrolling inpatients with similar disease characteristics. There were low concerns with the applicability of the studies included.

Summary of Studies Included

Eleven studies [16-26] were assessed to fulfil the inclusion criteria; these studies include a combined total of 880 participants all of whom have a confirmed diagnosis of haematological malignancy and have presented with febrile neutropenia. In eight studies[17, 19-23, 25, 26], participants presented with more than one episode of febrile neutropenia during the study period resulting in a total of 1, 111 febrile neutropenic episodes for inclusion. All participants had received antineoplastic chemotherapy with the exception of one study where exact treatment regimens were not specified[19]. Five studies included data from participants who were undergoing haematopoietic stem cell transplant[20-22, 24, 26], with one study being exclusive to this population[20].

Definitions

All studies defined microbiologically documented infection as the presence of bacterial growth in one or more blood cultures, with the exception of gram positive coagulase negative staphylococci that required two positive cultures taken from different sites[16-26].

All studies defined fever of unknown origin as the absence of clinical or micro-biologically evidence of infection[16-26].

Severe Sepsis has been defined as the presence of fever accompanied by other signs and symptoms suggestive of tissue hypo-perfusion[18].

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Study (Ref.)	Author	Year	No. Participants (Febrile episodes)	Accuracy	PCT Cut Off
1 (16)	Roukonen E et al.	1999	28 (28)	Sen: 54.5% Spec: 88.2% PPV: n/a NPV: n/a	0.5ng/ml
2 (17)	Engel A et al.	1999	69 (103)	Sen: 51% Spec: 89% PPV: 87% NPV: 57%	0.5ng/ml
7 (22)	Robinson J et al	2011	90 (194)	Sen: 43.1% Spec: 89.8% PPV: 90.3% NPV: 41.7%	0.5ng/ml
10 (25)	Liu X et al	2014	199 (212)	Sen: 83.5% Spec: 77.2% PPV: 86% NPV: 73.5%	0.5ng/ml

Table 1. Summary of studies assessing the accuracy of procalcitonin to diagnose a documented infection

Microbiological and Clinically Documented Infections

Elevated procalcitonin concentrations were reported in six studies at the onset of fever[16-19, 21, 22], and four studies reported a rise in procalcitonin concentration that peaked on the second day of fever all in those with documented infection[17,21,22,24]. In contrast Prat et al reported that patients with fever of unknown origin had stable procalcitonin concentrations throughout their febrile episode[21].

Four studies directly assessed the diagnostic accuracy of procalcitonin to discriminate between patients with documented infection and those with fever of unknown origin[16, 17, 22, 25], see Table 1.

All studies reported an optimum cut off value of 0.5ng/ml to discriminate between cases of documented infection and fever of unknown origin[16,17,22,25]. At this cut off value, procalcitonin has a high specificity ranging from 77.2% - 89.8%[16,17,22,25] and a strong positive predictive value ranging from 86% - 90% [3,8,11].

Moderate sensitivity ranging from 43.1% to 54.5% was reported in three studies[16, 17, 22] and two studies reported moderate negative predictive values ranging from 41.7%-57%, in contrast to a high sensitivity of 83.5% and negative predictive value of 73.5% reported by Liu et al[25], despite using equivalent cut off values. This in part maybe explained by the time of sampling, as Liu et al based their findings on samples measured within 48 hours of fever onset compared to the onset of fever used in the other studies[25].

Optimum sampling time is a contentious subject, with many studies reporting conflicting results. Two studies have reported that early sampling at time of fever onset is preferential to avoid the attenuating effects of antimicrobial therapy[19, 23], as it has been observed that procalcitonin levels fall rapidly if therapy is effective[23]. In contrast as previously stated, other studies report that procalcitonin levels do not peak until the second day of fever, raising a question over the reliability of early sampling.

Bacteraemia

The previous studies have established procalcitonin concentrations are raised amongst patients with documented infection[16,17,22,25]. It has been hypothesised that it is possible to further differentiate between those with localised infections and those with bacteraemia. Four studies have evaluated this concept[17-19, 23], see Table 2.

Three studies reported optimum cut off values ranging from 0.51ng/ml - 0.8ng/ml[17, 19, 23]. At these values, specificity ranged from 77%-86%, and negative predictive values ranged from 84%-86%[17, 19, 23]. Whilst these results indicate that procalcitonin concentrations in excess of 0.51 ng/ml can identify the majority of patients who do not have bacteraemia with a relative degree of accuracy, it is worth noting that all of these studies based their findings on samples drawn at the onset of fever and 86% of the participants enrolled across the three studies had a diagnosis of acute myeloid leukaemia[17, 19, 23], raising the question of how generalisable these results are.

Giamarellou et al in contrast reported a

Study (Ref.)	Author	Year	No. Participants (Febrile episodes)	Accuracy	PCT Cut Off
2 (17)	Engel A et al.	1999	69 (103)	Sen: 73% Spec: 86% PPV: 73% NPV: 86%	0.51ng/ml
3 (18)	Giamarellou et al.	2004	158 (158)	Sen: 44.2% Spec: 64.3% PPV: 82.1% NPV: 18.8%	1.0-5.0ng/ml
4 (19)	Von Lillienfeld-Toal M et al	2004	31 (53)	Sen: 72% Spec: 77% PPV: 62% NPV: 84%	0.62ng/ml
8 (23)	Gac AC et al	2011	29 (39)	Sen: 60% Spec: 82% PPV: 54% NPV: 86%	0.8ng/ml

Table 2. Summary of studies assessing the accuracy of procalcitonin to diagnose bacteraemia

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Study (Ref.)	Author	Year	No. Participants (Febrile episodes)	Accuracy	PCT Cut Off
3 (18)	Giamarellou et al.	2004	158 (158)	Sen: 83.3% Spec: 100% PPV: 100% NPV: 90.9%	>5ng/ml
9 (24)	Vanska M et al	2012	100 (100)	Sen: 100% Spec: 48% PPV: 18% NPV: 100%	0.13ng/ml
11 (26)	Aimoto M et al	2014	43 (75)	Sen: 80% Spec: 97% PPV: 67% NPV: 99%	1.87ng/ml

Table 3.
Summary of studies assessing the accuracy of procalcitonin to diagnose severe sepsis

high positive predictive value of 82%, moderate specificity, but a low sensitivity of 44.2%[18]. The wide cut off range, 1.0ng/ml – 5.0ng/ml, will have undoubtable affected the result but the larger sample size and greater variation in the study population reflect the potential for these results to be more generalisable[18].

Giamarellou et al also found that patients with coagulase negative staphylococci infections had low or normal levels of procalcitonin[18], thus resulting in lower sensitivity. Ruokonen et al also reported that three patients with proven gram positive infection had undetectable levels of procalcitonin throughout the study period, whereas patients with gram negative infection had procalcitonin levels >0.5ng/ml[16]. These results suggest that the species of infecting microorganism may play a significant role in procalcitonin concentration[16, 21].

Severe Sepsis

Three studies reported the accuracy of procalcitonin to determine episodes of severe sepsis from other causes of fever[18, 24,26].All three studies report high sensitivity and specificity, ranging from 80% - 100% and 48% - 100% respectively, and strong negative predictive values ranging from 90.9% - 100%[18, 24, 26]. Positive predictive values were much broader ranging from 18% - 100%. The optimum cut off value also varied across the three studies ranging from 0.13 - >5ng/ml[18, 24, 26].

Giamarellou et al and Aimoto et al reported the optimum results when comparing a diagnosis of severe sepsis to all other causes of fever[18, 26], whereas the study by Vanska et al included patients with a diagnosis of severe sepsis or gram negative bacteraemia in their findings[24]. This may explain the low positive predictive value at a cut off value of 0.13ng/ml, as other studies have reported higher procalcitonin concentrations in those with gram negative infections[16], leading to many patients without severe sepsis being included in the findings reported by Vanska et al[24].

Invasive Fungal Infection

Three studies reported a rise in procalcitonin concentration between days 3-5 amongst those patients who had persistent fever that was unresponsive to antimicrobial therapy, reporting that this finding was highly suggestive of an invasive fungal infection[20-22].

Ortega et al reported that in those patients with persistent fever at day five, procalcitonin concentrations ≥ 3ng/ml could accurately identify patients with invasive fungal infection with high sensitivity and specificity. They reported a sensitivity of 80%, specificity of 100%, positive predictive value of 100% and negative predictive value of 98%[20].

Robinson et al also reported that procalcitonin was a useful marker for assessing a patients response to anti-fungal therapy, with a decline in procalcitonin concentration observed before resolution of fever[22].

Discussion

Haematological patients who are undergoing antineoplastic chemotherapy and present with febrile neutropenia pose a diagnostic challenge for clinicians[7]. Patients in this population are susceptible to opportunist infection due to the myelosuppressive effects of chemotherapy and bone marrow failure caused directly by their underlying disease[1]. Some patients may also suffer from episodes of pyrexia and neutropenia secondary to their disease[5], most notably those with primary bone marrow disorders such a myelofibrosis and other myelodysplastic syndromes. This can lead to patients being admitted and treated under the neutropenic sepsis pathway despite an infective aetiology of fever not being present.

In an aim to prevent the disruptive effects of unnecessary antimicrobial therapy, prolonged hospital admissions and extensive investigations[2,5,9], procalcitonin has been identified as a potential biomarker that can differentiate between infective and non-infective causes of fever([11-13, 16-26].

Previous reviews evaluating procalcitonin concentrations in patients with neutropenic sepsis have reported that it is a specific marker of infection and can help to confirm the presence of infection rather than rule it out[11-13]. Although, previous reviews have included patients with both solid and haematological malignancies making it difficult to draw a conclusion regarding haematological malignancies specifically[11-13].

The aim of this was to evaluate the accuracy of procalcitonin to differentiate between infective and non-infective causes of fever in patients presenting with febrile neutropenia who have a confirmed diagnosis of haematological malignancy.

Procalcitonin has demonstrated that at a cut off value of 0.5ng/ml it has high specificity, ranging from 77.2% - 89.9%, when differentiating between documented infection and fever of unknown origin[16,

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[17,22,25]. The majority of studies reported low sensitivities when differentiating between documented infection and fever of unknown origin[16, 17, 22]. Although a study by Liu et al reported a high sensitivity of 83.5%, this result was based on samples drawn on the second day of fever[25], compared to the onset of fever in other studies[16, 17, 22]. Optimum sampling time is a contentious subject, but the study by Liu et al does appear to reduce the rate of false negative readings and support the hypothesis that procalcitonin levels peak on the second day of fever.

Another area of ambiguity highlighted by this review, is whether procalcitonin is released in response to both gram negative and gram positive bacteria. Many studies have reported normal or even low procalcitonin concentrations in patients with gram positive infections[16, 18], suggesting that the causative microorganism plays a role in procalcitonin concentration[16, 21].

Most interestingly, procalcitonin has been shown to elevate between days 3-5 of persistent fever in patients not responding to antimicrobial therapy[20-22]. In the three studies that reported this trend, all patients went onto be diagnosed with invasive fungal infection. Procalcitonin concentrations were also noted to rapidly decline, even before the resolution of fever, in those who responded positively to anti-fungal therapy[22]. Although the sample population was very small, this is a significant finding as invasive fungal infections are a significant source of morbidity in this population[1] and any development in the diagnosis and monitoring of treatment response is promising.

Despite strict inclusion criteria, this review is limited by the lack of standard definitions used to classify neutropenia and fever, the variation in the sensitivity of the assay used and the high possibility of bias in patient selection. Therefore, it has not been possible to perform a meta-analysis of the pooled data. Publication bias is also another area that must be considered as many studies reporting negative results may not have been published.

Previous reviews have suggested that future studies should evaluate the usefulness of procalcitonin when used in conjunction with scoring systems such as the MASCC index[12]. Whilst the results of this review are in agreement that procalcitonin shows promise as a potential biomarker in differentiating infective from non-infective causes of fever[11-13], the ambiguity surrounding optimum sampling time and whether procalcitonin concentrations rise in response to both gram negative and gram positive bacteria needs to be defined before studies can evaluate the usefulness of procalcitonin in conjunction with existing scoring systems with any degree of confidence.

In conclusion, procalcitonin has demonstrated high specificity in differentiating between infective and non-infective causes of fever in this population. Ambiguity surrounding the cause of low sensitivity will need to be resolved before procalcitonin can be considered for use within clinical decision making. Procalcitonin remains a biomarker of interest, but further studies are needed to evaluate optimum sampling time and its role in both gram negative and gram positive bacterial infections.

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REFERENCES

1. Clarke RT, Jenyon T, van Hamel Parsons V, King AJ. Neutropenic sepsis: management and complications. Clinical Medicine. 2013;13(2):185-7.
2. Zell JA, Chang JC. Neoplastic fever: a neglected paraneoplastic syndrome. Supportive Care in Cancer. 2005;13(11):870-7.
3. McCaughey C, Blackwood B, Glackin M, Brady M, McMullin MF. Characteristics and outcomes of haematology patients admitted to the intensive care unit. Nursing in Critical Care. 2013;18(4):193-9.
4. Ford A, Marshall E. Neutropenic sepsis: a potentially life-threatening complication of chemotherapy. Clinical Medicine.14(5):538-42.
5. Worth LJ, Slavin MA. Bloodstream infections in haematology: risks and new challenges for prevention. Blood Reviews. 2009;23(3):113-22.
6. (NICE) NIoHaCE. Neutropenic Sepsis: Prevention and Management in people with Cancer CG151. London: NICE; 2012.
7. Foggo V, Cavenagh J. Malignant causes of fever of unknown origin. Clinical Medicine. 2015;15(3):292-4.
8. Kallio R, Surcel HM, Bloigu A, Syrjala H. C-reactive protein, procalcitonin and interleukin-8 in the primary diagnosis of infections in cancer patients. European Journal of Cancer. 2000;36(7):889-94.
9. Rolston KVI. Neoplastic fever: all who shiver are not infected. Supportive Care in Cancer. 2005;13(11):863-4.
10. Limper M, de Kruif MD, Duits AJ, Brandjes DPM, van Gorp ECM. The diagnostic role of Procalcitonin and other biomarkers in discriminating infectious from non-infectious fever. Journal of Infection.60(6):409-16.
11. Sakr Y, Sponholz C, Tuche F, Brunkhorst F, Reinhart K. The role of procalcitonin in febrile neutropenic patients: review of the literature. Infection. 2008;36(5):396-407.
12. Wu CW, Wu JY, Chen CK, Huang SL, Hsu SC, Lee MT, et al. Does procalcitonin, C-reactive protein, or interleukin-6 test have a role in the diagnosis of severe infection in patients with febrile neutropenia? A systematic review and meta-analysis. Supportive Care in Cancer. 2015;23(10):2863-72.
13. Boysen A. Procalcitonin as a marker of infection in febrile neutropenia:A systematic review. Modern Chemotherapy. 2013;2:8-14.
14. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. Annals of Internal Medicine. 2011;155(8):529-36.
15. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(7):e1000097.
16. Ruokonen E, Nousiainen T, Pulkki K, Takala J. Procalcitonin concentrations in patients with neutropenic fever. European Journal of Clinical Microbiology & Infectious Diseases. 1999;18(4):283-5.
17. Andreas Engel GSPKWVK. Diagnostic Value of Procalcitonin Serum Levels in Neutropenic Patients with Fever: Comparison with Interleukin-8. Scandinavian Journal of Infectious Diseases. 1999;31(2):185-9.
18. Giamarellou H, Giamarellos-Bourboulis EJ, Repoussis P, Galani L, Anagnostopoulos N, Grecka P, et al. Potential use of procalcitonin as a diagnostic criterion in febrile neutropenia: experience from a multicentre study. Clinical Microbiology & Infection. 2004;10(7):628-33.
19. von Lilienfeld-Toal M, Dietrich MP, Glasmacher A, Lehmann L, Breig P, Hahn C, et al. Markers of bacteremia in febrile neutropenic patients with hematological malignancies: procalcitonin and IL-6 are more reliable than C-reactive protein. European Journal of Clinical Microbiology & Infectious Diseases. 2004;23(7):539-44.
20. Ortega M, Rovira M, Filella X, Almela M, Puig de la Bellacasa J, Carreras E, et al. Prospective evaluation of procalcitonin in adults with febrile neutropenia after haematopoietic stem cell transplantation. British Journal of Haematology. 2004;126(3):372-6.
21. Prat C, Sancho JM, Dominguez J, Xicoy B, Gimenez M, Ferra C, et al. Evaluation of procalcitonin, neopterin, C-reactive protein, IL-6 and IL-8 as a diagnostic marker of infection in patients with febrile neutropenia. Leukemia & Lymphoma. 2008;49(9):1752-61.
22. Robinson JO, Lamoth F, Bally F, Knaup M, Calandra T, Marchetti O. Monitoring procalcitonin in febrile neutropenia: what is its utility for initial diagnosis of infection and reassessment in persistent fever? PLoS ONE [Electronic Resource]. 2011;6(4):e18886.
23. Gac A-C, Parienti J-J, Chantepie S, Fradin S, Le Coutour X, Leclercq R, et al. Dynamics of procalcitonin and bacteremia in neutropenic adults with acute myeloid leukemia. Leukemia Research.35(10):1294-6.
24. Vanska M, Koivula I, Jantunen E, Hamalainen S, Purhonen AK, Pulkki K, et al. IL-10 combined with procalcitonin improves early prediction of complications of febrile neutropenia in hematological patients. Cytokine. 2012;60(3):787-92.
25. Liu X, Wang DF, Fang Y, Ye WF, Liu S, Lou N. Initial procalcitonin level predicts infection and its outcome in patients with non-Hodgkin lymphoma with febrile neutropenia. Leukemia & Lymphoma. 2015;56(1):85-91.
26. Aimoto M, Koh H, Katayama T, Okamura H, Yoshimura T, Koh S, et al. Diagnostic performance of serum high-sensitivity procalcitonin and serum C-reactive protein tests for detecting bacterial infection in febrile neutropenia. Infection. 2014;42(6):971-9.