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The role of temperature in the detection and diagnosis of neutropenic sepsis in adult solid tumour cancer patients receiving chemotherapy

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ABSTRACT

Purpose: The primary aim of this study was to examine the value of temperature as a diagnostic and prognostic indicator of infection and sepsis in neutropenic patients. A secondary aim was to gain insight into the presenting symptoms reported by these patients at home or on their initial admission assessment.

Methods: A cohort study was carried out using a case note review of 220 emergency admissions to a regional cancer centre. All participants were neutropenic and were diagnosed with infection on admission. The main outcome measures were relationships between Early Warning Scores and temperature values at home, on admission and during the hospital stay.

Results: 22% of patients who became acutely unwell did not have a fever. Pearson correlations showed only small associations between highest temperature value at any time point and highest early warning scores (r (202) = 0.176, P = .012). Temperature at home (B = 0.156, P = .336) and temperature on admission (B = 0.200, P = .052) did not predict highest Early Warning Scores.

Conclusions: Body temperature is not a consistently reliable diagnostic or prognostic indicator for outcomes in patients with neutropenia and symptoms of infection. It can assist with early presentation and recognition of infection in many neutropenic patients. However, over-reliance on temperature risks missing the opportunity for early detection and treatment.

1. Introduction

Sepsis is a life-threatening host response to infection that is a leading cause of mortality and critical illness (Singer et al., 2016). Prompt recognition, diagnosis and treatment are essential to improving outcomes with early signs of sepsis including increased respiration rate, hypotension and altered mental state (Singer et al., 2016; Shankar-Hari et al., 2016; National Institute for Health and Care Excellence (NICE), 2016). Patients who develop neutropenia due to systemic anti-cancer therapy, including chemotherapy, are at increased risk of developing sepsis as they are less able to marshal a response to infection. Early presentation to enable diagnosis and treatment has been identified as a priority for patient care but this can be challenged by diverse, often non-specific, presenting symptoms (Clarke et al., 2015; Wild, 2017) and a lack of evidence regarding their relationship to outcomes (NICE, 2012).

A growing body of evidence suggests that infection in neutropenic patients is a heterogeneous condition with diverse outcomes (Tueffel et al., 2011; Klatersky et al., 2013). This has led to the introduction of risk stratified pathways to promote appropriate treatment, such as immediate interventions for patients with signs of sepsis, prompt intravenous antibiotics for those at higher risk of serious complications and measures to avoid unnecessary hospitalisation in those at lower risk (Lee et al., 2013; NCCN, 2017; Worth et al., 2011). Early detection of infection in neutropenic patients remains essential to facilitate appropriate treatment (Warnock, 2016) and evidence-based parameters are needed to support this process.

A review of the evidence regarding the detection and management of neutropenic sepsis was carried out by the UK organisation, the National Institute for Health and Care Excellence (NICE, 2012). The

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review concluded that most studies regarding neutropenic sepsis have included pyrexia among their diagnostic criteria and have excluded patients whose temperature values remain within normal limits (NICE, 2012). Pyrexia consistently features in the inclusion criteria for research studies (Carmona-Bayonas et al., 2011) in parameters for clinical guidance (de Naurois et al., 2010; NCCN, 2017) and evaluations of practice (Innes et al., 2008; Wierema et al., 2013). However, recent reviews of the literature and UK cancer centre clinical guidelines have suggested that the role assigned to pyrexia in clinical practice regarding neutropenic sepsis is unclear (Clarke et al., 2011; NICE, 2012). The authors note that this can be seen in the range of different temperature values being used to denote a clinically significant fever which ranged from 37.5^{0}c to 38.5^{0}c. In addition, they found that the majority of clinical guidelines recommended suspecting neutropenic sepsis in patients receiving chemotherapy who were unwell even in the absence of a fever (Clarke et al., 2011; NICE, 2012). A recent example of this approach is seen in the UK Oncology Nursing Society triage tool which has been developed to support telephone advice services for patients receiving systemic anti-cancer therapy (SACT) (UKONS, 2016). The tool is widely used in the UK and provides guidance to identify appropriate care pathways following an assessment of symptom severity. In the advice relating to patients with a fever, the trigger temperature to seek urgent assessment and medical review is 37.5^{0}c. However, the guidance also recommends that this same action should be taken by patients receiving SACT who feel generally unwell but do not have a raised temperature (UKONS, 2016).

While questions have been raised about the clinical significance of particular temperature values there is a consensus that monitoring body temperature can play an important role in early detection (NICE, 2012). Many neutropenic patients with infection will have pyrexia as one of their symptoms and, for some, other presenting signs of infection may be reduced (Dunkley and Macleod, 2015). Neutropenia often occurs while the patient is at home, and self-monitoring of temperature to support early detection of infection by patients is recommended in local and national guidance (de Naurois et al., 2010). However, the lack of evidence regarding the clinical significance of temperature in neutropenic patients presents a challenge for patient education and clinical guidance. For example, what advice should healthcare staff give regarding trigger temperature values when they are providing patient information?

The complex issues that can arise when providing patients with information regarding temperature monitoring have been highlighted by two separate qualitative studies that explored help-seeking experiences in patients with neutropenic sepsis (Clarke et al., 2015; Oakley et al., 2016). Both studies found that the emphasis placed on temperature values by healthcare professionals led to some patients delaying contacting the cancer centre until they had a temperature above 38°c even when they felt unwell. However, Clarke et al. (2015) also found that advice regarding temperature values could facilitate early presentation, particularly in patients who were asymptomatic with symptoms of infection but detected a fever by self-monitoring their temperature at home (Clarke et al., 2015). Developing understanding of the relationships between temperature values, infection and outcomes in neutropenic patients may provide additional evidence to support patient information provision and clinical guidelines.

The lack of clarity on the role of temperature in diagnosing infection and sepsis in neutropenia, along with a gap in the evidence relating to outcomes associated with different temperature values, presents a challenge to clinical practice. The need for further research on this topic has been identified (NICE, 2012). To address this the study reported here examined temperature recordings in adult solid tumour cancer patients admitted to a regional cancer centre with chemotherapy-induced neutropenia. The primary aim of the research was to examine the value of temperature as a diagnostic and/or prognostic indicator of specific outcomes in neutropenic patients. A secondary aim was to gain insight into the presenting symptoms reported by patients at home or on their initial admission assessment.

2. Methods

A cohort study was carried out using case note reviews of patients admitted to a regional cancer centre in England, UK, who were neutropenic and were diagnosed with infection. The centre treats patients with solid tumours and does not provide high dose chemotherapy, stem cell transplant or haemato-oncology services. The cancer centre provides a 24 h, 7 days a week telephone triage advice service for patients receiving cancer treatment and it directly admits the patients from across the region who are triaged as needing clinical review. Self-monitoring of temperature at home is advised to all patients receiving systemic anti-cancer therapy. The centre uses the UKONS triage tool (UKONS, 2016) and the trigger temperature for contacting the advice line is 37.5^{O}c. Patients are also advised to ring if they have any signs of infection, including feeling “generally unwell”.

Inclusion criteria for the study were all emergency non-elective admissions for treatment of neutropenic infection who attended the regional cancer centre for medical review. All patients were currently receiving chemotherapy treatment, neutropenic on admission (defined as a neutrophil count of 0.9×10^{9}/L or less) and were diagnosed with actual or potential infection. Patients that met the inclusion criteria were identified from the record of non-elective admissions to the assessment unit and the inpatient wards at the cancer centre by the research team.

The cancer centre covers a wide geographical area which contains five district general hospitals, each with an accident and emergency department. All patients are advised to contact the phone service at the cancer centre and in most situations are asked to attend the centre when triaged for clinical review. However, a small number of patients do attend local services and the study sample did not include those who presented at their local accident and emergency department rather than contacting the phone advice line, or were admitted to their local district general hospital rather than the cancer centre.

2.1. Study measures

A proforma was designed to structure data collection which included demographic details along with cancer diagnosis, treatment data and the following measures.

2.1.1. Temperature

Data collected regarding temperature included the value reported by the patient prior to admission (as recorded on the telephone triage form), the value on admission to the assessment unit, the highest value during admission and the total time temperature was 38°c or above during admission (from the first to the last reading at this level).

2.1.2. Infection

All patients had a diagnosis of infection documented in their care record. Signs and symptoms of infection were defined as any symptom of infection documented in the patient record, including non-specific symptoms, with or without elevated temperature. The broad sampling criteria aimed to include apyrexial patients as this population had previously been excluded from research into neutropenic sepsis (NICE, 2012).

2.1.3. Early warning score

The measure used to evaluate patient outcomes was their early warning score (EWS). EWS are a validated system for recording observations that are used to identify acutely unwell and deteriorating patients (Downey et al., 2017). EWS function by assigning scores to physiological parameters which are then combined to provide an aggregated score. Typically, a score of 0 is normal and scores increase to a maximum of 3 for each item as the levels deviate from the norm (RCP,