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PRACTICE GUIDELINE

Approach to fever assessment in ambulatory cancer patients receiving chemotherapy: a clinical practice guideline

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ABSTRACT

Background This guideline was prepared by the Fever Assessment Guideline Development Group, a group organized by the Program in Evidence-Based Care at the request of the Cancer Care Ontario Systemic Treatment Program. The mandate was to develop a standardized approach (in terms of definitions, information, and education) for the assessment of fever in cancer patients receiving chemotherapy.

Methods The guideline development methods included a search for existing guidelines, literature searches in MEDLINE and EMBASE for systematic reviews and primary studies, internal review by content and methodology experts, and external review by targeted experts and intended users.

Results The search identified eight guidelines that had partial relevance to the topic of the present guideline and thirty-eight primary studies. The studies were mostly noncomparative prospective or retrospective studies. Few studies directly addressed the topic of fever except as one among many symptoms or adverse effects associated with chemotherapy.

The recommendations concerning fever definition are supported mainly by other existing guidelines. No evidence was found that directly pertained to the assessment of fever before a diagnosis of febrile neutropenia was made. However, some studies evaluated approaches to symptom management that included fever among the symptoms. Few studies directly addressed information needs and resources for managing fever in cancer patients.

Conclusions Fever in patients with cancer who are receiving systemic therapy is a common and potentially serious symptom that requires prompt assessment, but currently, evidence to inform best practices concerning when, where, and by whom that assessment is done is very limited.

Key Words Fever, chemotherapy, febrile neutropenia

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INTRODUCTION

Fever is a common symptom in cancer patients receiving chemotherapy. Chemotherapy can affect the production of neutrophils in bone marrow, reducing an individual's ability to respond to infection. In this patient population, fever can represent febrile neutropenia, a syndrome that is characterized by fever and a low neutrophil count, and that can be life-threatening.

Because chemotherapy is usually administered in an outpatient setting, most fevers will occur in patients at home between clinic visits. Because fever can signal febrile neutropenia, patients experiencing a fever during chemotherapy require urgent assessment. Episodes can occur during the night and on weekends; thus, recourse has often been for the patient to present to an emergency department for assessment. A visit to the emergency department might also be needed during business hours if clinics lack the resources to evaluate a patient with fever. In Ontario, almost one half of all colon and breast cancer patients who receive adjuvant chemotherapy regimens, and an even higher proportion of lymphoma patients receiving aggressive chemotherapy regimens, find themselves visiting hospital emergency departments after chemotherapy[1,2]. Fever is one of the most common reasons, but only a subset of patients with

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fever have febrile neutropenia or require admission for further management.

Despite the frequency of fever in patients on chemotherapy, consistent evidence-based guidance about assessment (when, where, and by whom) is lacking. The current approach to the evaluation of fever in such patients is not standardized. There is variability in the definition; in the information and instructions provided to patients, caregivers, and health care providers; and in the approaches to education.

Given the potential for serious complications associated with fever in patients with cancer receiving chemotherapy, the present guideline was formulated to provide advice about the assessment of such patients in the community. Specifically, we investigated whether there are predictors associated with a poor outcome, and we sought to determine where and how quickly the assessment should take place; who can or should perform the assessment; and what advice, information, or education should be provided to patients receiving chemotherapy in the community should they develop a fever.

TARGET POPULATION

The target population includes adult patients with cancer (that is, solid tumours or lymphoma, myeloma, or chronic lymphocytic leukemia) receiving chemotherapy in an outpatient setting who develop fever at home. Emergency department, in-hospital, and outpatient management of fever that has been diagnosed as febrile neutropenia or serious infection is beyond the scope of this guideline. Advice on managing patients after the diagnosis of febrile neutropenia is made is abundant[3–7]. Patients who have undergone hematopoietic stem-cell transplantation or who have acute leukemia or myelodysplastic syndrome are excluded secondary to the pathophysiologic differences in prognosis in the setting of fever.

RESEARCH QUESTIONS

- How does temperature relate to risk for febrile neutropenia, serious infection, or death?
- What are the clinical predictors for the development of febrile neutropenia?
- What is the relationship between the timing or location of fever assessment, the personnel doing the fever assessment, and the outcome of a fever episode?
- Do the type, quantity, and content of information provided to patients affect their choice about when and where to seek care for fever?

METHODS

The Program in Evidence-Based Care produces evidence-based and evidence-informed guidance documents using the methods of the practice guidelines development cycle[8,9]. That process includes a systematic review, interpretation of the evidence and preparation of draft recommendations by the Working Group, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

Search for Existing Guidelines

For the present guideline, a search was conducted of the Standards and Guidelines Evidence (SAGE) directory of cancer guidelines[10] and the U.S. National Guidelines Clearinghouse. In addition, the Web sites of several known high-quality guideline developers, including the American Society of Clinical Oncology, the U.K. National Institute for Health and Clinical Excellence, and the Infectious Diseases Society of America were searched. Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the AGREE II instrument[11].

Search for Systematic Reviews and Primary Studies

The literature in the MEDLINE and EMBASE databases was searched for the years from database inception to March 2014. The search strategies combined terms for fever, cancer, chemotherapy, outpatients, emergency care, and information. Separate searches were conducted to focus on risk assessment and body temperature. The Cochrane Library was also searched, and the reference lists in relevant retrieved articles were scanned. An updated search was subsequently conducted to retrieve any relevant articles between March 2014 and November 2015.

Study Selection Criteria

Articles (full-text reports or conference abstracts) were considered for inclusion according to study design and relevance of the content to the research questions. The questions pertained to risk factors, prediction models, and relationships rather than to management of the fever; therefore, prospective or retrospective studies with at least 30 participants were eligible for inclusion. All studies were required to include cancer patients receiving chemotherapy. Systematic reviews containing studies meeting those criteria were also considered.

Studies that examined unfavourable outcomes (for example, febrile neutropenia, serious infection, hospital admission, or death) in relation to various cut-offs of body temperature or that investigated the measurement of body temperature were eligible.

Studies of clinical prediction rules that generated the rule in one or more sets of patients (derivation set) and tested the rule in another set of real patients (validation set) were eligible. A study could also validate an already developed rule in a new set of patients. Studies with bootstrapped validation sets (derivation and validation sets taken from the same patient population) were excluded. The criteria for assessing those studies were based on the *Journal of the American Medical Association* article on clinical decision rules from their users' guides to the medical literature[12].

Prospective or retrospective studies of patient assessment focusing on location, timing, or personnel doing the assessment that evaluated the risk for an unfavourable outcome were eligible, as were prospective or retrospective studies of education or information about managing fever provided to patients or caregivers.

Synthesizing the Evidence

Because of the heterogeneity in study designs and outcomes assessed, a meta-analysis was not feasible.

Internal Review

The guideline document was circulated to two approval bodies before dissemination to the broader health care community. An expert panel comprising medical oncologists, pharmacists, an advanced practice nurse, and a patient advisor contributed to final interpretation of the evidence, refinement of the recommendations, and approval of the final version of the document. The document was also reviewed by the Report Approval Panel of the Program in Evidence-Based Care, a 3-person group with expertise in methodology and oncology.

External Review

The document underwent targeted peer review by a small group of invited clinicians who reviewed the document and completed a short questionnaire. The document was also disseminated to practitioner groups for whom the document was relevant. That group included medical oncologists, family practitioners, nurses, nurse practitioners, hematologists, emergency physicians, and infectious disease physicians, and the memberships of relevant Cancer Care Ontario committees and the Canadian Association of Provincial Cancer Agencies.

RESULTS

Eight guidelines were identified[3–7,13–15]. The primary focus of the guidelines was the management of febrile neutropenia, particularly the care of patients after febrile neutropenia is diagnosed. The guidelines offered limited information on the evaluation and management of fever in our target patient population before a definitive febrile neutropenia diagnosis. Although none of the guidelines directly addressed the target population, they contained some relevant information.

Thirty-eight studies from the search of the primary literature were included. Of the excluded articles, most were ineligible because they were nonsystematic reviews, studies that did not address a study question, or studies that described clinical prediction rules but that did not use a validation set of patients.

Overall, there was a dearth of evidence about the assessment of fever in cancer patients receiving chemotherapy before a diagnosis of febrile neutropenia is made. No evidence was found to support recommendations for alternatives to existing models of care.

Internal Review

Comments from the expert panel highlighted the lack of data to support strong recommendations or suggestions for reducing the number of unnecessary visits to the emergency department.

The Report Approval Panel comments emphasized that such a serious condition warrants specific recommendations. In the absence of high-quality supporting data, a default approach that optimizes patient safety was recommended. The Working Group ensured that, lacking evidence to suggest otherwise, the safest and most reasonable option—that is, the current practice of referring patients who experience a fever outside of clinic hours to the emergency department—was included in the recommendations.

External Review

Five Ontario clinicians considered to be experts in the topic provided targeted peer review. The guideline was also disseminated to more than 300 Ontario health professionals, 45 of whom provided comments through an online survey. The comments of the reviewers reflected their disappointment with the lack of evidence for assessing fever in cancer patients receiving chemotherapy. However, reviewers noted that the guideline pointed to the gaps in current knowledge, identified areas for future research, and emphasized the uncertainty of the topic and the current consensus on vigilance.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendations

- ***Temperature*** Cancer patients in the community receiving chemotherapy who experience a fever should be assessed. Although fever is not a reliable predictor of unfavourable outcomes such as febrile neutropenia, infection, or death, it is a serious symptom.
  - A fever is defined as an oral temperature of 38.3°C or greater, or a sustained temperature of 38.0°C lasting more than 1 hour.
  - Tympanic temperature measurement is a viable option and should be measured according to the instrument manufacturer's specifications.

- ***Assessment*** Patients with fever should seek urgent assessment. The evidence is insufficient to make specific recommendations with respect to the timing, location, or personnel involved in the assessment of fever in the target population.
  - If fever occurs outside of clinic hours, the current practice of referring patients who have developed a fever to the emergency department is the only tenable option in many communities.

- ***Education*** Cancer patients receiving chemotherapy in the outpatient setting should be provided with standardized information about fever and fever-associated infection.
  - Patients should be informed about how to measure their temperature and how to recognize when assessment by a health care provider is recommended.
  - The information should be delivered at the time of chemotherapy initiation and can be provided in conjunction with other self-assessment education and reinforced with take-home written material and communication with health care providers.

Qualifying Statements

- Quality primary evidence to inform the definition of fever is lacking; thus, the consensus definition from existing guidelines on febrile neutropenia was recommended.
- Temperature readings vary widely between thermometer types.
- Administration of antipyretic medication can mask the presence of fever and should be avoided if possible.
- Some patients might be receiving growth factors to lower the risk of febrile neutropenia. Their risk for

poor outcome in the setting of fever might be lower, and fever can be a side effect of the growth factors themselves. The evaluation of fever in chemotherapy patients who are also receiving growth factors to prevent febrile neutropenia was outside the scope of the present guideline; however, no obvious citations addressing that issue were identified during the literature review to inform management of that subgroup. However, given the conservative nature of the recommendations, the authors believe that the recommendations apply to that group as well.

Key Evidence

Temperature

The temperature recommendation has existing guidelines and consensus as its basis. Most of the existing related clinical practice guidelines focus on the management of febrile neutropenia and define fever as a 1-time temperature measurement of 38.3°C or 2 readings of 38.0°C 1 hour apart[4,6,7,13–15]. Slight variations in definition were noted in two guidelines[3,5]. Evidence from the review of the primary literature found six studies addressing the predictive value of body temperature. The patients who were involved had already been diagnosed with febrile neutropenia, and the cut-off used in five studies was 39°C[16–20]. In those studies, temperature was an unreliable predictor of poor outcome. A blinded diagnostic test study in neutropenic patients, in which the reference standard was rectal thermometry, reported sensitivity, specificity, positive predictive value, and negative predictive value of 68%, 98%, 90%, and 92% respectively in detecting fever (≥38°C) with tympanic membrane thermometry. The sensitivity, specificity, positive predictive value, and negative predictive value with oral thermometry were 56%, 98%, 90%, and 89% respectively[21].

Assessment

No evidence was found that directly pertained to the assessment of fever before a diagnosis of febrile neutropenia is made. Fever was included as one among several symptoms (for example, fatigue, pain, nausea, and vomiting) in some studies of the management of adverse effects of chemotherapy. Approaches to symptom management in those studies included patient-initiated drop-in clinics[22,23], health care provider–initiated case management programs[24,25], and various remote monitoring strategies using cellphone applications, Web-based and touch-tone telephone interfaces, and automated programs[26–30]. Evaluation of those symptom management systems is an active area of current research.

Education

There is a paucity of primary evidence directly addressing information needs and resources for managing fever in patients with cancer. Improvement in symptoms was seen with interventions such as cognitive behavioural therapy provided by nurses[31]; pre-chemotherapy education class supplemented with take-home reading materials and instructions on how and when to report symptoms[32]; a symptom management toolkit describing self-assessment activities[26]; and education, a fever management algorithm, and a thermometer[33].

Interpretation of Evidence

Few primary studies dealing with the target population for the present guideline (that is, pre-diagnosis of febrile neutropenia) were found. No evidence was found to support recommendations for existing or alternative models of care.

With respect to the definition of fever, a lower temperature cut-off implies that more people would be unnecessarily assessed, but fewer patients subsequently progressing to febrile neutropenia would be missed. A higher temperature cut-off implies that more people at risk for poor outcome would be missed. Although the evidence shows that fever is not a reliable predictor of poor outcome, the potential seriousness of a fever compels urgent assessment of the patient to determine the level of risk.

Although the optimal assessment has been poorly defined, no available evidence suggested that patients could delay getting medical attention. By default, many patients present to the emergency department for assessment. In that regard, the Working Group echoes the position of the U.K. National Institute for Health and Clinical Excellence guideline, which recommends urgent assessment of patients who develop a fever at home[3]. Although that recommendation could cause unnecessary emergency department visits (with potentially long wait times and exposure to other sick patients), needless use of antibiotics, and increased patient anxiety, the benefits conferred by urgent assessment currently outweigh the potential harms of febrile neutropenia complications and risk of death.

No available evidence suggested an ideal location for assessment of fever, but such studies would be welcome, given the prevalence of the symptom and the number of related emergency department visits. The Working Group strongly endorses the need for formal studies that include a rigorous evaluation of alternative models of care for this situation.

Implementation Considerations

There is concern in Ontario that emergency department services are overused by cancer patients who develop fever while undergoing chemotherapy. One goal of the present guideline was to determine whether alternative care paths could be supported by research evidence. At the present time, the conclusion reached here is that the evidence is insufficient to predict which patients who develop fever are at risk of poor outcome, and therefore all patients should be assessed given the serious consequences of infection.

Despite a lack of studies to define optimal models of care for patients receiving chemotherapy who experience a fever, we identified some evidence that could be used to guide future practice. Predictive models that have been developed and validated in patients already diagnosed with febrile neutropenia, such as the Multinational Association for Supportive Care in Cancer score[18], could be incorporated into assessment algorithms for chemotherapy patients with fever to identify low-risk patients who could safely be assessed outside the emergency department. That approach would require data collection to confirm its validity in a new, much larger, and heterogenous cohort of patients, including those on chemotherapy with fever without a febrile neutropenia diagnosis. Data on the feasibility and efficacy of using technology and telephone-based strategies for the remote management of chemotherapy-related

symptoms are also emerging. Participation in such studies is highly encouraged so that evidence can be generated to inform models of care.

One of the issues identified during the course of this guideline's development is that standardization is lacking with respect to the information provided to patients about what to do if they experience a fever. The Guideline Panel believed that patients should be effectively educated to expect potential adverse events during and after chemotherapy treatment, including fever and the consequences of infection. They should understand what fever is, how to measure it, and where to go for assistance. Innovative strategies to support their care should be considered, such as having a dedicated on-call nurse within the systemic treatment clinic or provision of community services through pharmacies or laboratories. Technological advancements in obtaining a definitive neutrophil count at home or in the community could be possible in the near future.

It is essential that knowledge transfer with respect to fever assessment involve caregivers and health care personnel who care for cancer patients receiving chemotherapy, particularly family physicians and emergency department physicians and nurses who are likely to be contacted by patients outside of clinic hours.

Lastly, it should be recognized that, for any strategies implemented, evaluation of effect is essential. Because best practice is not currently defined, the future must be based on demonstrated improvement in care to patients and more effective service provision.

FUTURE RESEARCH

Thus far, studies have not been designed to determine whether fever can reliably predict a bad outcome in patients receiving chemotherapy, and current guidelines show a lack of focus on fever. Studies are needed to examine the relationship, without the inclusion of neutrophil count, between temperature and undesirable outcomes, and how that relationship is modified by other factors such as patient characteristics, concurrent symptoms, or treatment regimen.

Although some research on the development and evaluation of remote symptom management and monitoring systems and patient self-assessment in chemotherapy patients is being conducted, studies focusing specifically on new models of care for fever either alone or in the context of multi-symptom management strategies are needed. Development and testing of modes of communication with patients through telephone, mobile phone apps, and Web-based interfaces are encouraged as part of such studies. Effectiveness of alternative assessment venues, such as urgent-care clinics within cancer centres, should also be considered. Easier access to a neutrophil count should be explored: for example, alternatives to the emergency department for blood analysis, including the possibility of performing neutrophil counts in the home with emerging point-of-care tools. The management of patients already receiving growth factors who develop fever during chemotherapy has to be defined. Management of fever in patients on emerging therapies such as immunotherapy also has to be considered.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: Of the Working Group, one author (MKK) is principal investigator for studies on toxicity management in chemotherapy patients that are funded by Cancer Care Ontario and the Ontario Institute for Cancer Research. Of the Expert Panel, one member, as head of a cancer centre systemic treatment program, declared receipt of support from Amgen for systemic treatment.

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